Water for Pharmaceutical uses

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Must to Know

- **Water Grades.**
- **Water Purification Processes.**
- **Importance Of Each Stage.**
- **WFI Production.**
- **Standards For PW - WFI.**
- **QC / QA for Water Systems.**
- **URS For Water Systems.**
- **Validation For Water Systems.**
- **Water System – Required Documents.**

Terminology

- ***Total dissolved solids:*** *The concentration of which is expressed in milligrams per liter (mg/L)/ parts per million (ppm) or parts per thousand (ppt).*
- ***Thermal distillation****: Freshwater is separated from the saline source by evaporation.*
- ***Reverse osmosis desalination****: Freshwater is produced from saline source water by pressure-driven* transport through semipermeable membranes.

- ***Electrodialysis (ED) :*** *Is electrically driven desalination in which salt ions are* removed out of the source water through exposure to direct electric current.
- ***Ion Exchange (IX) :*** Is the selective removal of salt ions from water by adsorption onto ion-selective resin media.

- ***Potable water standard:***

(US EPA) *Have established a maximum TDS concentration of 500 mg/L as a potable water standard.*

- ***Water classification according TDS :***

Type	TDS in mg/l	Example
Fresh	less than **500** mg/l	Rivers
brackish	500-15000 mg/l	Ground water wells
Sea water	Higher than 1**5000** mg/l	sea, bay, and ocean waters

Desalination Process Applicability

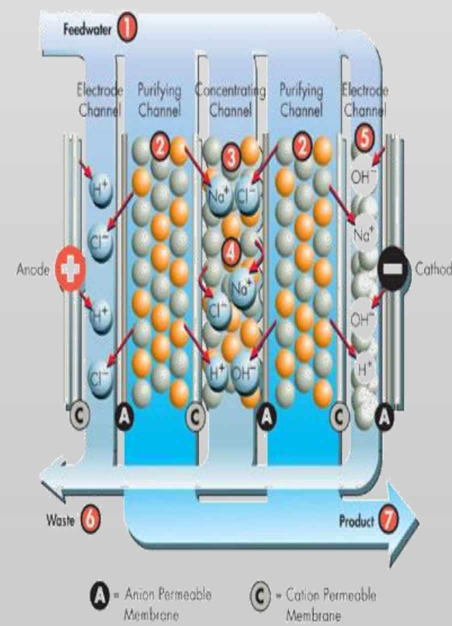
Separation Process	Range of Source Water TDS Conc. for Cost-Effective Application, mg/L
Distillation	20,000–100,000
Reverse osmosis	50–46,000
Electrodialysis	200–3000
Ion exchange	1–800

Thermal desalination technologies

- Thermal desalination technologies
  - Vapor compression (VC)
  - Multieffect distillation (MED)
  - Multistage flash distillation (MSF)

Electrodialysis

- In electrodialysis (ED)–based desalination systems, the separation of minerals and product water is achieved through the application of direct electric current to the source water.



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Contaminant removal efficiency

Contaminant	Distillation (%)	ED/EDR (%)	RO (%)
TDS	>99.9	50–90	90–99.5
Pesticides, Organics/VOCs	50–90	<5	5–50
Pathogens	>99	<5	>99.99
TOC	>95	<20	95–98
Radiological	>99	50–90	90–99
Nitrate	>99	60–69	90–94
Calcium	>99	45–50	95–97
Magnesium	>99	55–62	95–97
Bicarbonate	>99	45–47	95–97
Potassium	>99	55–58	90–92

Table 1.2 Contaminant Removal by Alternative Desalination Technologies

Source Water Temperature

Minimum Monthly Average Temperature, °C	Flux Correction, %
5	55
10	30
15	15
20	0
25	−10

Table 12.3 Temperature Correction Factor

- Saline water viscosity increases with a decrease in temperature. Viscosity affects a membrane's ability to produce filtered water, as more pressure is required to overcome the resistance associated with flow across the membrane surface area when operating at a constant flux .
- Typically, average design membrane flux is established for the average annual temperature, flow, and turbidity and adjusted down for the minimum monthly average temperature using the correction factor.

Chemist/Ahmed Hasham

WHO water treatment guidance

The following should be monitored

- Sources of water
- Treatment procedures
- Water treatment equipment
- Treated water tests
- Monitoring records required

Pretreatment

The purpose of the first step **source water pretreatment** is to remove the suspended solids and prevent some of the naturally occurring soluble solids from turning into solid form and precipitating on the RO membranes during the salt separation process.

RO system

- The second step the RO system **separates the dissolved solids from the pretreated source water**, thereby producing fresh low-salinity water suitable for human consumption, agricultural uses, and for industrial and other applications.
- The key components of the RO separation system include filter effluent transfer pumps , high-pressure pumps, reverse osmosis trains, energy recovery equipment, and the membrane cleaning system.

post-treatment

The third step of the desalination plant treatment process is referred to as post-treatment once the desalination process is complete, the freshwater produced by the RO system is further **treated for corrosion and health protection and disinfected prior to distribution for final use.**

