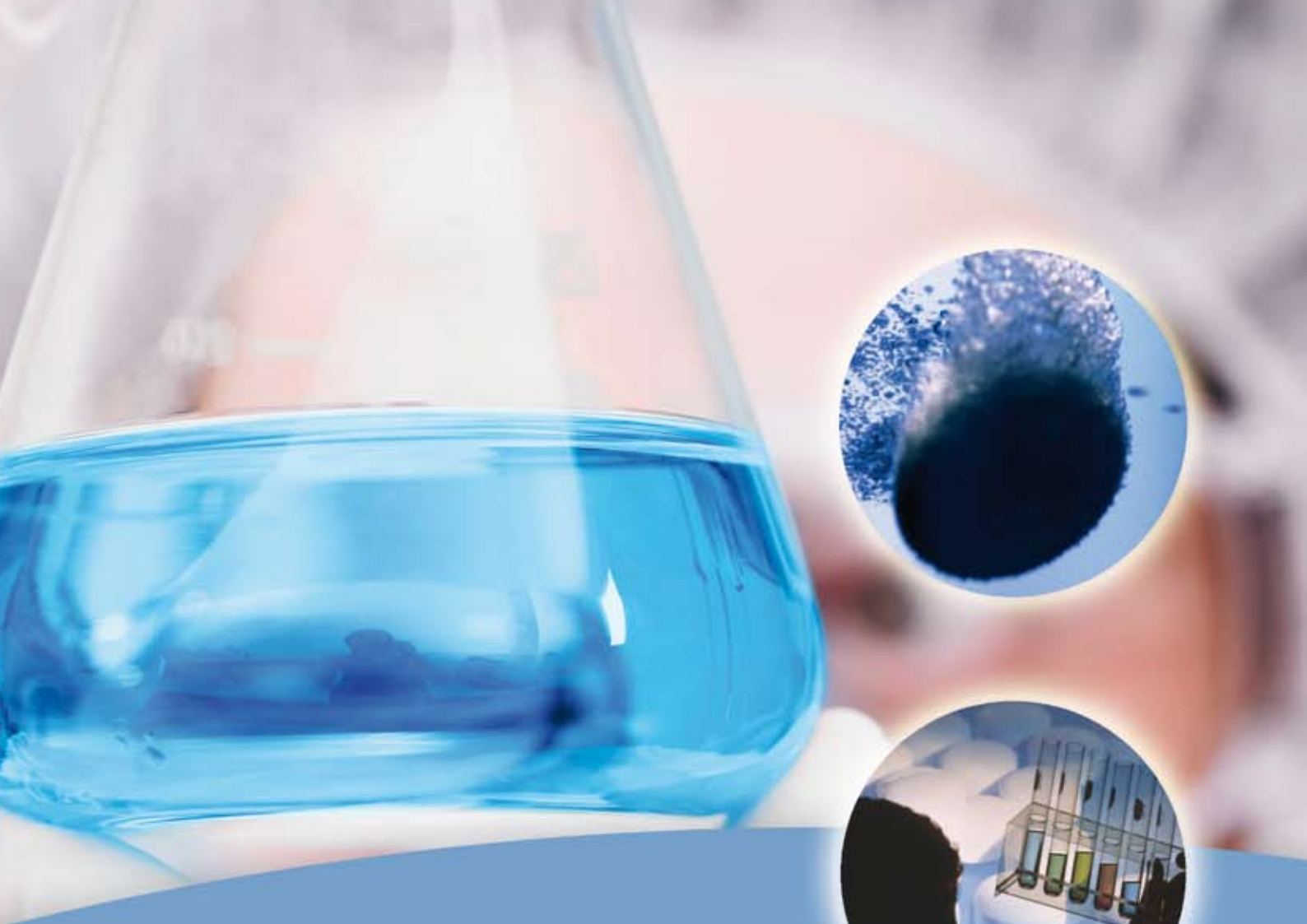




Pharmaceutical Pure Water Guide



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Veolia water solutions & technologies...

...partner in filtration



VFICE
industrial housings



VSHCE
sanitary housings



HIGH FLOW BIO-X
tank venting



MAXIGAS
tank blanketing with Nitrogen



CO₂RP
CO₂ reduction in
compressed air



SPUNFLOW
melt blown depth filtration



CARBOFLOW
chlorine removal filters



PLEATFLOW
absolute prefiltration



PROPOR PES
microbial reduction



DEMICA
disposable filter capsules

PRE-TREATMENT

Particulate trapping following sand filtration

Chlorine removal

FINAL TREATMENT

RO protection

Microbial reduction

STORAGE & DISTRIBUTION

Tank venting

Tank venting for ozonated water systems

Point-of-use sterilisation

Tank blanketing with Nitrogen

Microbial reduction

dedicated materials designed for your installation

dedicated filters to suit your application



domnick hunter ...more than just a filter

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An educational overview of water purification techniques in the pharmaceutical industry.

Veolia Water Solutions & Technologies specialises in delivering solutions to service all your process water needs. We are committed to providing process water treatment systems and service to the pharmaceutical, scientific and healthcare sectors.

With over 80 years water treatment experience, our focused approach and in-depth knowledge, backed by exemplary customer service, means we can expertly guide your business by delivering process water solutions that meet your needs, giving you peace of mind every time.

Contents

1 Introduction	2
2 Methods of water purification	4
3 Purified water	14
4 Monitoring the purity of purified water	15
5 Water purity standards	18
6 Purified water applications	20
7 Pure Water - hints & tips	22
8 Glossary of terms	23
Further reading	26
Contact information	Back page

1 Introduction

In today's pharmaceutical facilities the availability of purified water is essential. While the domestic consumer considers tap water to be "pure", the pharmaceutical end-user regards it as grossly contaminated.

Within the pharmaceutical industry, water is most commonly used in liquid form, not only as an ingredient in many formulations but also as a cleaning agent. Production of Purified Water, Highly Purified Water, Pyrogen Free Water and WFI to international pharmaceutical standards is widely recognised as a critical process.

The production of potable water

Purified water used in pharma processes is usually produced in-situ from local potable water which has been produced by the treatment of natural water sources.

For potable water the overall requirement is to produce drinking water that conforms to regulations and that has acceptable clarity, taste and odour. Natural water is taken from upland sources, such as reservoirs, from rivers or from underground aquifers and potable water is produced by a series of steps which vary with the water source, local and national regulations and the choice of technologies. One approach is outlined here.

After passing through a series of screens to remove debris, the water is mixed with ozone in contact tanks to oxidise pesticides and herbicides and kill bacteria and algae. Excess ozone is destroyed. Water is then clarified to remove suspended solids, which are collected as a sludge cake. A flocculent such as poly-aluminium chloride may be added to help this process. A sand gravity filter and/or further ozonation may also be used before the final filtration stage with

granular activated carbon (GAC). This traps the solids and organic matter. Finally chlorine is added to kill remaining bacteria. A small residual of chlorine is left to maintain low bacterial levels. An extra ultrafiltration stage is sometimes used to remove cryptosporidium.

Impurities in potable water

The unique ability of water to dissolve, to some extent, virtually every chemical compound and support practically every form of life means that potable water supplies contain many substances in solution or suspension.

Variations in raw water quality

Unlike other raw materials, potable water varies significantly in purity both from one geographical region to another and from season to season. Water derived from an upland surface source, for instance, usually has a low content of dissolved salts and is relatively soft, but has a high concentration of organic contamination, much of it colloidal. By contrast, water from an underground source generally has a high level of salts and hardness but a low organic content. River sources are intermediate in quality but also often contain products from industrial, agricultural and domestic activities.

Seasonal variations in water quality are most apparent in surface waters. During the autumn and winter months, dead leaves and decaying plants release large quantities of organic matter into streams, lakes and reservoirs. As a result, organic contamination in surface waters

reaches a peak in winter, and falls to a minimum in summer. Ground waters are much less affected by the seasons.

The quality and characteristics of the potable water supply have an important bearing on the purification regime required to produce purified water.

Suspended particles

Suspended matter in water includes silt, pipework debris and colloids. Colloidal particles, which can be organic or inorganic, give rise to haze or turbidity in the water.

Suspended particles can foul reverse osmosis membranes and electrodeionisation stacks, as well as interfere with the operation of valves and meters.

Dissolved inorganic compounds

Inorganic substances are the major impurities in water. They include:

- Calcium and magnesium salts which cause 'temporary' or 'permanent' hardness
- Carbon dioxide, which dissolves in water to give weakly acidic carbonic acid
- Sodium salts
- Silicates leached from sandy river beds
- Ferrous and ferric iron compounds derived from minerals and rusty iron pipes
- Chlorides from saline intrusion
- Aluminum from dosing chemicals and minerals
- Phosphates from detergents
- Nitrates from fertilisers

Dissolved organic compounds

Organic impurities in water arise from the decay of vegetable matter, principally humic and fulvic acids, and from farming, paper making and domestic and industrial waste. These include detergents, fats, oils, solvents and residues from pesticides and herbicides. In addition, water-borne organics may include compounds leached from pipework, tanks and purification media.

Micro-organisms

The chief micro-organisms of concern for water purification systems are bacteria. A typical bacterial level for a potable pharmaceutical water supply is ten colony forming units per one hundred milliliter (10 CFU/100ml) or less. Bacteria are usually kept at these low levels by the use of residual levels of chlorine or other disinfectants. Once the disinfectants are removed during purification, bacteria have the chance to proliferate.

Dissolved gases

Potable water is in equilibrium with the air and so contains dissolved oxygen and carbon dioxide. Carbon dioxide behaves as a weak acid and uses the capacity of anion exchange resins. Dissolved oxygen is usually only an issue where bubble formation is a problem. In applications where the purified water is used in open containers it will rapidly re-equilibrate with the gases in the air.

Measuring impurities in potable water

In order to design or select a water purification system it is necessary to have information on the composition of the feedwater, usually local potable water. Average data can often be obtained from the local water supplier, however, an analysis of the water gives the information directly.

The filter-blocking potential of the water can be estimated using a fouling index (FI) test or, less reliably, turbidity. A wide range of methods are available for determining inorganic components. Ion chromatographic, ICP-mass spectrometric or spectrophotometric methods are often used. Electrical conductivity provides a guide to potential problems. Organic compounds can be determined individually, e.g. chromatographically, or an overall indication of organic content can be provided by a total organic carbon (TOC) measurement. Total viable bacterial counts as well as those of individual species can be measured by filtration or inoculation and incubation in a suitable growth medium.

