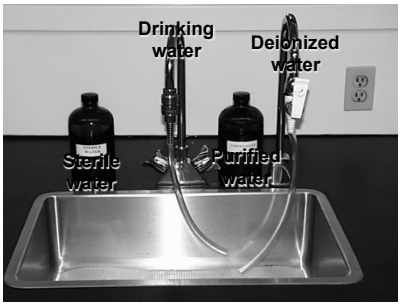
Pharmaceutical Waters

- Learning objectives
  - Define pharmaceutical waters
  - Know the different quality requirements for pharmaceutical waters
  - The student should be able to chose for different processes e.g. compounding using the appropriate pharmaceutical water
  - The student demonstrates knowledge of the processes how pharmaceutical waters are made and tested

Quality of the solvent



Pharmaceutical Waters

<1231> Water for Pharmaceutical purposes

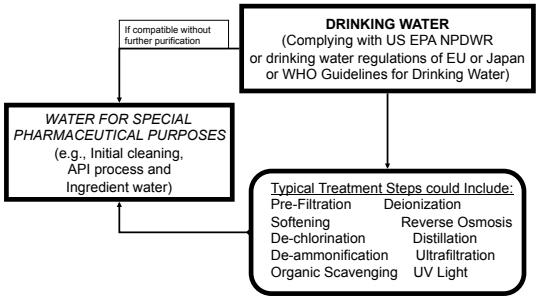
Water is the most widely used substance, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbiological quality of these waters is important because proliferation of microorganisms ubiquitous to water may occur during the purification, storage, and distribution of this substance. If water is used in the final product, these microorganisms or their metabolic products may eventually cause adverse consequences.

Water

Reservoir or
Ground water
Sand prefilter
Alum
Filter
Chlorination
Fluorination
Drinking water
Municipal water

Pharmaceutical plant
Ion exchange (-)
Ion exchange (+)
Charcoal (Cl^-, F^-)
Filter
Filter
Reverse osmosis
Distillation
Water for injection

Pharmaceutical Waters



QC of Water

- **Water source must comply with EPA (environmental Protection Agency)**
- **Drinking Water—Drinking Water is not covered by a compendial monograph but must comply with the quality attributes of the' EPA NPDWR or comparable regulations of the European Union or Japan.**

USP- water
Organic carbon
Water conductivity
Containers glass I or II & vol
Labeling e.g. not for parenteral administration
Sterility
pH
Ammonia
Calcium
Carbon dioxide
Chloride
Sulfate
Oxidizable substances
Bacterial endotoxins

<1231> Water for Pharmaceutical purposes

- There are also other types of water for which there are no monographs.
- These are all bulk waters, with names given for descriptive purposes only.
- Many of these waters are used in specific analytical methods.

<1231> Water for Pharmaceutical purposes
no monographs

- Drinking Water— This type of water can be referred to as Potable Water (meaning drinkable or fit to drink), National Primary Drinking Water, Primary Drinking Water, or National Drinking Water.

<1231> Water for Pharmaceutical purposes
no monographs

- Distilled Water— This water is produced by vaporizing liquid water and condensing it in a purer state.
- Deionized Water— This water is produced by an ion-exchange process in which the contaminating ions are replaced with either H+ or OH– ions.

<1231> Water for Pharmaceutical purposes
no monographs

- Filtered Water— This water is *Purified Water* that has been filtered to remove particles that could interfere with the analysis where the water is used .
- High Purity Water— It is water that is prepared by deionizing previously distilled water, and then filtering it through a 0.45-µm rated membrane.
- Ammonia-Free Water— Functionally, this water must have a negligible ammonia concentration to avoid interference in tests sensitive to ammonia.

<1231> Water for Pharmaceutical purposes
no monographs

- Carbon Dioxide-Free Water— The introductory portion of the *Reagents, Indicators, and Solutions* section defines this water as *Purified Water* that has been vigorously boiled for at least 5 minutes, then cooled and protected from absorption of atmospheric carbon dioxide.
- Deaerated Water— This water is *Purified Water* that has been treated to reduce the content of dissolved air by "suitable means". In the *Reagents* section, approaches for boiling, cooling (similar to *Carbon Dioxide-Free Water* but without the atmospheric carbon dioxide protection), and sonication are given as applicable for test uses other than dissolution and drug release testing.

<1231> Water for Pharmaceutical purposes
no monographs

- LAL Reagent Water— This water is also referred to as endotoxin-free water.
- Organic-Free Water— This water is defined by *Organic Volatile Impurities* 467 as producing no significantly interfering gas chromatography peaks.
- Lead-Free Water— This water is used as a transferring diluent for an analyte in a *Lead* <251> test.

Reagent Grade Water (not any more USP text)

- Water suitable for use in making up reagents or for use in sensitive analytical procedures.
- There are several grades of reagent grade water as defined by various professional organizations
  - American Society for Testing and Materials (ASTM)
  - College of American Pathologists (CAP)
  - National Committee for Clinical Laboratory Standards (NCCLS)
- ASTM D 1193 *"Standard Specification for Reagent Water"*
  - This specification covers requirements for water suitable for use in methods of chemical analysis and physical testing and is intended to provide the user with a choice of four different grades of water having different purities.
  - It is intended to satisfy the requirements for normal laboratories procedures, but does not necessarily apply to the large-scale production of pure water or for specific applications.