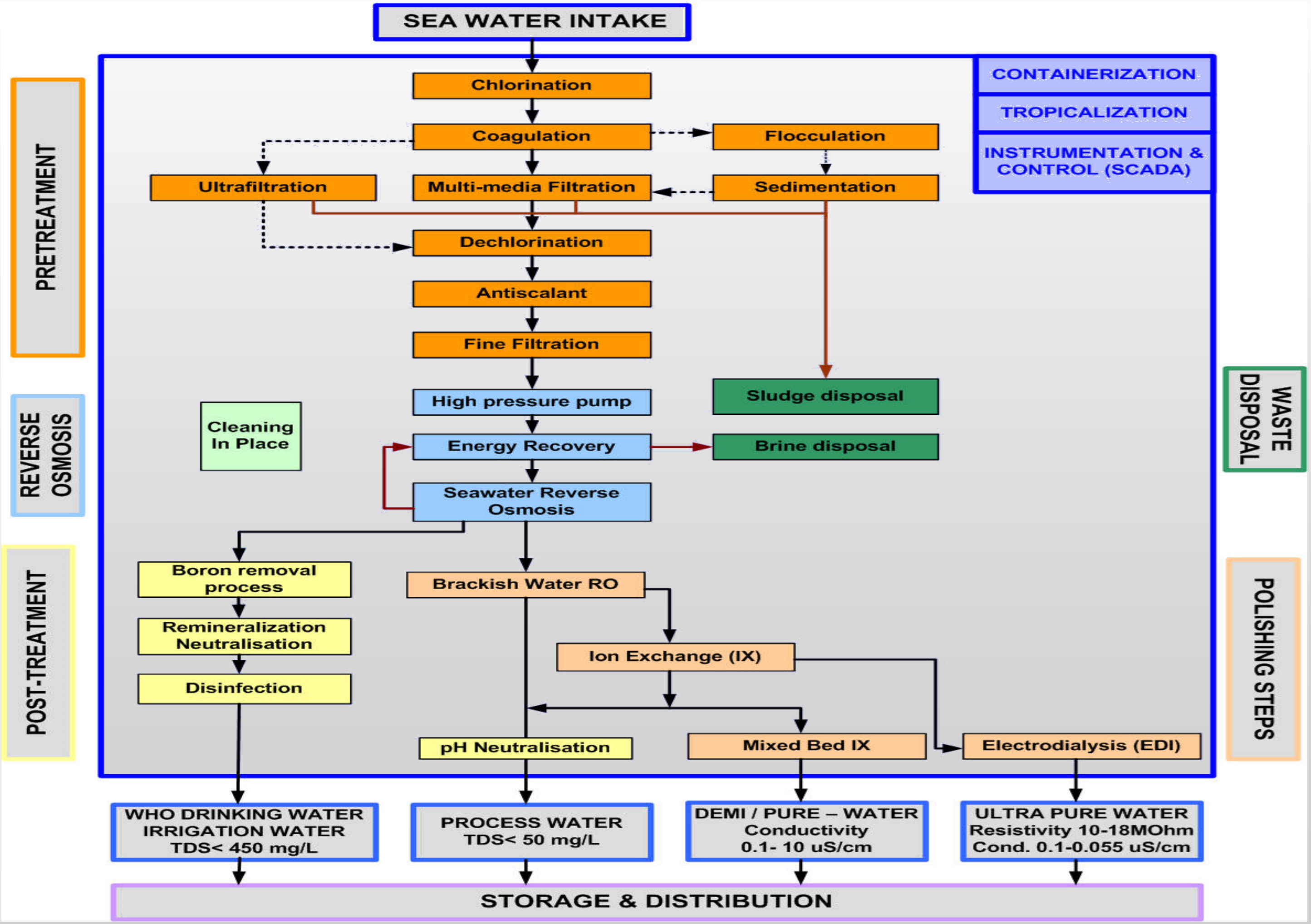
SEA WATER INTAKE
PRETREATMENT
Chlorination
Coagulation
Flocculation
Ultrafiltration
Multi-media Filtration
Sedimentation
Dechlorination
Antiscalant
Fine Filtration
CONTAINERIZATION
TROPICALIZATION
INSTRUMENTATION & CONTROL (SCADA)
REVERSE OSMOSIS
High pressure pump
Energy Recovery
Seawater Reverse Osmosis
Cleaning In Place
Sludge disposal
Brine disposal
WASTE DISPOSAL
POST-TREATMENT
Boron removal process
Remineralization Neutralisation
Disinfection
Brackish Water RO
Ion Exchange (IX)
pH Neutralisation
Mixed Bed IX
Electrodialysis (EDI)
POLISHING STEPS
WHO DRINKING WATER IRRIGATION WATER TDS< 450 mg/L
PROCESS WATER TDS< 50 mg/L
DEMI / PURE – WATER Conductivity 0.1- 10 uS/cm
ULTRA PURE WATER Resistivity 10-18MOhm Cond. 0.1-0.055 uS/cm
STORAGE & DISTRIBUTION

Diagram of a conventional pretreatment process

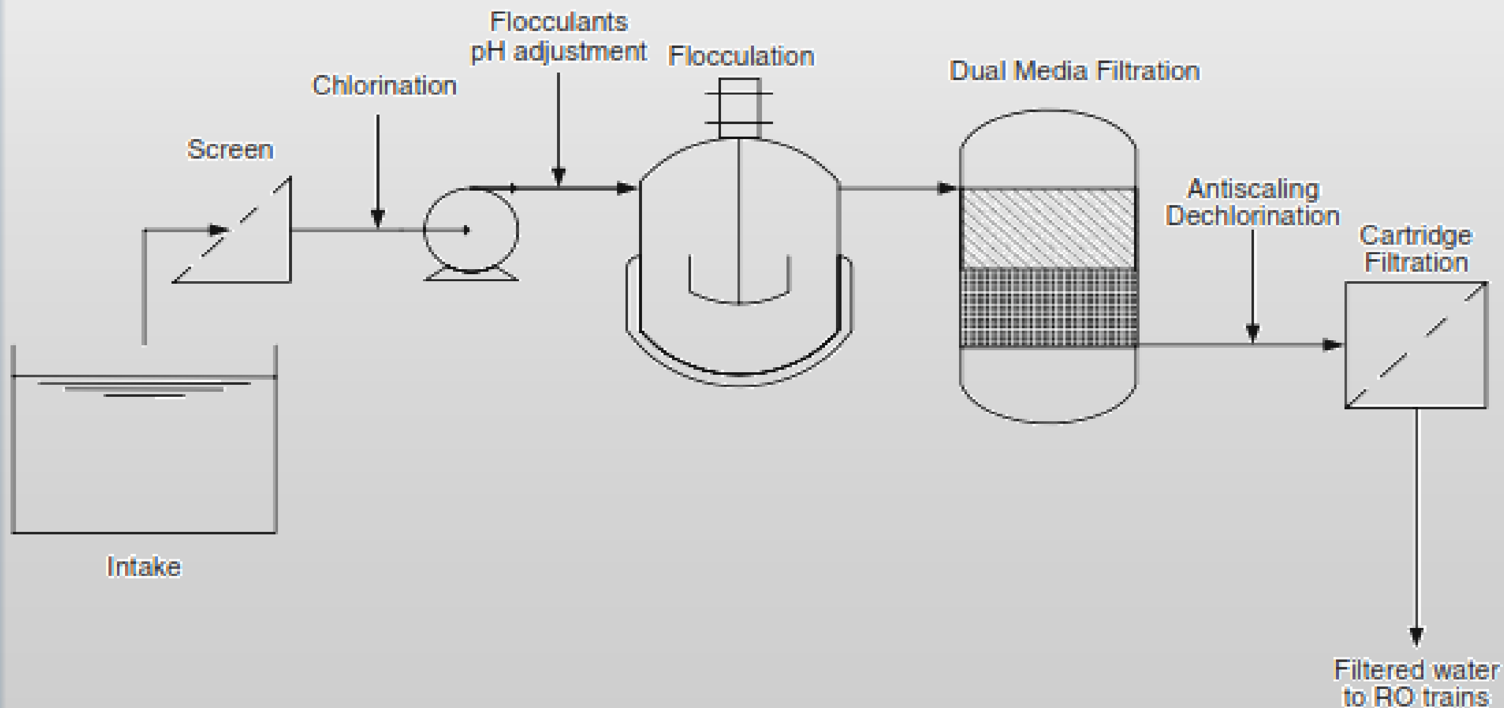

Fig. 3.13 Typical process diagram of a conventional pretreatment process

Dual Media Filtration

- Dual media filters (DMFs) remove remaining suspended solids and lower the turbidity of the RO feed water to about 0.4 NTU with an SDI of 2.5 or less.