Total dissolved solids (TDS) is the residue in ppm obtained by the traditional method of evaporating a water sample to dryness and heating at 180°C. By far the greatest proportion of the filtered residue is inorganic salts and TDS is used as an indicator of the total level of inorganic compounds present. It can be measured directly or estimated by multiplying the conductivity of the water in $\mu\text{S}/\text{cm}$ at 25°C by 0.7.



2 Methods of water purification

Purifying potable water sufficiently for use in the pharmaceutical industry, usually requires a series of purification stages. The overall objective is to remove the impurities in the feedwater while minimising additional contamination from the components of the purification system and from bacterial growth. System design and component selection are critical to success.

The selection of the initial stages of a purification system will depend on the characteristics of the feedwater. The primary purpose of the pretreatment stages is to reduce damage to subsequent components, to ensure reliable operation of the water purification system, and to decrease the cost of operation by preventing excessively frequent replacement of more expensive components.

Bacteria

Micro-organisms and their by-products are a particular challenge. Micro-organisms will enter an unprotected water purification system from the feedwater, any openings in the system, or through the point of use. They will grow as biofilms on all the wetted surfaces of water purification components including storage tanks and the plumbing of a distribution system. A biofilm is a layer composed mostly of glycoproteins and heteropolysaccharides in which bacteria can multiply even when the concentration of nutrients in the water is very low, and the layer protects the organisms from periodic treatment with biocides that are primarily effective in killing planktonic (free-floating) micro-organisms. Sloughing biofilm and by-products of micro-organism growth and metabolism (e.g. endotoxins) are always potential contaminants of water.

The challenges for a purified water generation system are to:

- Meets all of the requirements for US and/or European Pharmacopoeia Monographs
- Remove the bacteria present in the feedwater
- Prevent bacteria from entering the system and causing re-contamination
- Inhibit the growth of bacteria in the system by design and by periodic sanitisation

Pretreatment

Microporous depth filters

Microporous depth filters provide a physical barrier to the passage of particles, and are characterised by nominal particle size ratings. Depth filters are matted fibre or material compressed to form a matrix that retains particles by random adsorption or entrapment. Most raw waters contain colloids, which have a slight negative charge (measured by the Zeta potential). Filter performance can be enhanced by using micro filters that incorporate a modified surface, which will attract and retain these naturally occurring colloids, which are generally much smaller than the pore sizes in the membrane.

Depth filters (typically 1-50 µm) are commonly used as an economical way to remove the bulk of suspended solids and to protect downstream purification technologies from fouling and clogging. They are replaced periodically.



Activated carbon (AC)

Activated carbon is used in pretreatment to remove chlorine and chloramine from feedwater so they do not damage membrane filters and ion exchange resins.

Most activated carbon is produced by “activating” charcoal from coconut shells or coal by roasting at 800 – 1000 °C in the presence of water vapour and CO₂. Acid washing removes much of the residual oxides and other soluble material. Activated carbon used in water treatment usually has pore sizes ranging from 500-1,000 nm and a surface area of about 1000 square meters per gramme. Carbon is used as granules or moulded and encapsulated cartridges which produce fewer fine particles.

Activated carbon reacts chemically with 2-4 times its weight of chlorine, producing chlorides. This reaction is very rapid and small carbon filters can effectively remove chlorine from water. The breakdown of chloramine by carbon is a relatively slow catalytic reaction producing ammonia, nitrogen and chloride; larger volumes of carbon are needed. Organic fouling can reduce the effectiveness of the carbon and is dependent on the local water supply. This should be considered when sizing its carbon units.

The second application of activated carbon is in the removal of organic compounds from potable water. Activated carbon takes up water contaminants by virtue of ionic, polar and Van der Waals forces, and by surface-active attraction. Activated carbon beds are prone to releasing fines and soluble components into the water stream and do not remove all dissolved organic contaminants, but their use can produce a significant reduction in TOC. A purer form of activated carbon made from polymer beads is sometimes used for this application.

The large surface area and high porosity of activated carbons along with material they trap, make them a breeding place for micro-organisms. Activated carbon beds need to be periodically sanitised or changed regularly to minimise bacterial build-up.



Water softening (SO)

Hardness in a water supply can result in scale formation, which is a deposit of minerals left over after the water has been removed or evaporated. This can be found in reverse osmosis systems, clean steam generators and distillation systems.

The most common technology used for removing scale formed by calcium and magnesium ions is ion exchange water softening. A water softener has four major components, a resin tank, resin, a brine tank and valves or controller. When hard water is passed through the resin, calcium, magnesium, and other multivalent ions such as iron adheres to the resin, releasing the sodium ions until equilibrium is reached. A regeneration is needed to exchange the hardness ions for sodium ions by passing a sodium chloride (NaCl) solution (called brine) through the resin.

Acidification/Degasification can be used as a softening process but it has numerous disadvantages, such as handling chemical (sulphuric acid, anti-scalant) and instrumentation for two pH adjustments. Nanofiltration is sometimes referred to as a softening membrane process and will remove anions and cations. The feedwater requirement for a nanofiltration

system is about the same as for a reverse osmosis system and feed water should be pre-treated prior to going to the membranes.

Major purification technologies

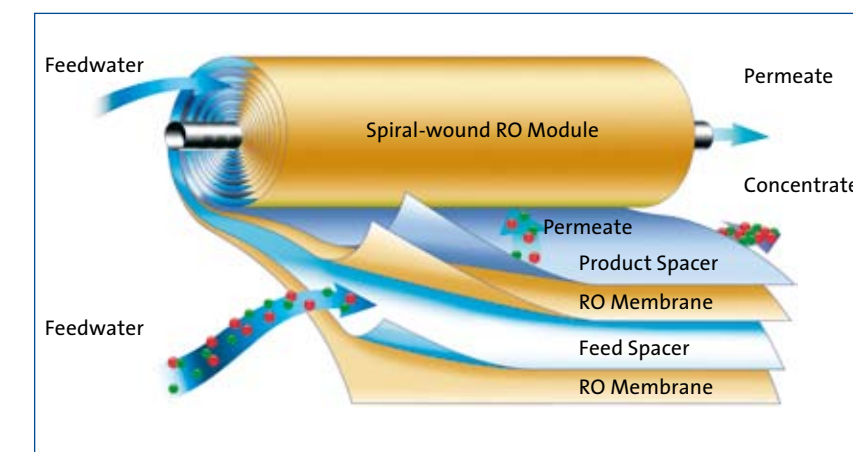
Reverse osmosis (RO)

RO membranes are used to remove contaminants that are less than 1 nm nominal diameter. Reverse osmosis typically removes 90% to 99% of ionic contamination, most organic contamination, and nearly all particulate contamination from water. RO removal of non-ionic contaminants with molecular weights <100 Dalton can be low. It increases at higher molecular weights and, in theory, removal will be complete for molecules with molecular weights of >300 Dalton and for particles, including colloids and micro-organisms. Dissolved gases are not removed (eg. CO₂).

During reverse osmosis, pretreated water is pumped past the input surface of an RO membrane under pressure (typically 4–15 bar, 60–220 psi) in cross-flow fashion. RO membranes are typically thin film composite (polyamide). They are stable over a wide pH range, but can be damaged by oxidizing

agents such as chlorine, present in municipal water. Pretreatment of the feedwater with microporous depth filters, softener and activated carbon is usually required to protect the membrane from large particulates, hardness and free chlorine. Typically 75%-90% of the feedwater passes through the membrane as permeate and the rest exits the membrane as concentrate, that contains most of the salts, organics, and essentially all of the particulates. The ratio of the volume of permeate to the volume of feedwater is referred to as the “recovery”. Operating an RO system with a low recovery will reduce membrane fouling, especially that due to precipitation of low solubility salts. However, recoveries of up to 90% are possible, depending on the quality of the feedwater and the use of filtration and softening pretreatment.

The performance of the RO component of a water purification system is typically monitored by measuring the percent ionic rejection, which is the difference between the conductivities of the feed and permeate divided by the feed conductivity, calculated as a %. The “ionic rejection” and “recovery” will vary with the feedwater, the inlet pressure, the water temperature and the condition of the RO membrane.

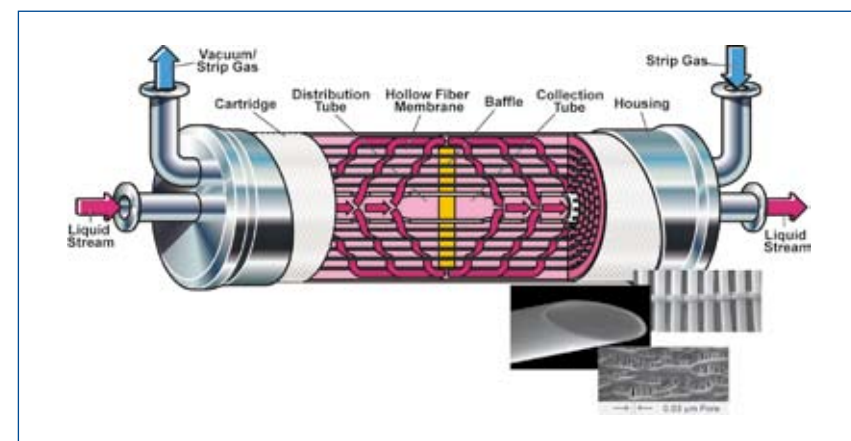


Due to its exceptional purifying efficiency, reverse osmosis is a very cost-effective technology for the removal of the great majority of impurities. Reverse osmosis protects the system from colloids and organic fouling. It is often followed by ion exchange or electrodeionisation. Reverse osmosis units need periodic cleaning & sanitisation with acid and alkaline solutions. Specially constructed membranes are available for hot water sanitisation at 85°C.

Degassing Membrane (DG)

A membrane contactor is a hydrophobic membrane device that allows water and a gas to come into direct contact with each other without mixing. Water flows on one side of a membrane and a gas

flows on the other. The small pore size and hydrophobic property of the membrane prevents water from passing through the pore. The membrane acts as a support that allows the gas and water to come into contact with each other across the pore. By controlling the pressure and composition of the gas in contact with the water, a driving force can be generated to move dissolved gasses from the water phase into the gas phase. The membrane contactor works under the same basic principles that vacuum degassifiers or forced draft deareators operate under. However, the membrane-based technology offers a cleaner, smaller and more stable operating system than the conventional degasification tower design. The pore size of the membrane is in the order of 0.03 microns, so air-borne contamination will not pass through the pore and enter the water stream. Membrane degassing is frequently used when treating feed water that has a high level of dissolved CO₂ (>10-15 ppm). Carbon dioxide will freely pass through an RO membrane. As it passes through an RO membrane it will dissociate and raise the conductivity of water. Membrane degassing effectively removes the dissolved CO₂, and maintains a low conductivity, which is important for subsequent treatment steps, particularly continuous electro-deionisation (CEDI).