Selected Water Treatment Unit Operations

- Compendial waters must be generated from potable water.
- Water purification methods vary widely depending upon water source and locality.
- **Filtration**
  - Filtration technology plays an important role in water systems to remove particulate material and filtration units are available in a wide range of designs and for various applications.
  - Removal efficiencies differ significantly from coarse filters, such as granular anthracite, quartz, or sand for larger water systems and depth cartridges for smaller water systems, to membrane filters for very small particle control.

Selected Water Treatment Unit Operations

- **Activated Carbon Beds**
  - Granular activated carbon beds adsorb low molecular weight material and oxidizing additives, such as chlorine and chloramines, and remove them from the water prior to a reverse osmosis or deionized water system.
  - They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes.
  - Alternative technologies such as chemical additives and regenerable organic scavenging devices can be used in place of activated carbon beds.
- Some of the advantages of activated carbon are safe chlorine removal, organics removal, and some particulate removal.
- Notorious among their disadvantages are bacteria proliferation due to the chlorine removal capacity versus the organic removal capacity, which is much less, and pharmaceutical systems employing granular activated carbon must be hot water or steam sterilized.

Selected Water Treatment Unit Operations

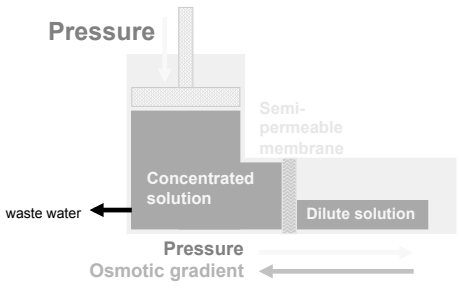
- **Deionization (DI)**
  - Deionization systems have charged resins that require periodic regeneration with an acid and base.
  - Typically, cationic resins are regenerated with either hydrochloric or sulfuric acid, which replace the captured positive ions with hydrogen ions.
  - Anionic resins are regenerated with sodium or potassium hydroxide, which replace captured negative ions with hydroxide ions.
  - Both regenerant chemicals are biocidal and offer a measure of microbial control.
  - The system can be designed so that the cation and anion resins are separated or that they form a mixed bed.

Selected Water Treatment Unit Operations

- **Reverse Osmosis (RO)**
  - Reverse osmosis units employ a semipermeable membrane and a substantial pressure differential to drive water through the membrane to achieve chemical, microbial, and endotoxin quality improvement.
  - The process streams consist of supply water, water passing through the membrane (permeate), and waste water (reject).
  - RO units can be used alone or in combination with DI and Electro De-Ionisation units for operational and quality enhancements*.
- **NOTE** - The FDA specifically addresses the chemical and microbiological quality of water produced by RO.

*The configuration of the RO unit offers control opportunities by expanding the single-pass scheme to parallel staged, reject staged, two-pass, and combination designs.

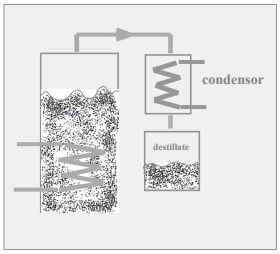
Reverse Osmosis



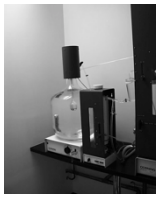
Selected Water Treatment Unit Operations

- **Distillation**
  - Distillation units provide chemical and microbial purification via thermal vaporization of the feed water, mist elimination, and condensing.
  - A variety of designs are available including single effect (SE), multiple effect (ME), and vapor compression (VC).
  - The latter two configurations are normally used in larger systems because of their generating capacity and efficiency.
  - Distilled water systems may require less rigorous control of feed water quality than do membrane systems.

Still



WFI distillation

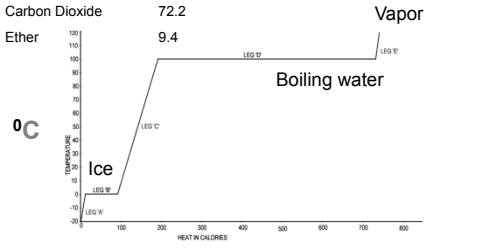


Heat of Vaporization Examples

Substance	Heat Required cal/g
Water at 0 C	596
Water at 100 C	540
Water at 180 C	478
Ethyl Alcohol	236.5
Carbon Dioxide	72.2
Ether	9.4