- The DMF consists of coarse anthracite coal over a bed of fine sand .

- A process called backwashing is used to break up surface scum and dirt in the filter medium. Gravity flow is more economical than pressure flow as a means of cleaning filters for large storage tanks.

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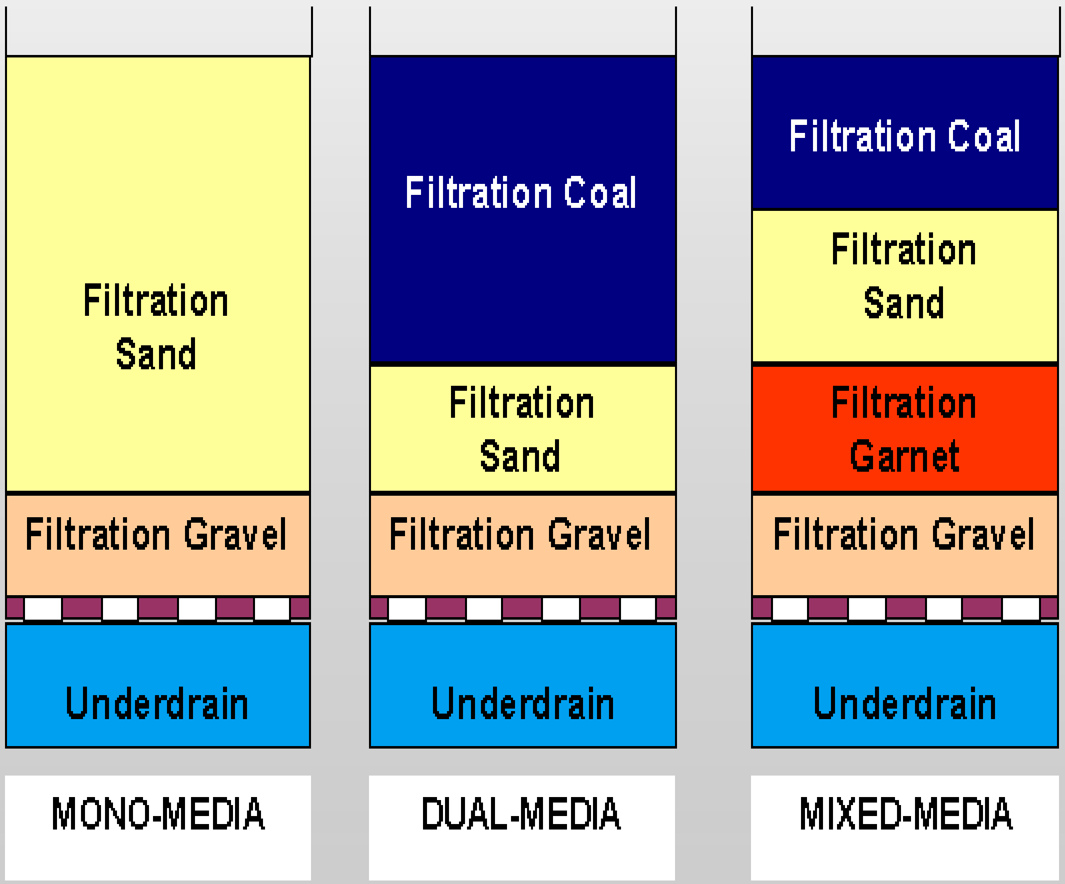

Filtration Sand
Filtration Gravel
Underdrain
MONO-MEDIA
Filtration Coal
Filtration Sand
Filtration Gravel
Underdrain
DUAL-MEDIA
Filtration Coal
Filtration Sand
Filtration Garnet
Filtration Gravel
Underdrain
MIXED-MEDIA

Reverse Osmosis

- **Reverse osmosis (RO)** Is a process where *source water contaminants* is forced under pressure through a semipermeable membrane.

- **semipermeable membrane** : Selectively allows water to pass through it at much higher rate than the transfer rate of any *contaminants* in the water.

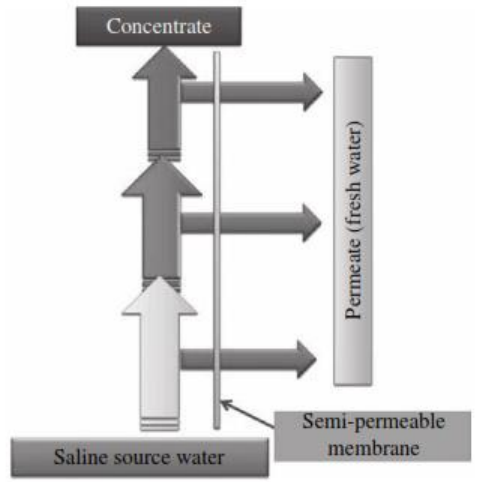


Figure 3.2 Reverse osmosis process.