Ion exchange (IX)

Beds of ion exchange resins can efficiently remove ionised species from water by exchanging them for H⁺ and OH⁻ ions. Ion exchange resins are sub-1 mm porous beads made of highly cross-linked insoluble polymers with large numbers of strongly ionic exchange sites. Ions in solution migrate into the beads; where, as a function of their relative charge densities (charge per hydrated volume), they compete for the exchange sites. Beads are either cationic or anionic. Strong cation resins are usually polysulfonic acid derivatives of polystyrene cross-linked with divinylbenzene. Strong anion resins are benzyltrimethyl quaternary ammonium hydroxide (Type 1) or benzyldimethylethyl quaternary ammonium hydroxide (Type 2) derivatives of polystyrene cross-linked with divinylbenzene.

Beds of ion exchange resins are available either in cartridges or cylinders, which are replaced /removed from site for remote regeneration, or as an arrangement of tanks, vessels, valves and pumps, which allows on site regeneration of the ion exchange resins.



Positively charged ions (e.g. calcium, magnesium) are removed by the cation resin by exchanging hydrogen ions for the heavier more highly charged cations. Once "exhausted" the cation resin is regenerated by exposing the resin to an excess of strong acid, usually hydrochloric (HCl).

Similarly, negatively charged ions (e.g. sulphate, chloride) exchange with hydroxyl ions on the anion resin. Anion resin is regenerated using strong sodium hydroxide solution (NaOH).

The very large surface areas of ion exchange resins makes them a potential breeding place for micro-organisms and can lead to the release of fines and soluble components. For these reasons, good quality resins should be used and bed volumes kept as small as reasonably possible. Filters are typically installed after the beds to trap fines and other particulate matter. Bacterial build up can be minimised by frequent recirculation of the water and by regular cartridge replacement.

Modern ion exchange plant design uses relatively small resin beds and frequent regeneration – this minimises the opportunity for microbial growth.

With suitable choice of resin, pretreatment and system design, ion exchange enables the lowest levels of ionic contamination to be achieved.

Continuous electrodeionisation (CEDI)

Continuous electrodeionisation is a technology combining ion exchange resins and ion-selective membranes with direct current to remove ionised species from water. It was developed to overcome the limitations of ion exchange resin beds, notably the release of ions as the beds exhaust and the associated need to change or regenerate the resins.

Reverse osmosis permeate passes through one or more chambers filled with ion exchange resins held between cation or anion selective membranes. Ions that become bound to the ion exchange resins migrate from the dilute chamber to a separate chamber (concentrate) under the influence of an externally applied electric field, which also produces the H⁺ and OH⁻ necessary to maintain the resins in their regenerated state. Ions in the concentrate chamber are recirculated to a break tank or flushed to waste.

The ion exchange beds in continuous electrodeionisation (CEDI) systems are regenerated continuously, so they do not exhaust in the manner of ion exchange beds that are operated in batch mode (with chemical regeneration). CEDI beds are typically also smaller and remain in service for much longer periods.

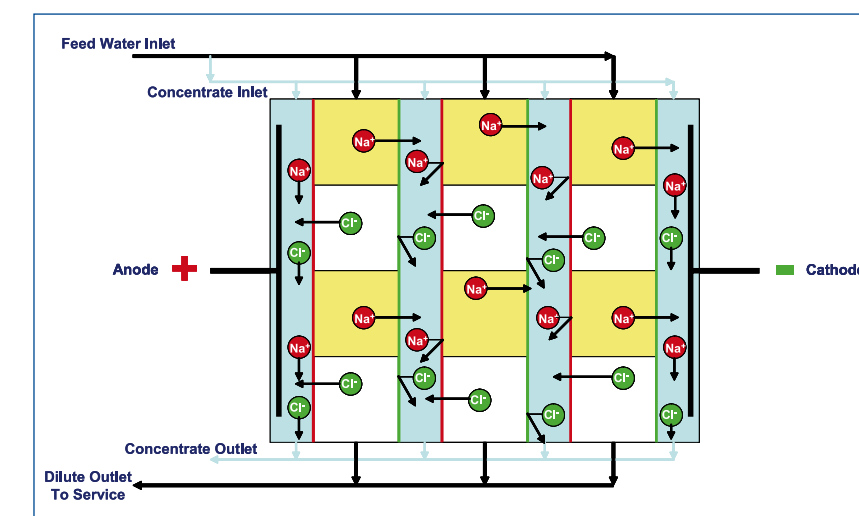
CEDI is preferred for many purified water generation applications in Pharma, because of its "clean" non-chemical nature and constant high quality water produced.

The resins used in CEDI systems can either be separate chambers of anion or cation beads, layers of each type within a single chamber or an intimate mixture of cation and anion beads.

Veolia Water Solutions & Technologies' pharmaceutical CEDI process utilizes cation beads in the concentrate stream and layered beds of cation and anion resins in dilute stream.

The resins are housed in wide cells that provide a flow path for the ions in transit. This offers advantages in the flexibility of design and mechanical simplicity on an industrial scale. The ion migration from dilute to concentrate is enhanced by the layered resin bed in the dilute.

Reverse osmosis (and sometimes membrane degassing) is typically used before CEDI to ensure that the CEDI "stack" is not overloaded with high levels of salts. The small volume of resins in the stack results in low bleed of organic molecules. Typically,





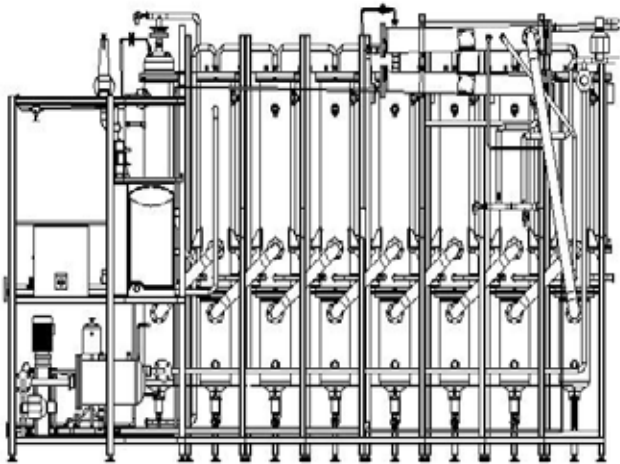
RO removes about 95% of ions; CEDI will remove 99% of the remaining ions as well as carbon dioxide, organics and silica.

Typically, CEDI product water has a resistivity of 1 to 18.2 MΩ-cm (at 25°C) and a total organic carbon content below 20 ppb. Bacterial levels are minimised because the electrical conditions within the system inhibit the growth of micro-organisms. Current CEDI stacks development allow the user to carry out hot water sanitisation at 85°C, for a period of 1 to 4 hours.

Distillation

The pharmaceutical still chemically and microbiologically purifies water by phase change and entrainment separation. In this process, water is evaporated producing steam. The steam disengages from the water leaving behind dissolved solids, non-volatiles, and high molecular weight impurities. However, low molecular weight impurities are carried with water mist/droplets, which are entrained in steam. A separator removes fine mist and entrained impurities, including endotoxins. The purified steam is condensed into water for injection. Distillation systems are available to provide a minimum of 3 log10 reduction in contaminants such as micro-organisms and endotoxins. Three designs are available including single

Multi-Effect Water Still Generator



effect (SE), multi-effect (ME) and vapour compression (VC). In a multi effect still, purified steam produced in each effect is used to heat water and generate more steam in each subsequent effect. Purity increases with each effect added. In a vapour compression still, steam generated by the evaporation of feedwater is compressed and subsequently condensed to form distillate. All distillation units are susceptible to scaling and corrosion. VC stills require water softening for removing calcium and magnesium as minimum. ME stills require higher water quality. Ion exchange or reverse osmosis units are usually used as pretreatment. Stills are sensitive to chlorine and should be protected with activated carbon or sodium bisulfate injection.

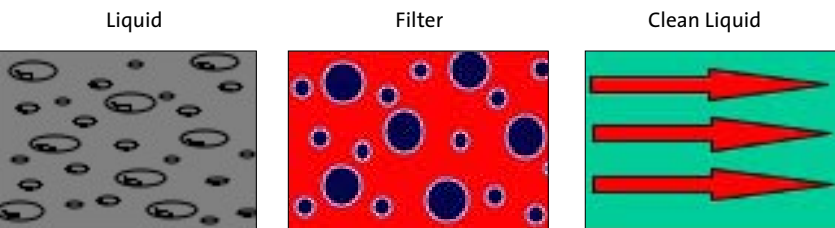
Microporous Filters

Microporous filters provide a physical barrier to the passage of particles and micro-organisms in purified water systems. Cartridge filters, characterised by absolute particle size ratings, have uniform molecular structures, which, like a sieve, retain all particles larger than the controlled pore size on their surface.

Cartridge filters (0.05 to 0.22 µm) are typically used before the purified water distribution tank to trap micro-organisms and fine particulates.

Trapped particulates, including micro-organisms or their metabolic products, and soluble matter, can be leached from filters and suitable maintenance (regular sanitisation and periodic replacement) is necessary to maintain desired levels of performance. Newly installed filters usually require rinsing before use to remove extractable contaminants.

A microporous filter membrane is generally considered to be indispensable in a water purification system, unless it is replaced by an ultraviolet generator or ultrafilter.



Ultrafilter

Ultrafiltration (UF) is a cross-flow process similar to reverse osmosis. The membrane rejects particulates, organics, microbes, pyrogens and other contaminants that are too large to pass through the membrane. UF has a stream to waste (concentrate) that can be recirculated. In polishing applications, this is generally 5% of the feed flow. Membranes are available in both polymeric and ceramic materials. The former is available in spiral wound and hollow fibre configurations and the ceramic membranes are available in single and multiple channel configurations. Ultrafiltration is frequently used downstream of ion exchange deioniser or reverse osmosis/ continuous electrodeionisation processes for microbial and endotoxin reduction. The rating of UF membranes varies in molecular weight cut-offs from 1 000 to 100 000 and UF has reduction of endotoxin (pyrogens) from 2 log 10 to 4 log10. UF is capable of consistent production of water meeting the USP WFI endotoxin limit of 0.25 Eu/ml. UF membranes can be sanitised with a variety of chemical agents such as sodium hypochlorite, hydrogen peroxide, peracetic acid and with hot water and / or steam.

Vent filters

Hydrophobic microporous filters are often fitted to water storage containers as vent filters in order to prevent particulates, including bacteria, from entering the stored water. Regular replacement is essential to maintain effectiveness.



Why Integrity Test ?

To assure filter performance prior to use

- To meet regulatory requirements
- FDA
- cGMP guidelines to achieve Best Practice
- Prevention of batch loss/ reprocessing

What is an Integrity Test ?

- A non-destructive test which is directly correlated to a destructive bacterial challenge test

Integrity Testing

- Through proving the link between bacterial challenge testing and Integrity Testing, the user can be sure that if filters pass an Integrity Test they would also pass a challenge test with live bacteria - in other words, the filters are working correctly.

The Different Integrity Test Methods

1. Bubble Point

The pressure at which liquid is ejected from the largest pores thus allowing mass flow of gas.

2. Pressure Decay

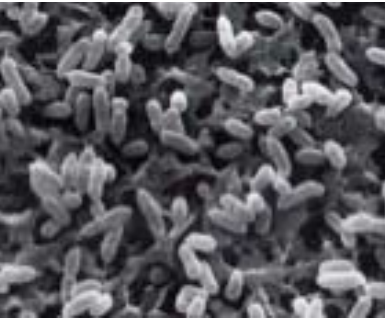
The most commonly adopted method with wide acceptance.

3. Diffusion Flow

Uses the same principles and is closely related to Pressure Decay.

4. Water Intrusion Test (WIT)

Only used to test hydrophobic PTFE membrane filters used for gas sterilisation.



bacterial challenge test organism Brevundimonas diminuta trapped on a membrane

Technologies used to control Micro-organisms

	Microporous filter	Ultra filter	Reverse osmosis	Ultra-violet light
Micro-organisms	√√√	√√√	√√	√√√
Endotoxins	√	√√√	√√	√

Key
√√√ Excellent removal
√√ Good removal
√ Partial removal

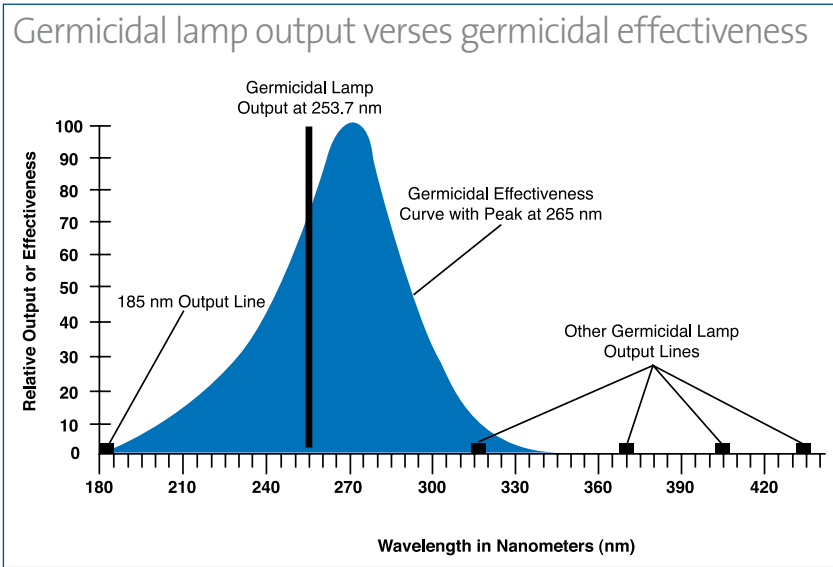
Ultraviolet light

Ultraviolet light is used as a bactericide and to break down and photo-oxidise organic contaminants to polar or ionised species for subsequent removal by ion exchange. The UV sources in pharmaceutical water purification systems are low or medium pressure mercury vapour lamps.

Radiation with a wavelength of 240-260 nm has the greatest bactericidal action with a peak at 265nm. It damages DNA and RNA polymerase at low doses preventing replication. For most Pharma applications, UV chambers and lamps need to be designed to provide a sufficient dosage of UV to achieve a 6 log¹⁰ reduction of typical pathogenic contaminants.

Radiation at shorter wavelengths (185 nm) is effective for the oxidation of organics. The UV breaks large organic molecules into smaller ionised components, which can then be removed by a downstream continuous electrodeionisation. 185 nm UV is also used to destroy excess chlorine or ozone.

UV radiation at 185 nm is a highly effective photo-oxidant and a key component in producing purified water with the lowest levels of organic contaminants.



System design

The different technologies described on the previous pages can be combined in a variety of ways to achieve the desired degree of water purification.

Each system will require some pretreatment based on the particular feedwater to remove particulates, chlorine or chloramines, calcium and magnesium. This is preferably followed by reverse osmosis to remove virtually all colloids, particles and high molecular weight organic compounds and over 90% of ions. The resultant deionised water will contain some organic compounds, some ions, some bacteria and cell debris and all the dissolved carbon dioxide and oxygen.

The water is next treated by one or more techniques depending on the required purity - ion exchange or second stage reverse osmosis or CEDI to remove ions, UV light to kill bacteria and/or to oxidise residual organic compounds and ultrafiltration to remove endotoxin, protease and nuclease. Any or all of these stages can be combined in the same unit as the reverse osmosis or separately in a “polisher”.



Storage tank and distribution are potential sources of contamination, particularly from bacteria. Good design and proper maintenance regimes are needed to minimise problems. The choice of materials of construction is also critical. Metals, other than stainless steel, should be avoided. There are many high purity plastics available but care needs to be taken to avoid those with fillers and additives which could contaminate the water. Storage tanks should be protected from ingress of contaminants with suitable vent filters. The purified water is recirculated continuously and cooled down to maintain purity. UV disinfection is often used to maintain microbial purity in the distribution loop.

Maintenance of the water purification system

In order to ensure that once qualified, the facility remains in a state of qualification, a preventative maintenance programme must be developed. In order to enable this programme to be established, detailed operating and maintenance instructions together with monitoring log sheets and spares lists, need to be provided. The specialist water treatment supplier can typically

provide maintenance contracts. These types of maintenance contracts focus on maintaining the system in a state as close to that at which it operated at commissioning. All parameters are recorded during the contract visit and adjusted accordingly with all changes recorded. Cleaning, repairs and preventative maintenance operations are recorded within the report sheets. The final report will also give details of any recommended and necessary actions.



Validation and trend monitoring

Process Validation is defined as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. Validation is the process of documenting the design, installation, operation and performance of an operating system. Periodically all water treatment systems may be inspected by the local or international inspecting authorities to ensure that the pharmaceutical facility complies with the local or international regulations. Ultimately the user is responsible for validating the water system to make sure that it meets the requirements of the inspectors, however the supplier will need to provide most of the test documentation for the water treatment plant.

The validation documentation package should follow the various regimes, protocols and guidelines laid out by the regulatory authorities and the industry bodies, typically:



The water standards in the pharmacopoeias

- USP – United States Pharmacopoeia
- Ph Eur – European Pharmacopoeia
- JP – Japanese Pharmacopoeia

‘Good Manufacturing Practice’ (GMP)

- FDA Code of Federal Regulations 21CFR210 & 21CFR211
- ‘The Rules Governing Medicinal Products in the European Union’ Volume 4

ISPE ‘Baseline® Guide’

- Volume 4 – Water and Steam Systems
- Volume 5 – Commissioning & Qualification
- Volume 8 – Maintenance

US regulation 21CFR11 Electronic records and electronic signatures

‘GAMP 4’ – a guideline for the validation of automated systems

ISO 9001 – Quality Management System approval

The documents created for a validated water treatment system may vary from site to site, however the standard documents are generally covered in the following list of documents.

Documentation list

Abbreviation / Document	Full Title	What it is for	Abbreviation / Document	Full Title	What it is for
URS	User Requirement Specification	To tell the supplier what the customer requires, what specification that needs to be adhered to, how much water is needed, what the water system is to do etc. Document created by the client or his engineer.	DQ	Design Qualification	The design qualification or enhanced design review is carried out to ensure that the designed equipment, using the design documents, meets the user requirements. The review is documented and created by the supplier.
VMP	Validation Master Plan	This documents the client’s approach to validation on site and in particular to the current site project. It identifies the scope of the validation exercise allowing the validation on site to be suitably managed. Created by the client or his engineer.	SDS	Software Design Specification	To describe the control panel software function and design
QPP	Quality & Project Plan	This document defines how the supplier will fulfil the user and supplier’s quality requirements on the project. It also provides details of the project management on the contract. This may include a Gantt chart for the project management of the contract. This is the supplier’s response to the VMP. Document created by the supplier.	STS	Software Test Specification	To test the functions described in the SDS
QIP	Quality Inspection Plan	This document gives details of how and when the equipment that is to be supplied is inspected at the supplier’s works. This details the type of inspection and who will inspect, also giving options as to when it is suggested that the client inspects. The document is created by the supplier.	HDS	Hardware Design Specification	To describe the control panel hardware function and design
FDS	Functional Design Specification	To describe the components of the equipment, how it will be connected together and how the system functions. This is the supplier’s response to the clients URS. Document created by the supplier.	HTS	Hardware Test Specification	To test the functions described in the HDS
P&ID	Process & Instrument Diagram	Drawing of the system, that shows all valves, instruments, and equipment. This is the principal design document created by the supplier.	GAMP Categorisation	Good Automated Manufacturing Practice Categorisation	To categorise configurable instruments. This gives information on how to record configuration and validation process that should be used
Valve Schedule	Valve Schedule	Lists all the valves and the valve specification. Created by the supplier.	MFAT	Mechanical Factory Acceptance Test	To test the equipment at the supplier’s factory without running water through the system. The system does not have to be fully assembled for this. Checks include ensuring the correct equipment is available
Instrument Schedule	Instrument Schedule	Lists all the instruments and the instrument specification. Created by the supplier.	FAT	Factory Acceptance Test	To test the equipment operationally in the factory with water. This tests all the equipment functionality.
Equipment Schedule	Equipment Schedule	Lists all the equipment and the equipment specification. Created by the supplier.	SAT	Site Acceptance Test	This document tests the equipment on site. The SAT can be a combination of the IQ, Commissioning and OQ documents, depending on each client’s understanding. The supplier creates the SAT document.
Utilities Schedule	Utilities Schedule	Lists all the utilities and the utility specification, such as water, drains, electricity, steam, air, chemicals etc. Created by the supplier.	IQ	Installation Qualification	To document that the equipment is correctly installed on site as intended. The supplier normally creates this document.
GA Drawing	General Arrangement Drawing	Equipment layout drawing, showing information as to the connections to the equipment and their locations.	Commissioning Protocol	Commissioning	To document that the system is correctly set up and that the system is made ready for full functional operation. This document records all the start up data. The supplier creates this document.
			OQ	Operation Qualification	To document that the system functions and operates as described in the FDS. The supplier normally creates this document.
			PQ	Performance Qualification	To record that the system produces good quality water and that the quality is consistent when the system is on line. The user creates this document.