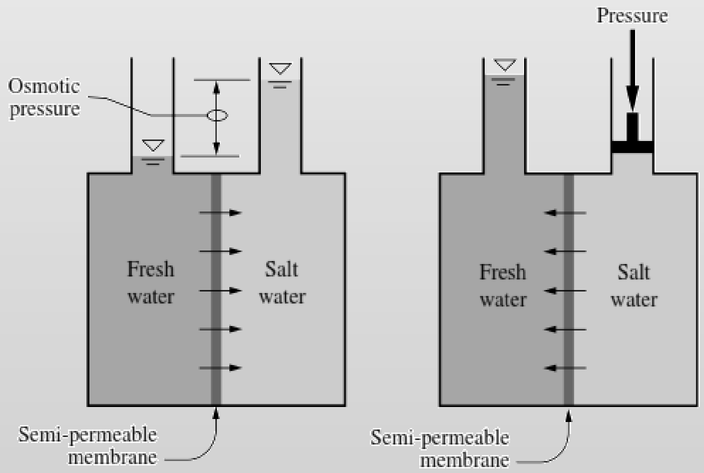
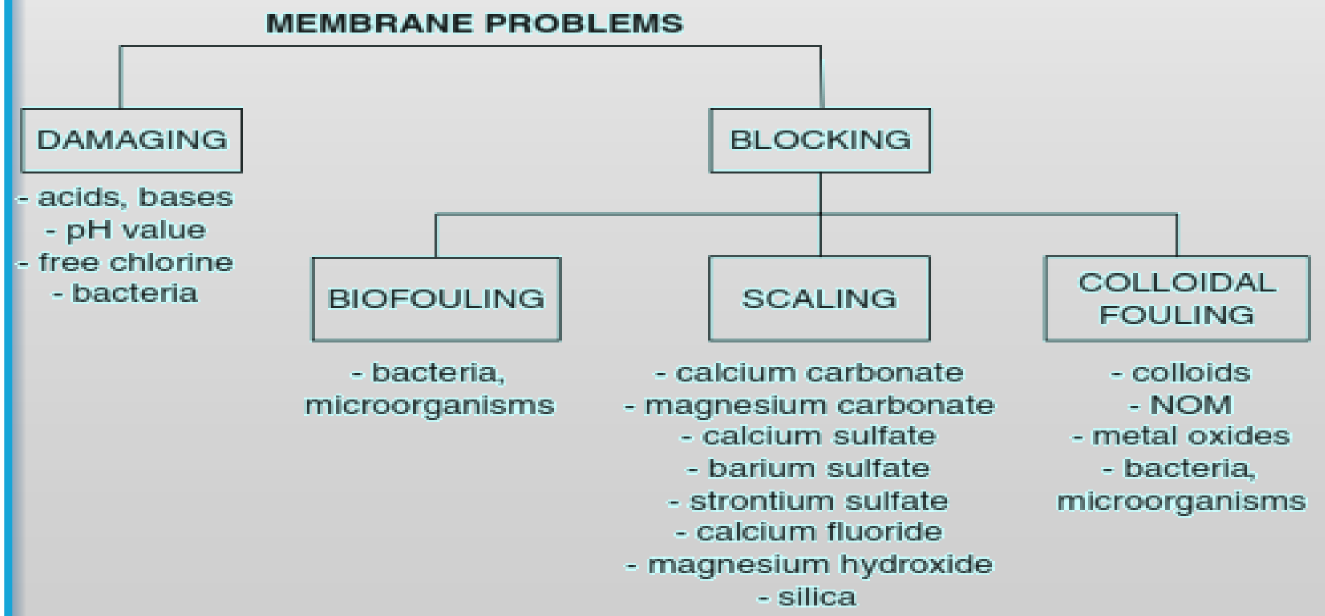


Figure 3.1 Osmosis and reverse osmosis.

Membrane problems



Source Water Quality Characterization

Source water quality has an impact on the treatment needed and ultimately on the quality of the produced water.

Cations	Anions
Sodium	Chloride
Magnesium	Carbonate
Calcium	Bicarbonate
Potassium	Sulfate
Barium	Nitrate
Strontium	Fluoride
Boron	Phosphate
Bromide	Sulfur

Parameter	Orange County, California	Rio Grande, Texas	Tularosa, New Mexico	Cape Hatteras, North Carolina
Cations, mg/L				
Calcium	140.0	163.0	420.0	545.0
Magnesium	10.0	51.0	163.0	1398.0
Sodium	300.0	292.0	114.0	4961.0
Potassium	35.0	0.0	2.30	99.0
Boron	0.8	0.0	0.14	1.2
Bromide	7.4	4.5	0.70	12.5
Total Cations	**493.2**	**510.5**	**700.14**	**7016.7**
Anions, mg/L				
Bicarbonate	275.0	275.0	270.0	223.0
Sulfate	350.0	336.0	1370.0	173.0
Chloride	350.0	492.0	170.0	6523.0
Fluoride	0.8	0.08	0.0	1.3
Silica	10.0	35.0	22.0	22.0
Nitrate	1.0	1.5	10.0	1.0
Total Anions	**986.8**	**1139.58**	**1842.0**	**6943.3**
TDS mg/L	**1480.0**	**1650.0**	**2542**	**13,960.0**

Table 2.3 Brackish Water Quality of Several Sources

Iron in reduced form (Fe^{2+}), mg/L	Foulant if > 0.05 mg/L
Iron in oxidized form, mg/L	Foulant if > 2.0 mg/L Membrane damage by chlorine if > 0.5 mg/L
Manganese, mg/L	Foulant if > 0.02 mg/L
Aluminum, mg/L	Foulant if > 0.1 mg/L
Copper, μg/L	Potential membrane damage if > 50 μg/L
Arsenic	Potential toxicant if > 10 μm/L in permeate
Turbidity	Accelerated fouling if > 0.1 NTU
Total suspended solids (TSS), mg/L	Accelerated fouling if > 1 mg/L
Silt density index (SDI)	Accelerated fouling if > 5
Total hydrocarbons, mg/L	Foulant if > 0.02 mg/L
Silica (colloidal), mg/L	Foulant if > 100 mg/L in concentrate
Total organic carbon (TOC), mg/L	Potential for accelerated fouling if > 2 mg/L
UV_{254}, cm^{-1}	Potential for accelerated fouling if > 0.5 cm^{-1}
Total algal count, algal cells per milliliter	Algal bloom if > 2000 algal cells per milliliter
Hydrogen sulfide	Odor and membrane fouling if > 0.1 mg/L.
Ammonia, mg/L	Membrane damage if bromide > 0.4 mg/L
Free chlorine, mg/L	Membrane damage if > 0.01 mg/L
Oxidation reduction potential, mV	Membrane damage if > 250 mV
Total coliform count, Most Probable Number (MPN) per 100 mL	Potential pathogen contamination if > 10^4

Table 2.9 Source Water Quality Analysis for Reverse Osmosis Desalination

Total Dissolved Solids TDS

- The TDS of the source water is the most important water quality parameter in RO desalination for two main reasons:
  1. **TDS is a main factor in determining the feed pressure.**
  2. **And therefore, the energy needed to produce freshwater from a given saline water source.**
- The ratio between TDS and EC in source water is site specific and usually varies in a range between 0.67 and 0.70.
- Every 100 mg/l of TDS in the source water creates approximately 0.07 bar of osmotic pressure

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RO membrane element

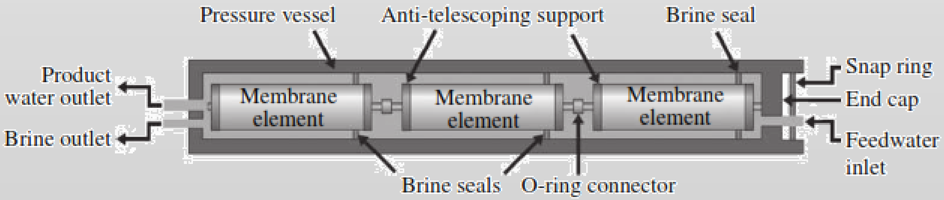
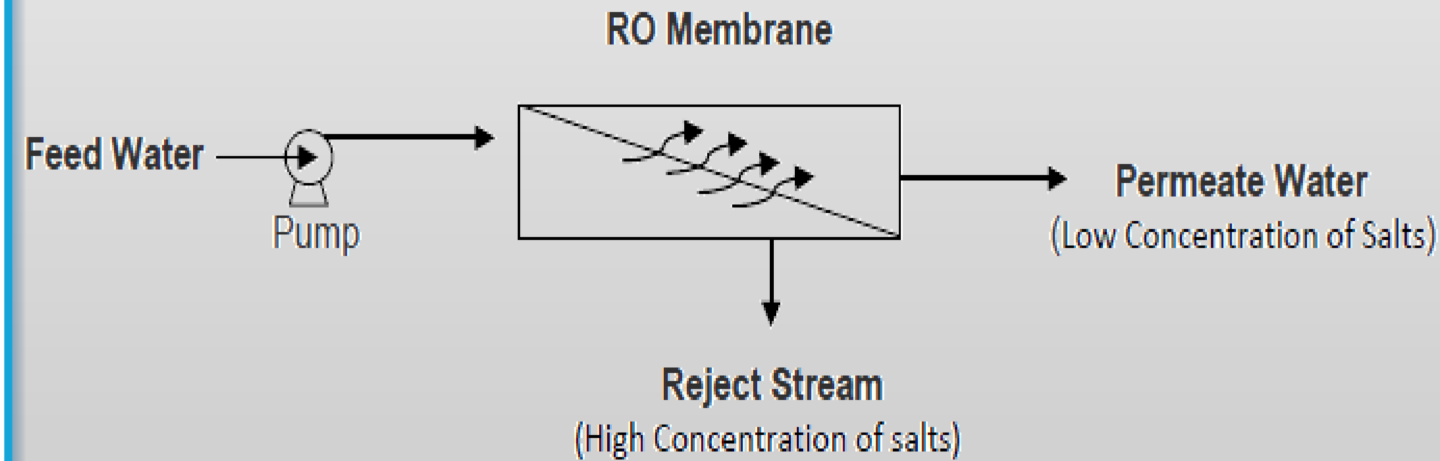


FIGURE 3.9 Membrane elements installed in a pressure vessel.

How does Reverse Osmosis work?



Permeate water :

The good produced water that comes out of an RO system has the majority of contaminants removed

Concentrate , Reject , Brine :

Is the water that contains all of the contaminants that were unable to pass through the RO membrane.

Recovery % :

Percent Recovery is the amount of water that is being 'recovered' as good permeate water.

$$\% \text{ Recovery} = \frac{\text{Permeate Flow Rate (gpm)} \times 100}{\text{Feed Flow Rate (gpm)}}$$

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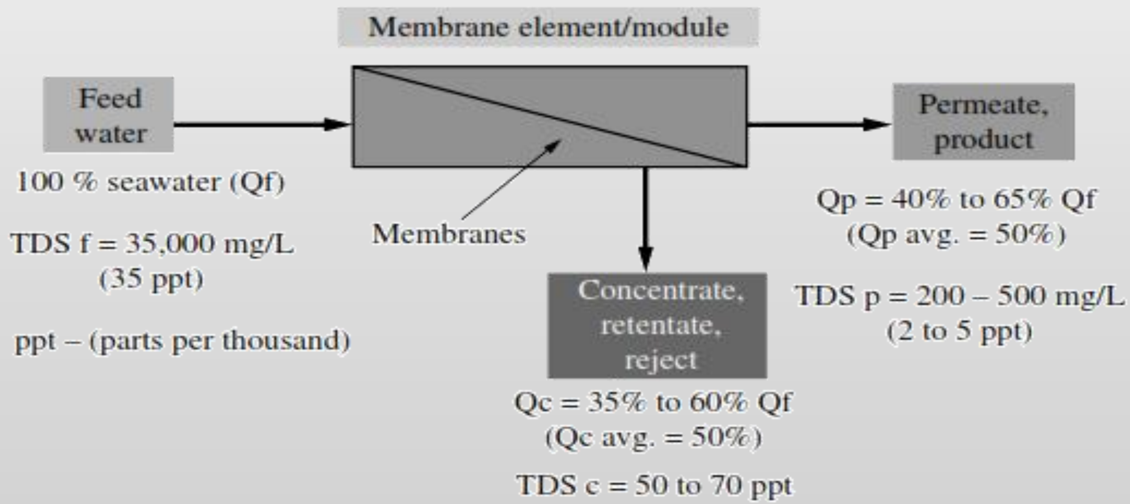
Recovery



$$\% \text{ Recovery} = \frac{\text{Permeate Flow (Qp)}}{\text{Feed Flow (Qf)}} \times 100 = \frac{50\% \text{ Qf}}{\text{Qf}} = 50\%$$

Salt Rejection % :

This equation tells you how effective the RO membranes are removing contaminants.
A well designed RO system with properly functioning RO membranes will reject
95% to 99% of most feed water contaminants.

$$\text{Salt Rejection \%} = \frac{\text{Conductivity of Feed Water} - \text{Conductivity of Permeate Water} \times 100}{\text{Conductivity of Feed}}$$

Salt Passage % :

This is the amount of salts expressed as a percentage that are passing through the RO system. The lower the salt passage, the better the system is performing

$$\text{Salt Passage \%} = (1 - \text{Salt Rejection\%})$$

Concentration Factor :

- The concentration factor is related to the RO system recovery and is an important equation for RO system design.

- The more water you recover as permeate (the higher the % recovery), the more concentrated salts and contaminants you collect in the concentrate stream.

- This can lead to higher potential for scaling on the surface of the RO membrane when the concentration factor is too high for the system design and feed water composition.