Change Control

Key to the validation effort is the control and evaluation of change both during the time scale of the project and in subsequent ongoing use. Inspectors mandate change control for processes, equipment and control systems. The aim of any change control is to provide an auditable trail and to ensure a state of control.

Performance

The ongoing performance of the plant is monitored regularly by the user. The user needs to be in control of the quality of water produced by the system. Typically the bacteria content of the water is the most variable component of a water system and so regular and detailed monitoring is required. This monitoring will aid the determination of when the system should be sanitised.

Sanitisation

Sanitisation of the water purification and distribution system is critical to ensure that microbial contamination is controlled within specifications. Sanitisation frequency must be adequate to maintain the purity specifications and is established based on system usage, regular quality control trend data, and the system manufacturer's recommendation. Sanitisation of a water system is carried out on a regular basis, determined by the monitoring of bacteria in the system. The method used for sanitisation depends on a number of factors such as the materials of construction and the design intent. If the system is made of plastic materials then a chemical sanitisation method is used, as most plastics cannot accept high temperatures. Per-acetic acid and hydrogen peroxide are often used as chemical sanitants. Where the materials of construction are metal or plastics suitable for high temperature then heat is frequently used. Hot water (85°C), over heated water (121°C), steam or ozone are frequently used for sanitisation.

3 Purified water

Veolia Water Solutions & Technologies differentiates between two kind of applications of process water used in the Pharmaceutical industry:

Non-Critical utilities & Critical utilities

Non-Critical utilities

These are non-validated systems for applications such as boiler feed, cooling tower make up, feed to large glass washers and autoclaves. Reverse Osmosis and Ion Exchange are the most commonly used water treatment technologies in non-critical utilities.

Critical Utilities

Purified Water not only has relatively high purity in ionic terms, but also low concentrations of organic compounds and micro-organisms. A typical specification would be a conductivity of <1.0 µS/cm (resistivity >1.0 MΩ-cm), a total organic carbon (TOC) content of less than 500 ppb and a bacterial count below 100 CFU/ml. Water of this quality can be used for a multiplicity of applications, including make up and rinse water for large and small volume parenterals, genetically engineered drugs, Serum/media, ophthalmic solutions, antibiotics, vaccines, cosmetics, veterinary products, OTC and ethical products, fermentation, medical devices, nutraceuticals and diagnostics. Purified water can be produced by water purification systems incorporating reverse osmosis and ion exchange, second pass RO or CEDI, and often also with UV treatment.

Purified apyrogenic water is required in applications such as mammalian cell culture. Ultrafiltration is used to remove any significant levels of biologically active species such as endotoxin (typically <0.25 IU/ml) and nucleases and proteases (not detectable).

4 Monitoring the purity of purified water

It is impractical to monitor all potential impurities in purified water. Different approaches are used for different types of impurities. The key rapid, on-line techniques commonly used are resistivity and TOC measurement.

Control of impurities	
Impurity	Control and measurement approaches
Ions	Use of RO, ion exchange, CEDI, in-line Resistivity monitor
Organics	Use of RO, carbon, UV photo-oxidation, in-line TOC monitor
Particles	Use of absolute filter Occasional on-line testing, if needed
Bacteria	Use of microfilter, UV & sanitisation Off-line testing
Endotoxins	Use of ultrafilter, UV photo-oxidation Off-line testing
Bio-active species	Use of ultrafilter, UV photo-oxidation Off-line testing

Conductivity/Resistivity

Historically, the quality tests for bulk Purified Water (PW) and Water for Injection (WFI) were confined to the laboratory. Water samples were checked for single chemical impurities, such as carbon dioxide, ammonia, chloride, sulphate and calcium, using traditional wet chemistry methods. Other wet chemistry tests for screening classes of impurities were oxidisable substances, heavy metals, and pH; these tests complemented other existing tests for particulates, micro-organisms, and endotoxins. In some pharmacopoeia, tests for nitrate, nitrites, and other impurities were required also.

As far back as 1989, the U.S. Pharmacopoeia (USP) and the Pharmaceutical Researchers and Manufacturers of America (PhRMA, formerly PMA), began investigating alternatives to the wet chemistry tests. At that time, the principal focus was not the water, but the reliability of the water testing. The water was "not broken", but the testing was archaic (several tests go back to the mid-nineteenth century), labour intensive, susceptible to analyst bias, and very sensitive to container cleanliness and analyst handling. PhRMA and USP investigated the measurement technologies of conductivity and total organic carbon (TOC) as a direct replacement for the wet chemistry methods. Both of these technologies have the distinct advantage of being widely used for industrial on-line process control for years. These measurements were critically relied upon in the growing microelectronics industry of the 1980's and 1990's where water purity was critical to the efficiency, device speed, and product cost of advanced semiconductors. At that time, conductivity measurements already existed on laboratory and skid-based pharmaceutical water systems, and TOC measurements were becoming increasingly relied upon. These measurements were primarily used to verify that the water purification equipment specification was met. The technical group leaders on these committees realised the potential to take advantage of these process analytical measurements, and use them for greater and productive means.

In 1996, in USP 23 Supplement 5, conductivity and TOC measurements were recognized as the best means to assure ionic and organic impurity control in PW and WFI. The advent of <645> Water Conductivity and <643> Total



Total Organic Carbon

With the addition of the new 5000TOC Total Organic Carbon Sensor, THORNTON's 770MAX is the first on-line instrument to offer multiple TOC and conductivity measurements in a multiparameter instrument platform.

Low detection limits with quick, continuous response provide complete, accurate and reliable data; and, THORNTON smart sensor technology makes installation fast and simple.

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Organic Carbon represented the first test methods which could be used for equipment verification, on-line process control, and release of water to production for the first time in the pharmaceutical industry. In addition, the USP specifications set standards for the measuring instrumentation used for TOC and conductivity measurements, such as system suitability, limit of detection, instrument resolution, and calibration requirements for sensor and transmitter. Concurrently, all of the USP wet chemistry tests for bulk waters were deleted, with the exception of micro-organisms and endotoxins (for WFI only). The Stage 1 conductivity test has a conductivity limit that is temperature dependent, thereby allowing the user to measure uncompensated conductivity and temperature on-line, in real-time, and release water to production continuously and without having to wait hours or longer for a test result from the lab. This temperature dependent limit remains in place today. The TOC limit is approximately 500 ppb.

In 2000, the European Pharmacopoeia (Ph Eur) deleted most of its wet chemistry tests and replaced them with TOC and conductivity testing for bulk Aqua Purificata and bulk Aqua ad Injectabilia, while retaining testing for Heavy Metals and Nitrates. The Ph Eur TOC test, listed as 2.2.44, is nearly identical to the USP <643> method in terms of limits and methods, though there is a subtle difference in the limit, and it is widely considered harmonized. However, while conductivity was also adopted by the Ph Eur, the calibration methods and the test methods and test limits were substantially different than the USP. The Ph Eur method called for a limit of 4.3 µS/cm at 20°C for PW and 1.1 µS/cm at 20°C for WFI. While the replacement of the Ph Eur wet chemistry tests represented an advancement for the pharmaceutical industry in terms of testing, it was not harmonized.

Continued industry requests and pharmacopoeial efforts for more uniform global testing renewed the harmonization efforts between the U.S., European and Japanese (JP) pharmacopoeias. In July 2004, the Ph Eur conductivity requirements were modified and are given by two tables, one each for PW and WFI, showing conductivity limits as a function of temperature. The Ph Eur’s Stage 1 conductivity specification for WFI is identical to the USP conductivity specification for both PW and WFI. However, the Ph Eur limit for PW is also

temperature dependent, but at a higher conductivity than of the USP. The Ph Eur has also retained testing for nitrate, heavy metals, and aluminum (when used for dialysis solutions), though there is discussion within the Ph Eur to eliminate the heavy metals testing.

In July 2004, the Ph Eur also revised the requirements for calibrating the sensors and transmitter. The requirement for the meter tolerance will be 3% + 0.1 µS/cm and the sensor tolerance will be 2%, which is the same as the current USP requirement. The differences in the details of conductivity calibration requirements between Ph Eur and USP are minor.

Until 2006, the JP relied on the same types of wet chemistry tests for control of pharmaceutical waters, but 2006 new tests were adopted. Developed in cooperation with the USP Pharmaceutical Water Expert Committee, conductivity and TOC testing has been adopted. The JP conductivity test is written identically to the USP <645>, with an uncompensated conductivity limit that is temperature dependent. The same JP conductivity limits are in place for PW and WFI like the USP, and in contradiction to the Ph Eur which has higher limits for PW.

The TOC requirement in the JP specifically references methods in USP <643> and Ph Eur 2.2.44, but the JP is also recommending lower TOC limits of 400 ppb when measured off-line and 300 ppb when measured on-line. These limits are based on a survey of the industry in Japan, and

Typical Values of Conductivity at 25°C

	µS/cm
1 mg/l NaCl	2.2
10 mg/l NaCl	22.0
100 mg/l NaCl	220.0
1 mg/l HCl	8.0
10 mg/l CO ₂	4.0



Variations of resistivity with temperature

Temperature (°C)	Resistivity of pure water (MΩ-cm)	Resistivity of 20.7 ng/g NaCl in water (MΩ-cm)
0	86.19	28.21
5	60.48	22.66
10	43.43	18.30
15	31.87	14.87
20	23.85	12.15
25	18.18	10.00
30	14.09	8.28
35	11.09	6.90
40	8.85	5.79
45	7.15	4.89
50	5.85	4.15

an acknowledgement that samples are adversely contaminated when collected and transported for off-line measurement. This is not an indictment of off-line measurement methods, but it is an affirmation that high purity water samples are easily contaminated, and they are well-suited to on-line measurements.

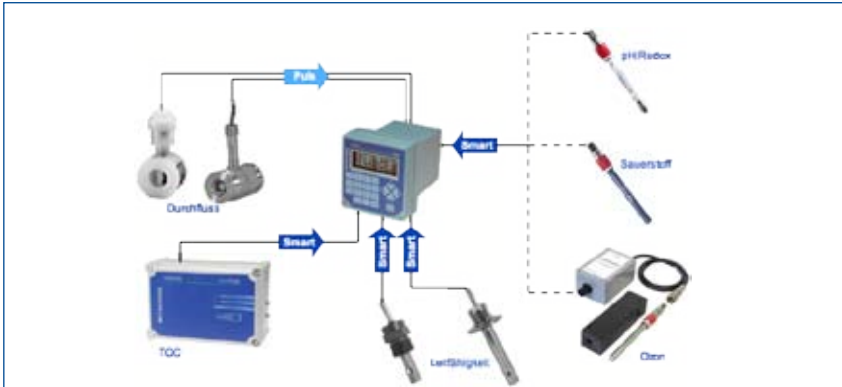
Historically, the pharmacopoeia had no monographs for steam quality requirements. A survey of the industry revealed that there are many descriptions for steam and its uses and quality attributes, but there was no single recognised authoritative body which defined steam for use in high purity applications (not “plant” steam). The industry has often turned to a British Health Technical Memorandum HTM 2010 which described the requirements for the production of steam and other agents used for sterilisation, but not the chemical attributes. Industry requested some input from the USP, and in 2006 the USP added a new monograph – Pure Steam. Pure Steam can be qualitatively described as steam that meets all the requirements of WFI, after condensation. There are no physical tests for limits on non-condensable gasses or % saturation, as there is in HTM 2010. The USP monograph specifically notes the physical requirements are not stated, but adds “The level of steam saturation or dryness, and the amount of noncondensable gases are to be determined by the Pure Steam application.” This puts the burden on the user to determine appropriate physical properties depending on the use of the steam.

Last, the most significant change in the water testing across the pharmacopoeia is the subtle endorsements of on-line, real-time testing. The JP is promoting the use of real-time measurement tools, where appropriate. This has been discussed in an FDA training session and at seminars. The science is very simple. Whether you produce water that is 0.055 µS/cm or 0.8 µS/cm (14x greater), the resulting water will be ~1 µS/cm when exposed to the atmosphere due to the immediate infusion of CO₂. Likewise, exposure of water with 5 ppb TOC or 50 ppb TOC to the environment is easily contaminated by air-borne impurities and particulates, perfumes, container residue or soaps, and other matter. For water conductivity and TOC, the original purity of the water is obscured by external contamination, thereby hiding the true quality of the water. On-line, real time testing gives a more accurate representation of the quality of the water used in Production.

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Total Organic Carbon (TOC)

Due to the potential variety and complexity of organic compounds present in purified water it is not practical to measure them all routinely. An indicator of overall organic contamination is needed. The most useful has proved to be TOC. Organic substances in a water sample are and the resultant oxidation products



detected. A wide range of TOC analyzers exist and can be broadly divided into those which oxidise all the carbon to carbon dioxide and measure the CO₂ selectively and those that either partially oxidise the organic compounds, to acids for example, or fully oxidise all species present and measure the change in conductivity due to all the oxidised species. The latter reading will include, for example, nitric and sulphuric acids from the oxidation of N and S atoms. The former are usually used off-line to show compliance with TOC specifications. The latter are used for in-line monitoring. Due to the risks of contamination, in line measurements are essential for TOC levels <25 ppb and recommended at <50 ppb.

The main role of TOC is for monitoring and trending. In most waters TOC cannot be related directly to the concentration of organic molecules in the water as the amount of carbon is different in different molecules. For example, 100 ng/g (ppb) of carbon is present in a solution of 131 ng/g (ppb) phenol or 990 ng/g (ppb) chloroform, because phenol contains 76% by weight of carbon and chloroform contains 10% by weight of carbon. The requirements for TOC monitoring are a very rapid response and continuous availability, with sufficient sensitivity and precision.

Typical Values of TOC ppb

Mains water	500 - 5000*
RO permeate	25 – 100
DI water	50 – 500
RO + CEDI	5 – 30

* (typically 1000 – 3000)

5 Water purity standards

Purified water is used in most Pharmaceutical manufacturing processes all around the world. Therefore, international and national authorities have established water quality standards for purified and other “regulated” grades of water. Key authorities include:

- The United States Pharmacopoeia (USP)
- The European Pharmacopoeia (Ph Eur)
- The Japanese Pharmacopoeia (JP)

The standards in this section are a summary and correct at the time of going to press. Standards are regularly reviewed and updated and users should refer to the latest version of the full standards.

Pharmacopoeia standards

Separate pharmacopoeia are produced by a number of authorities, notably in the USA, Europe and Japan. Each specifies materials, including water, to be used in pharmaceutical work. The standards for purified water are similar in each case. Extra criteria are set for water required for sterile applications. The standards for purified water given in the European Pharmacopoeia (Ph Eur) and in the US Pharmacopoeia (USP) are summarized below. Water for injection has stringent bacterial/pyrogen criteria and methods of preparation are specified.

Pharmacopoeia requirements for ‘purified water’		
Properties	Ph Eur	USP
Conductivity	<4.3 µS/cm at 20°C	<1.3 µS/cm at 25°C*
TOC	<500 µg/l C**	<500 ppb
Bacteria (guideline)	<100 CFU/ml	<100 CFU/ml
Nitrates	<0.2 ppm	-
Heavy metals	<0.1 ppm	-

Temperature/Conductivity Requirements (for Ph Eur) (for non-temperature compensated conductivity measurements)			
Temperature °C	Conductivity µS/cm	Temperature °C	Conductivity µS/cm
0	2.4	60	8.1
10	3.6	70	9.1
20	4.3	75	9.7
25	5.1	80	9.7
30	5.4	90	9.7
40	6.5	100	10.3
50	7.1		

Pharmacopoeia requirements for ‘water for injection’ & ‘highly purified water’		
Properties	Ph Eur	USP
Conductivity	<1.1 µS/cm at 20°C***	<1.3 µS/cm at 25°C*
TOC	<500 µg/l C**	<500 ppb
Bacteria (guideline)	<10 CFU/100ml	<10 CFU/100ml
Endotoxins	<0.25 IU/ml	<0.25 EU/ml
Nitrates	<0.2 ppm	-
Heavy metals	<0.1 ppm	-

* Offline conductivity measurements possible. If in-line conductivity exceeds values then refer to USP tables in section 645 (Table 1). If value exceeds that in table 1, refer to Three Stage Philosophy.
** Or pass oxidisable substances test
*** If in-line conductivity exceeds values then refer to the European Pharmacopoeia (Ph Eur)

Three Stage Philosophy

Stage 1

- Temperature not less than 25°C and conductivity not greater than 1.3 µS/cm
- SAMPLE PASSES TEST

If measured on-line the conductivity meter must be calibrated and non temperature compensated, the temperature must be measured independently by an adjacently installed calibrated temperature meter. If the temperature is less than 25°C or the conductivity greater than 1.3 µS/cm then the conductivity measured must be checked against the Temperature/Conductivity chart table 1.

Stage 2

- The temperature adjusted to 25°C when change in conductivity is less than a net 0.1 µS/cm per 5 minutes take a conductivity reading:
- If it is not greater than 2.1 µS/cm then it meets the requirements
- If it is greater than 2.1 µS/cm then go to stage 3

Stage 3

- Temperature @ 25°C
- Determine pH
- If conductivity reading in stage 2 is not greater than conductivity reference for given pH (table 2) it meets the requirements. If the pH is outside the range 5.0 – 7.0 the water does not meet requirements.

Table 1

Stage 1: Temperature/Conductivity Requirements (for USP)
(for non-temperature compensated conductivity measurements)

Temperature °C	Conductivity µS/cm	Temperature °C	Conductivity µS/cm
0	0.6	55	2.1
5	0.8	60	2.2
10	0.9	65	2.4
15	1.0	70	2.5
20	1.1	75	2.7
25	1.3	80	2.7
30	1.4	85	2.7
35	1.5	90	2.7
40	1.7	95	2.9
45	1.8	100	3.1
50	1.9	-	-

Table 2

Stage 3: Conductivity Requirements (for USP) as a Function of pH

pH	µS/cm	pH	µS/cm
5.0	4.7	6.1	2.4
5.1	4.1	6.2	2.5
5.2	3.6	6.3	2.4
5.3	3.3	6.4	2.3
5.4	3.0	6.5	2.2
5.5	2.8	6.6	2.1
5.6	2.6	6.7	2.6
5.7	2.5	6.8	3.1
5.8	2.4	6.9	3.8
5.9	2.4	7.0	4.6
6.0	2.4	-	-

As well as defining the absolute water quality standards, the pharmacopoeia monographs give guidance on appropriate treatment processes for producing the various types of regulated water. These are generally non-prescriptive. The exception is the Ph Eur monograph on WFI, which stipulates the use of distillation. Both the USP and JP allow the use of other technologies, such as reverse osmosis and ultrafiltration, for the production of WFI.

6 Purified water applications

Buffer and Media Preparation

The grade of pure water required for reagent make-up or dilution will depend on the sensitivity of the intended application. For many general pharmaceutical applications where sensitivity is not the primary factor, purified water is sufficiently pure. It has the added advantage of not only having high purity in ionic terms, but, by also incorporating UV and filtration, can also ensure low levels of organic contaminants and micro-organisms.

Feed to Ultra-pure Water Systems

The production of ultra-pure water (18.2 Mohm-cm resistivity, <5ppb TOC) from tap water or its equivalent is usually carried out in two stages - pretreatment and polishing. Ideally, pretreatment reduces all the major types of impurities - inorganic, organic, microbiological and particulate - by over 95%. This can be most effectively achieved using reverse osmosis or reverse osmosis combined with CEDI.

Feed to Stills

A long-established method for water purification, distillation is most effectively performed with pretreated water to minimise the build up of precipitates and the carry over of impurities. It is common practice to feed a still with purified water, particularly where multi-effect stills are used.

Pure Steam Generators (PSG)

Steam generators are used in a range of applications including clean room humidification, moisturisation, direct steam heating, injection and in autoclaves and sterilisers. Most steam generators benefit from pretreatment of the water supply to avoid build-up or precipitation of contaminants and so reduce maintenance, improve performance and enhance hygiene levels. Steam generators can use purified water with conductivity of <1 µS/cm (> 1.0 MΩ-cm resistivity). It is typically produced by reverse osmosis coupled with electrodeionisation after suitable pretreatment

Glassware Washing/Rinsing

Glassware washing is an everyday practice in most Pharmaceutical laboratories and the grade of water required for the task will depend on the nature of the intended application. To minimise costs, most general-purpose glassware can be washed with purified water.