Concentration Factor = (1 / (1-Recovery %)

Flux :

It's the rate of permeate transferred per unit membranes area (gfd) or (L/m2.h)

$$\text{Flux (Gfd)} = \frac{\text{permeate flow (gpd)}}{\text{total no of membranes} \times \text{membrane surface area}}$$

Flux value is Known depending on the source of feed water and type of used membranes for example for DOW filmtec mem. LE---440i

Feed Water Source	**Gfd**
Sewage Effluent	5---10
Sea Water	8---12
Brackish Surface Water	10---14
Brackish Well Water	14---18
RO Permeate Water	20---30

Fouling

Membrane biofouling.

Membrane biofouling is defined as the adherence and growth of algae and bacteria on a membrane surface.

TYPES OF WATER SYSTEMS

- **For the manufacture of pharmaceutical and biopharmaceutical products, it is essential that :**

1- water does not contain chemicals which may react with active ingredients in the product.

2- in addition, it must be free from pathogenic organisms, toxic substances and any other contaminants which may adversely affect the product, its appearance, shelf-life and other similar properties.

3- if **the water is being utilized in the manufacture of a parenteral product, the water must also have a bioburden less than 10 CFU /1ooml (colony forming units per ml) and be free from pyrogens.**

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The two principal types

1- Purified water (PW)

2- Water for Injection (WFI)

Occasionally a lower grade of water is used in bulk pharmaceutical facilities, i.e. Water produced by deionization or demineralization. This type of water has no pharmacopoeial specifications but it would certainly be expected to meet the specifications for potable water as a minimum.

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Distillation

- **Distillation is a method of obtaining chemically and microbiologically pure water. Stills purify the feed water by vaporization, separation of droplets from the vapor by circular velocity or entrainment separators and condensation of the purified vapor in a heat exchanger.**

- **There are three main methods of distillation:**
  1. **Single effect**
  2. **Multiple effect**
  3. **Vapor compression**

Multistage Flash Distillation

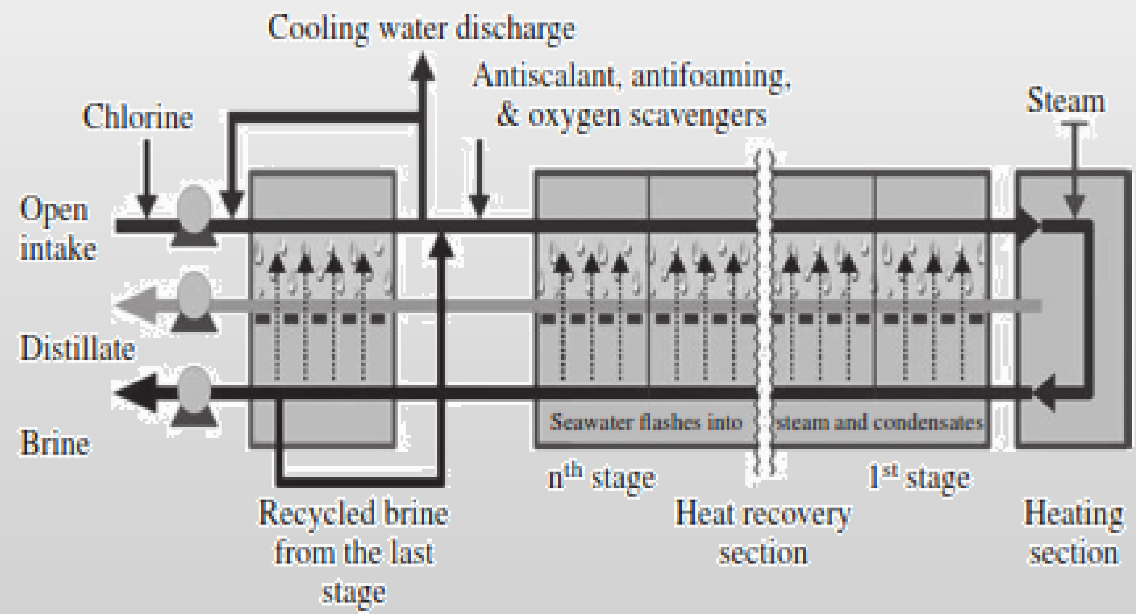

FIGURE 1.2 Schematic of an MSF distillation system.

Recovery of MSF plant

- ***The total MSF plant recovery (i.e., The volume of distillate expressed as a percentage of the total volume of processed source water) is typically 19 to 28 percent.***

- ***For comparison, RO seawater desalination plants have a recovery of 40 to 45 percent.***

Multiple-Effect Distillation

- In multiple-effect distillation (MED) systems, saline source water is typically not heated; cold source water is sprayed via nozzles or perforated plates over bundles of heat exchanger tubes.
- This feed water sprayed on the tube bundles boils, and the generated vapor passes through mist eliminators, which collect brine droplets from the vapor.

Multiple-Effect Distillation

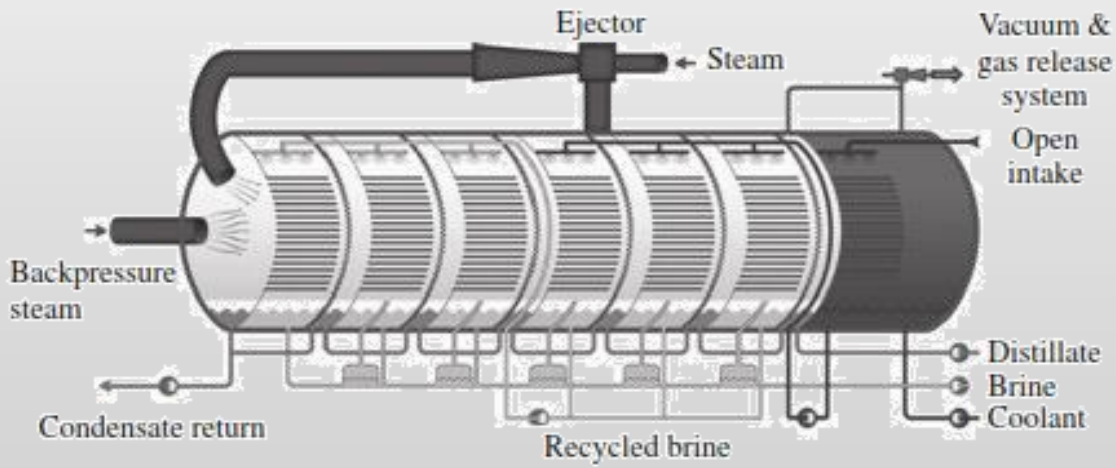

FIGURE 1.3 Schematic of an MED system.