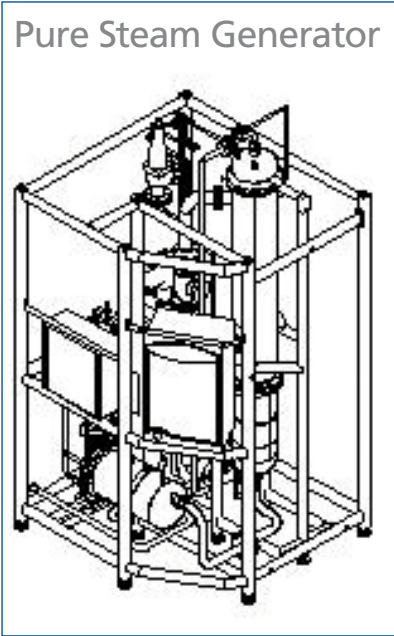
For more sensitive analytical or genetic techniques, water for injection or highly purified water grade can be used. Conductivity should be <0.05 µS/cm, TOC less than 10 ppb and bacterial counts <10 CFU/100ml.

Cleaning in Place

Cleaning in place (CIP) is an everyday practice in Pharma manufacturing. CIP involves periodically cleaning reactors, pumps, heat exchangers, distribution loops and process filling machines. Some processes are cleaned between each batch. The sporadic nature of CIP means that demand flowrate can vary widely, and this has to be factored into the design of the water generation and storage system that provides the CIP make up and rinse water. Different water types are used to suit different manufacturing processes. Purified water is most commonly used.

Microbiological Analysis

Routine microbiological analysis requires purified water. This will be largely free of bacterial contamination and have low levels of ionic, organic and particulate impurities. Typical values are a resistivity of <1 µS/cm, TOC <50 ppb and <100 CFU/ml bacteria count.



Qualitative Analyses

The water required for most qualitative analysis methods for major or minor constituents is general grade purified water with resistivity <1 µS/cm, TOC less than 50 ppb and low particulates and bacterial counts.

Water Analysis

Water analyses are carried out for many different reasons. Requirements include ensuring that potable water meets current standards, checking that purification processes have been successfully carried out and environmental testing of feed sources such as lakes and rivers.

Water analysis requires purified water for the preparation of samples, standards and blanks. This water must be of a known purity that is sufficiently high so as not to interfere with the analytical techniques. Water analysis applications are usually performed with water with resistivity of <0.2 µS/cm, TOC <50 ppb and a bacterial count below 1 CFU/ml.

Applications at a glance

Analytical and General Applications

Technique	Sensitivity	Conductivity µS/cm	TOC ppb	Filter µm	Bacteria CFU/ml	Endotoxin IU/ml	Grade of Pure Water
Buffer & media preparation	General	<1	<500	NA	<100	NA	Purified Water
Feed to stills	Low	<1	<500	NA	<100	NA	Purified Water
Feed to Ultra-pure water systems	General	<1	<50	NA	<1	NA	WFI HPW
Glassware washing	General	<1	<50	<0.2	<10	NA	Purified Water
	High	<0.05	<10	<0.2	<1	NA	WFI HPW
Cleaning In Place	General	<1	<50	NA	<100	NA	Purified Water
	High	<0.05	<10	NA	<0.1	<0.25	WFI HPW
Microbiological Analysis	General	<1	<50	<0.2	<100	NA	Purified Water
Qualitative Analyses	General	<1	<50	<0.2	<1	NA	WFI HPW
Steam generation	General	<1	<500	NA	<100	NA	Purified Water
Water analysis	General	<0.2	<50	<0.2	<1	NA	Purified Water
	High	<0.05	<10	<0.2	<0.1	<0.25	WFI HPW

Critical impurities - NA Not applicable

7 Pure water - hints & tips

1. Stored purified water, must be continuously recirculated and the equipment periodically sanitised.
2. Temperature should be actively controlled in the system by means of either heating or cooling heat exchangers, or by periodic "purging" to avoid overheating.
3. The microbiological purity of the water in a water treatment system can only be maintained by recirculating the water through the various purification processes via the break tank. The break tank should be of sanitary design and construction.
4. Regular sanitisation is essential to prevent build-up of biofilm. Heat is the preferred sanitisation method although hydrogen peroxide and ozone can also be effective. Ozone and hot water sanitisation are suitable for the storage and distribution loop.
5. To prevent algal growth, use of translucent tanks and pipework should be avoided and storage vessels should not be installed close to direct sunlight or sources of heat.
6. Appropriate pipework, fittings quality and finishing must be used in order to avoid dead-legs, crevices, etc...
7. The 0.22µm cartridge filter and vent filter should be changed regularly; typically at least every six months, to minimize the build-up of bacterial contamination.



8. At least 5–10 minutes of purified water should be run to drain after a period of inactivity, e.g. before feeding purified water tank or during the week-end.
9. To ensure efficient operation of the resistivity meter, a qualified individual should clean the electrodes of the line cell and calibrate the resistivity meter every 12 months.
10. To prolong the life of a reverse osmosis membrane, it should be regularly flushed and cleaned. Flushing removes particulate matter or precipitated solids from the membrane surface.
11. CEDI technology module must be fed with reverse osmosis quality water. Hardness, particules, organics, oxidizing agents, iron and manganese must be removed before the module.
12. For chemical or hot water sanitization of the CEDI module, the module must be able to bear chemical agent, such as peracetic acid and hydrogen peroxide or hot water at >85°C for minimum 1 hour. This should be checked before initial sanitisation.
13. For pretreatment UV, proper pre filtration should be implemented to keep particulate from shielding organisms from UV light.
14. UV lamps should be replaced at appropriate intervals (4,000–10,000 hours depending on type) and the quartz thimble/sleeve should be cleaned at the same time.

8 Glossary of terms

Absorption – A process by which a substance is taken up chemically or physically in bulk by a material (absorbent) and held in pores or interstices in the interior.

Activated Carbon – A highly porous form of carbon used for sorption of organics and removal of free chlorine and chloramine.

Adsorption – Adherence of molecules, atoms and ionised species of gas or liquid to the surface of another substance (solid or liquid) as the result of a variety of weak attractions.

Anion Exchange Resin – An ion exchange resin with immobilised positively charged exchange sites, which can bind negatively charged ionised species, anions.

Azeotrope – A blend of two or more components with equilibrium vapour phase and liquid phase compositions that are the same at a given temperature and pressure.

Backwash – The upward flow of water through a resin or carbon bed to clean it, and in the case of a mixed bed, to separate anion and cation resins.

Bactericide – A chemical or physical agent that kills bacteria.

Biocide – A chemical or physical agent that kills micro-organisms.

Biofilm – A layer of micro-organisms enclosed in a glycoprotein polysaccharide matrix which are adherent to each other and/or to surfaces.

Calibration – A comparison of a measurement instrument to detect, correlate or eliminate by adjustment of any variation.

Carbon Fines – Very small particles of carbon that may wash out of an activated carbon bed.

Cartridge – A pre-packed disposable container for housing a water purification media or membrane.

Cation Exchange Resin – An ion exchange resin with immobilised negatively charged exchange sites, which can bind positively charged ionised species, cations.

CFU/ml – Colony Forming Units per milliliter. A measure of viable microbial populations.

Channeling – Preferential flow of water through a resin/granular activated carbon bed effectively causing by-pass of ion exchange/activated carbon sites. Poor quality and capacity will result.

cGMP – Current Good Manufacturing Practice.

Colloid – A stable dispersion of fine particles in water that have a typical size less than 0.1 µm. Colloids containing iron, aluminum, silica and organics are commonly found in natural and potable waters.

Color Change Resin – A resin that is dyed with a pH indicator so that it changes color upon exhaustion to indicate when the cartridge needs replacing.

Concentrate – The liquid containing dissolved and suspended matter that concentrates on the inlet side of a membrane and flows to drain.

Condenser – The stage of a distillation system that removes sufficient heat from a vapourised liquid to cause the vapour to change to a liquid phase.

Conductivity – Conductivity is the reciprocal of resistivity. For water purification systems, conductivity is usually reported as microsiemens per centimeter (µS/cm).

Contact Membrane (DG) – A hydrophobic membrane used in removing dissolved gases (CO₂ or O₂) from water.

Continuous Electrodeionization (CEDI) – Technology combining ion exchange resins and ion selective membranes with direct current to remove impurity ionised species from water without regeneration phase.

Deadleg/Dead Volume – A region or volume of stagnation in an apparatus or distribution system.

De-gassing – The removal of O₂ and CO₂ from water, usually by transfer across a hydrophobic membrane. CO₂ is removed to increase ion exchange capacity and improve electrodeionisation efficiency.

Deionisation (DI) – Removal of impurity ions from water. Usually used to refer to ion exchange – see Ion Exchange.

Deionisation Service – see Service Deionisation.

Distillation – A purification process that takes advantage of changing the phase of a substance from liquid to vapour and back to liquid usually at the boiling temperature of the substance, in order to separate it from other substances with higher or lower boiling points.

Endotoxin – A thermally stable lipopolysaccharide component from the cell wall of viable or nonviable Gram-negative micro-organisms. Can act as a pyrogen.

Endotoxin Units (IU/ml or EU/ml) – A quantification of endotoxin levels relative to a specific quantity of reference endotoxin. 1 IU/ml is approximately equal to 0.1 ng/ml.

Exotoxin – A toxic substance secreted by a bacterium, often causing disease, which can also act as a pyrogen.

FDA – United States Food and Drug Administration.

Feedwater – The water that is introduced into a purification process.

Filtration – A purification process in which the passage of fluid through a porous material results in the removal of impurities.

Fines – Particulates released from a bed of material such as ion exchange resins.

Fouling Index – see Silt Density Index.

GAMP – Good Automated Manufacturing Practice.

Gram-negative – refers to bacteria that do not absorb a violet stain originally described by Gram.

Gram-positive – Refers to bacteria that absorb a violet stain originally described by Gram.

Hardness – The scale-forming and lather-inhibiting qualities of some water supplies, caused by high concentrations of calcium and magnesium. Temporary hardness, caused by the presence of magnesium or calcium bicarbonate, is so called because it may be removed by boiling the water to convert the bicarbonates to the insoluble carbonates. Calcium and magnesium sulfates and chlorides cause permanent hardness.

HPW – Highly Purified Water.

Ion – Any non-aggregated particle of less than colloidal size possessing either a positive or a negative electric charge.