Multiple-Effect Distillation

MED desalination systems typically operate at lower temperatures than MSF plants

The newest MED technologies, which include vertically positioned effects may yield a GOR of up to 24 kg of potable water per kilogram of steam.

GOR gain output ratio

Vapor Compression

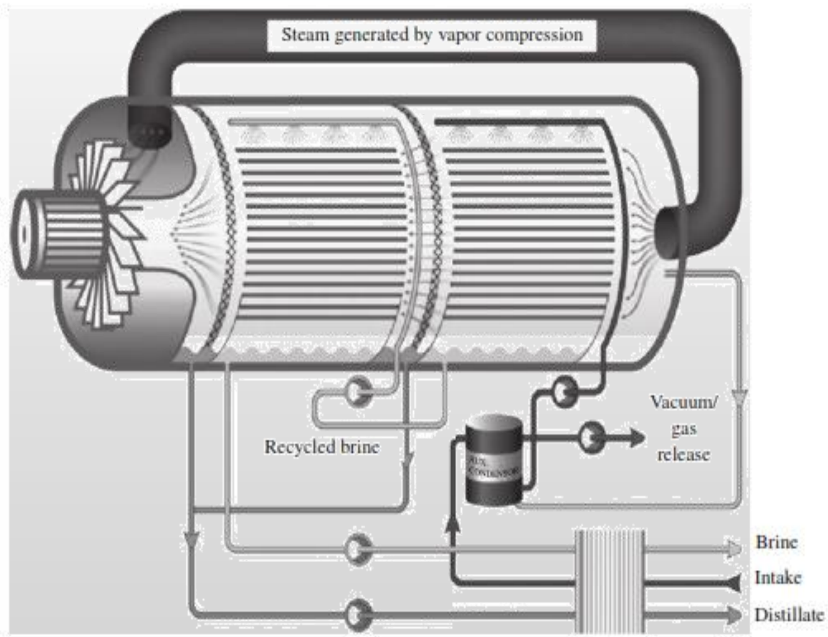

Figure 1.4 Schematic of a VC system.

- The heat source for vapor compression (VC) systems is compressed vapor produced by a mechanical compressor or a steam jet ejector rather than a direct exchange of heat from steam.

Water Specification

- Purified water in bulk is prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method.
- Purified water in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Sampling

1. There must be a sampling procedure
2. Sample integrity must be assured
3. Sampler training
4. Sample point
5. Sample size

Sampling (2)

1. Sample container
2. Sample label
3. Sample storage and transport
4. Arrival at the laboratory
5. Start of test

Testing

1. Method verification
2. Chemical testing
3. Microbiological testing
   - test method
   - types of media used
   - incubation time and temperature
   - objectionable and indicator organisms
   - manufacturer must set specifications

Water for Injections

1. International pharmacopoeia requirements for WFI are those for purified water plus it must be free from pyrogens
2. Usually prepared by distillation
3. Storage time should be less than 24 hours
4. Microbial limits must be specified

Water for Final Rinse

- Water for final rinse must be of the same quality as the water required for pharmaceutical preparation

Pyrogens and endotoxins

1. Any compound injected into mammals which gives rise to fever is a “Pyrogen”
2. Endotoxins are pyrogenic, come from Gram negative bacterial cell wall fragments.
3. Detect endotoxins using a test for *lipopolysaccharides (LPS)*
   - rabbit test detects pyrogens.
   - LAL test detects endotoxins.
4. Uultrafiltration, distillation, & RO may remove pyrogens

Suggested bacterial limits *(CFU/mL)*

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
Points of Use	1	10	100

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Conductivity

- The water to be examined meets the requirements if the measured conductivity at the recorded temperature is not greater than the value in the table .

Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
0	2.4
10	3.6
20	4.3
25	5.1
30	5.4
40	6.5
50	7.1
60	8.1
70	9.1
75	9.7
80	9.7
90	9.7
100	10.2

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Water for injection

- Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets.
- The correct maintenance of the apparatus is essential.
- The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected.

Table no 2

Temperature (°C)	Conductivity (μS·cm⁻¹)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Conductivity of WFI

- If the measured conductivity is not greater than the value in table in the previous slide the water to be examined meets the requirements of the test for conductivity.
- If the conductivity is higher than the value in table in the previous slide , proceed with stage 2.

Stage 2

Transfer a sufficient amount of the water to be examined (100 ml or more) to a suitable container, and stir the test sample.

Adjust the temperature, if necessary, and while maintaining it at 25 ± 1 °c, begin vigorously agitating the test sample while periodically observing the conductivity.

When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than 0.1 $\mu s.Cm^{-1}$ per 5 min, note the conductivity.

If the conductivity is not greater than 2.1 $\mu s.Cm^{-1}$, the water to be examined meets the requirements of the test for conductivity. If the conductivity is greater than 2.1 $\mu s.Cm^{-1}$, proceed with stage 3.

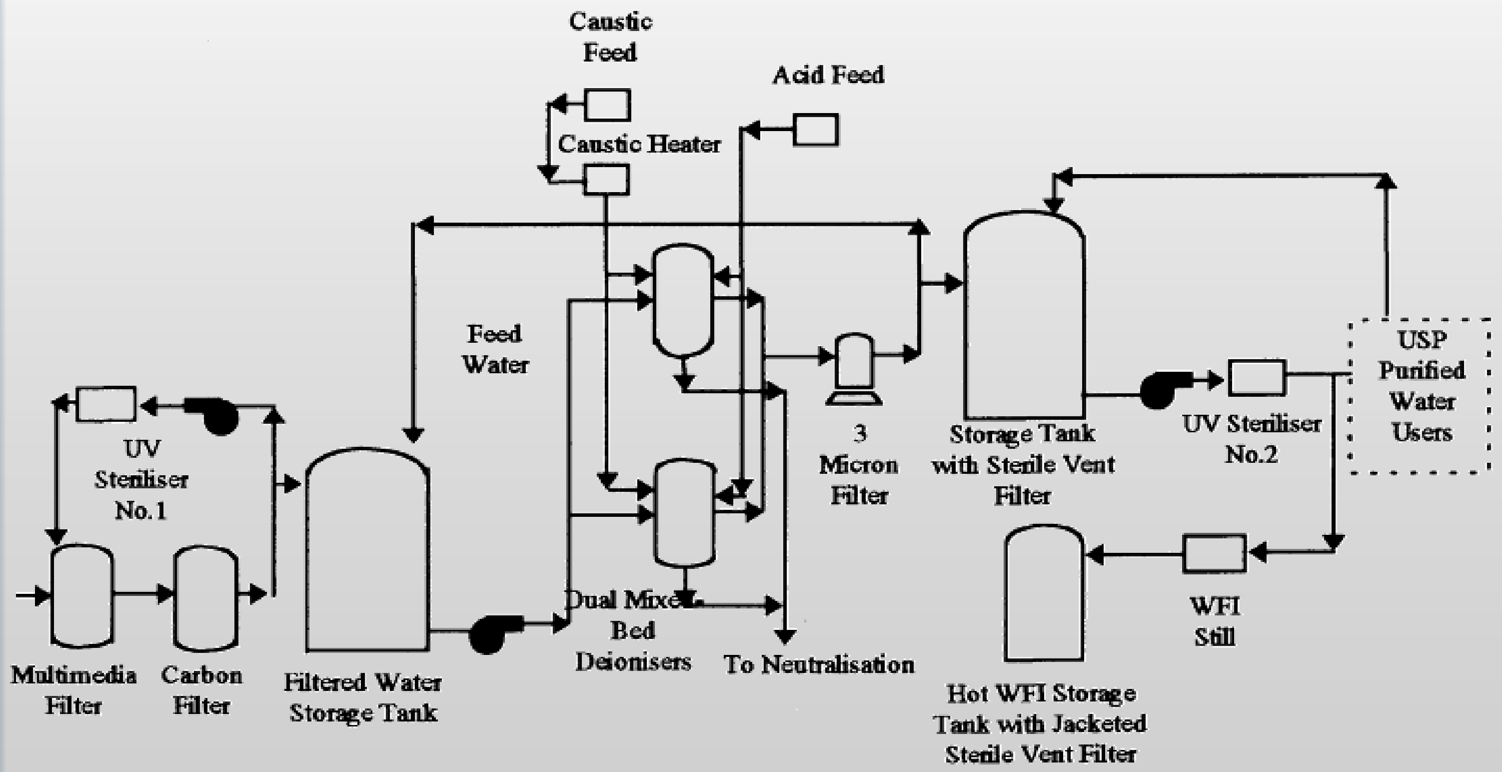
Stage 3

- **Perform this test within approximately 5 min of the conductivity determination under stage 2, while maintaining the sample temperature at 25 ± 1 °C.**
- **Add a recently prepared saturated solution of *potassium chloride r* to the test sample (0.3 ml per 100 ml of the test sample), and determine the pH to the nearest 0.1 pH unit.**
- **Using table 3, determine the conductivity limit at the measured pH value. If the measured conductivity in stage 2 is not greater than the conductivity requirements for the pH determined, the water to be examined meets the requirements of the test for conductivity.**
- **If either the measured conductivity is greater than this value or the pH is outside the range of 5.0-7.0, the water to be examined does not meet the requirements of the test for conductivity.**

Table 3

Table 3

pH	Conductivity ($\mu S \cdot cm^{-1}$)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6


Caustic Feed
Acid Feed
Caustic Heater
Feed Water
UV Steriliser No.1
Multimedia Filter
Carbon Filter
Filtered Water Storage Tank
Dual Mixed Bed Deionisers
To Neutralisation
3 Micron Filter
Storage Tank with Sterile Vent Filter
UV Steriliser No.2
USP Purified Water Users
WFI Still
Hot WFI Storage Tank with Jacketed Sterile Vent Filter

DESIGN GUIDELINES

- **Recommended guidelines for WFI systems.**
  1. Product contact materials of construction are usually 316 L stainless steel
  2. Polished pipework (often electro polished)
  3. Gaskets and elastomers such as EPDM, PTFE and PVDF must be able to withstand steam sterilization and be resistant to passivation solutions .
  4. butt weld and sanitary fittings, no threaded joints.
  5. Tri-clamp fittings
  6. Orbital welding and weld logging including 100% borescope, videoed
  7. Zero dead leg valves
  8. Double tube sheet shell & tube heat exchangers
  9. Temperature sensing devices should be mounted in wells.
  10. Pressure sensing instruments should be flush mounted with sanitary seals to isolate the instrument workings from the WFI.

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Holding and Distribution Systems

- **Recommendations for design and installation regarding the holding and distribution systems:**
  1. Sterile hydrophobic vent filters of 0.2 micron rating should be fitted on storage tanks.
  2. In hot services, the filter must be steam jacketed or electrically heated to prevent condensation.
  3. Wfi should be kept between 65 and 80 ◦C and should be drawn off immediately before use.
  4. It should not be allowed to stand for more than 8 hours before use.
  5. Piping must be installed in accordance with current GMP regulations , which state that piping must be mounted in a continuous slope, in order that it is completely drainable .
  6. No dead legs of> 6 times pipe diameter.
  7. 2 - 2.5 m/s circulating velocity.
  8. Routine sanitization with ozone or heat
  9. Routine maintenance
  10. Sampling points
  11. UV lamps

Welding

Orbital welding is generally recommended, although some manual welding will always be required. 100% inspection by borescope is becoming the industry standard, with a videotaped record.

Ultra Pure Water

Ultra pure water is mainly used in the semi conductor and pharmaceutical industry. Because of the continuing miniaturilisation in the semi conductor industry, the specifications become more strict every year.

Ultra-pure water contains by definition only H_20, and H^+ and OH^- ions in equilibrium.

Therefore, ultrapure water conductivity is about 0,054 uS/cm at 25°C, also expressed as resistivity of 18,3 MOhm.

Ultrapure water production often has to be done in 2 steps. For example, from tapwater or fresh groundwater, the water should first be demineralised by membrane filtration or ion exchange to reach the ultimate conductivity of 10 uS/cm.

The demineralised water is then processed through a high performance Mixed Bed or by Electrodionisation.

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Review validation

Validation for water systems consists of three phases

- Phase 1: 2 – 4 weeks
- Phase 2: 4 weeks
- Phase 3: 1 year

Review validation

Phase 1 – Investigational Phase (2 – 4 weeks)

- DQ, IQ and OQ
- Develop
  - operational parameters
  - cleaning and sanitization procedures and frequencies
- Sample daily at each point of use
- End of Phase I, develop SOPs for the water system

Review validation

Phase 2 – verifying control (4 - 5 weeks)

- Demonstrate the system is in control
- Same sampling as in phase 1

Phase 3 – verifying long-term control (1 year)

- PQ
- Demonstrate the system in control over a long period of time
- Weekly sampling

References

1. **ISPE & FDA Baseline Pharmaceutical Engineering Guide, Volume 4: Water and Steam Guide , Draft Working Document (Revision B).**
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THANKS FOR LISTENING

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