Ion Exchange (IX) – The process of purifying water by removing ionized salts from solution, by replacing hydrogen ions for cation impurities and hydroxyl ions for anion impurities.

LAL – Limulus Amoebocyte Lysate, an extract from the horseshoe crab which forms a gel in the presence of sufficient endotoxin. Used as the basis for the LAL test for endotoxins.

Line Cell – An electrode assembly inserted into a water stream by which the conductivity or resistivity is measured.

Micro-organism – Any organism that is too small to be viewed by the unaided eye, such as bacteria, viruses, molds, yeast, protozoa, and some fungi and algae.

Nuclear Grade Resin – A high purity (analytical) grade of ion exchange resin originally developed for the nuclear energy industry.

Off-line – In water monitoring systems, referring to measurement devices that are not directly coupled to the water stream.

On-line – In water monitoring systems, referring to measurement devices directly coupled to the water stream.

Ozone – Ozone is used in the pharmaceutical industry as a sanitizing agent. O₃ is a very strong oxidising agent, kill bacteria and reduce TOC in water.

Particulates – Discrete quantities of solid matter dispersed in water.

Permeate – The purified solution which has been produced by passage through a semi-permeable reverse osmosis membrane.

pH – A measure of the acidity or alkalinity of a solution equal to -log (H+).

PhEur – European Pharmacopoeia.

Photo-oxidation – see Ultra Violet (Photochemical) Oxidation.

Planktonic – Used to describe aquatic micro-organisms that float.

Point of Use – A dispense point from a purified water system from which water can be taken.

Polishing – The final treatment stage(s) of a water purification system.

Potable Water – Water which meets regulations as suitable for ingestion by humans.

PPB – Parts per billion is a unit equal to microgramme per kilogram of water. Numerically ppb are equivalent to microgramme per litre in dilute aqueous solutions.

PPM – Parts per million is a unit equal to milligramme per kilogram of water. Numerically ppm are equivalent to milligrammes per litre in dilute aqueous solutions.

PPT – Parts per trillion is a unit equal to nanogramme per kilogram of water.

PSG – Pure Steam Generator.

Pyrogen – A category of substances, including bacterial endotoxins, which may cause a fever when injected or infused.

Qualification – The act of establishing with documented evidence that the process, equipment, and/or materials are designed, installed, operated and perform according to the pre-determined specifications.

Regeneration – The method by which exhausted ion exchange resins are reactivated by treatment with strong acid or alkali.

Resistivity – The electrical resistance between opposite faces of a one-centimetre cube of a given material at a specified temperature. Resistivity is the reciprocal of conductivity. For water analysis, resistivity is usually reported in megohm-centimetres (MΩ-cm).

Storage Tank – In water purification systems, a container holding quantities of purified water.

Reverse Osmosis (RO) – A process in which water is forced under pressure through a semi-permeable membrane leaving behind dissolved organic, dissolved ionic, and suspended impurities.

Sanitisation – Chemical and/or physical processes used to kill micro-organisms and reduce contamination from micro-organisms.

Service Deionisation (SDI) – Deionisation service provided by exchanging cylinders containing ion exchange resins, which have been regenerated or replaced at a regeneration station.

Silt Density Index – Also called the Fouling Index (FI) is a test used to estimate the potential of the water to block filters, derived from the rate of blockage of a 0.45 micron-filter under standard conditions.

SJP (JP) – The Society of Japanese Pharmacopoeia (SJP) is a non-profit foundation authorised by the Ministry of Health, Labour and Welfare (MHLW).

It was established mainly to promote dissemination of the Japanese Pharmacopoeia (JP) for the purpose of maintenance and improvement in the efficacy, safety and quality of pharmaceutical drugs.

Softening – A water treatment process whereby cations, notably hardness-forming calcium and magnesium ions, are exchanged for sodium using cation exchange resins in the sodium form.

Stagnation – State of a liquid without current or circulation.

Sterilisation – Destruction or removal of all living micro-organisms.

Total Dissolved Solids (TDS) – A measure of the total of organic and inorganic salts dissolved in water, obtained by drying residue at 180°C.

Total organic carbon (TOC) – Total concentration of carbon present in organic compounds.

Turbidity – The degree of cloudiness of water caused by the presence of suspended particles or colloidal material. Turbidity reduces the transmission of light and is measured in Nephelometric Turbidity Units (NTU).

Ultrafiltration – A process in which water is filtered through a polymeric membrane having a very fine pore structure.

Ultra-violet (Photochemical) Oxidation – A process using short wavelength light to kill micro-organisms and cleave or oxidise organic molecules.

USP – United States Pharmacopoeia The United States Pharmacopoeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. USP sets standards for the quality of these products and works with healthcare providers to help them reach the standards. USP's standards are also recognised and used in more than 130 countries.

Validation – Confirmation, through the provision of objective evidence, that requirements for a specific intended use or application have been fulfilled.

Verification – Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

WFI – Water For Injection.

Further reading

There are several books in English focusing specifically on purified water for pharmaceutical industry.

The ISPE not-for-profit professional society has issued several Baseline® guides, Volume 4 Water and steam systems (2001), Volume 5 Commissioning and Qualification (2001).

The Ultra-pure Water journal (Tall Oaks Publishing) contains articles of interest as do two books by T.H. Melitzer from the same publisher: High Purity Water Preparation for the semiconductor, pharmaceutical and power industries (1993) and Pharmaceutical water systems (1996).

Handbook of Water Purification, edited by Walter Lorch, published by McGraw Hill.

Water Treatment Handbook – Degremont, published by Lavoisier.

Many of the ASTM standards in volumes 11.01 and 11.02 are relevant to purified water. (www.astm.org).

Information on water treatment can be found at www.veoliawater.com and www.veoliawaterst.com

Every effort has been made to ensure that the information in this publication is correct. Veolia Water Solutions & Technologies cannot be held responsible for any errors or omissions due to changes in technology or standards that have occurred since publication date.

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VWS Pharmaceutical Group specialises in providing pharmaceutical water treatment technology solutions and services.

Within the pharmaceutical industry, water is most commonly used in liquid form, not only as an ingredient in many formulations but also as a cleaning agent. Production of Purified Water, Highly Purified Water, Pyrogen Free Water and WFI to international pharmaceutical standards is widely recognised as a critical process.

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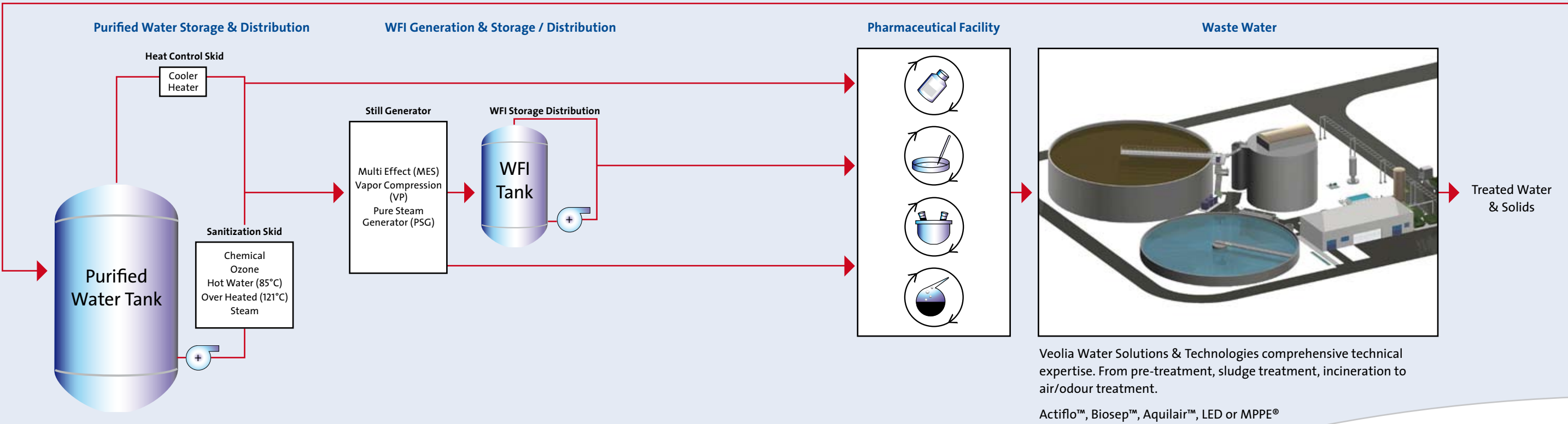
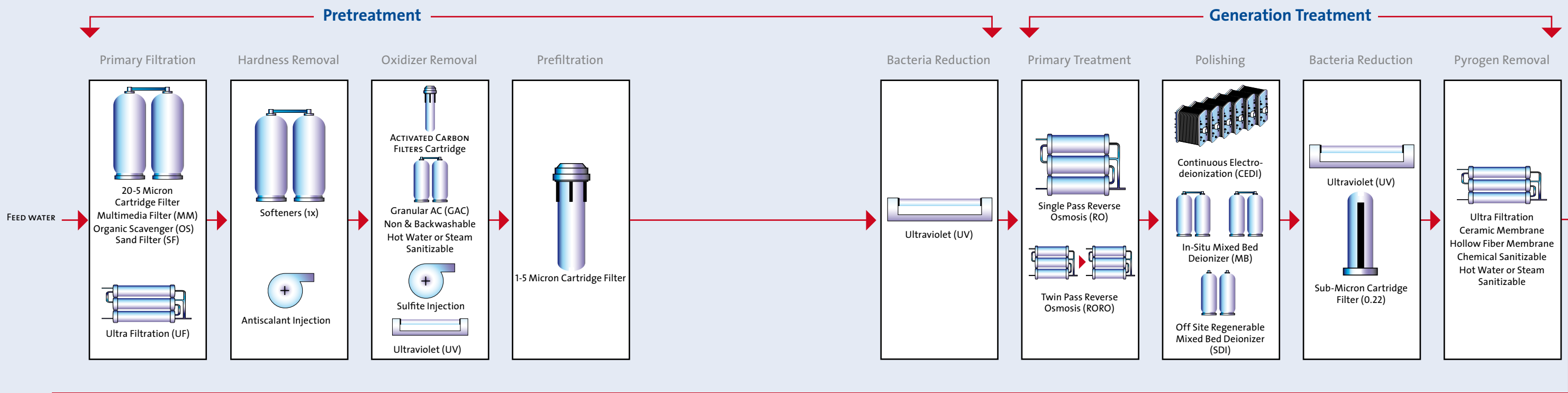
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