Water

for 1 kg steam 8 kg 5^{0}C cold water



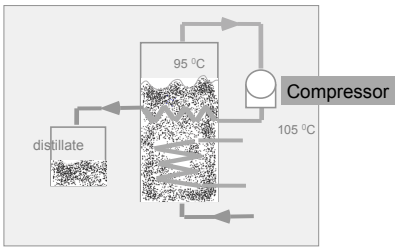
Ideal Gas Law

P1 V1/T1 = P2 V2/T2

PV/T = R
Or
PV = RT
For one mole of gas or
PV = nRT

General ideal gas law
Equation of state of an ideal gas

Vapor compression still



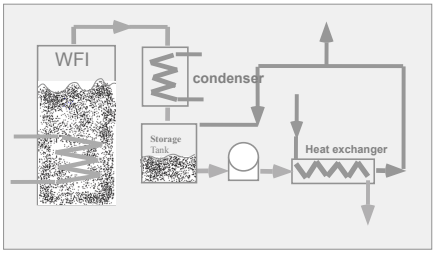
Energy use to produce 100 l WFI

	Energy	Steam	Cooling water	Distillate temperature
Classic Still	65 kW	110 kg	1000	30 ^{0}C
Thermo-compress-ion still	3.7 kW 1.6 kW	3.4 kg	-	30 ^{0}C

Selected Water Treatment Unit Operations

- **Distillation**
  - In comparing VC versus ME processes, VC is generally considered a more efficient means to produce distilled water.
  - In theory, it would take approximately 10 effects in a ME plant to match the performance of a VC distiller producing hot WFI.
- Although all commercially available ME systems are configured similarly and supplied with the same basic components, opportunities for cost savings exist in the areas of construction materials, surface finishes, and instrumentation.
- Concerns about operating costs of ME systems are associated mainly with plant steam and cooling fluid.
- Utilities consumption rates vary among ME manufacturers.

Water storage system



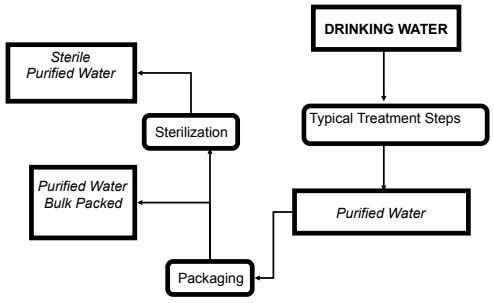
<1231> Water for Pharmaceutical purposes

- Even if produced and controlled exactly as stated, the waters must be suitable for their intended use.
- Wherever the term “water” is used within this compendia without other descriptive adjectives or clauses, the intent is that water of no less purity than *Purified Water* be used.

<1231> Water for Pharmaceutical purposes

- There are many different grades of water used for pharmaceutical purposes.
- Several are described in *USP* monographs that specify uses, acceptable methods of preparation, and quality attributes.
- These waters can be divided into two general types:
  - bulk waters, which are typically produced on site where they are used;
  - packaged waters, which are produced, packaged, and sterilized to preserve microbial quality throughout their packaged shelf life.
- There are several specialized types of packaged waters, differing in their designated applications, packaging limitations, and other quality attributes.

Pharmaceutical Waters USP



Water

USP monographs

- Purified water
- Sterile purified water
- Water for Injections
- Sterile water for Injection
- Bacteriostatic water for injection
- Sterile Water for Irrigation
- Sterile Water for Inhalation
- Water for Hemodialysis

Water

- **USP 29**

Purified water

(Suitable process e.g. ion exchange)

Purified Water—Purified Water is used as an excipient in the production of official preparations in pharmaceutical applications, such as cleaning of certain equipment; and in the preparation of some bulk pharmaceutical chemicals. Purified Water must meet the requirements for ionic and organic chemical purity and must be protected from microbial proliferation. It is prepared using Drinking Water as a feed water and is purified using unit operations that include deionization, distillation, ion-exchange, reverse osmosis, filtration, or other suitable procedures.

Purified Water systems must be Validated

Water

- **USP 29 monograph**

Sterile Purified water

Sterile, not for parenteral use!!!

Sterile Purified Water—Sterile Purified Water is *Purified Water* that is packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms where a sterile form of *Purified Water* is required.

Water

- **USP 29 monograph**

Water for Injections

Water for Injection—Water for Injection is an excipient in the production of injections and for use in pharmaceutical applications, such as cleaning of certain equipment, and sterile preparation of some bulk pharmaceutical chemicals.

The source or feed water for this article is Drinking Water, which may have been preliminarily purified but which is finally subjected to distillation or reverse osmosis. It must meet all of the chemical requirements *for Purified Water* and in addition the requirements under *Bacterial Endotoxins Test* <85>. It also must be protected from microbial contamination.

The system used to produce, store, and distribute Water for Injection must be designed to prevent microbial contamination and the formation of microbial endotoxins, and it must be validated.

Water

- **USP 29 monograph**

Sterile water for Injection

Sterile, bacterial endotoxins 0.25, 1 L, glass I or II

Sterile Water for Injection—Sterile Water for Injection is *Water for Injection that is* packaged and rendered sterile. Sterile Water for Injection is intended for extemporaneous prescription compounding and is distributed in sterile units.

It is used as a diluent for parenteral products. It is packaged in single-dose containers not larger than 1 liter in size.

Pharmaceutical Compounding – Nonsterile Preparations <795>

Purified Water **must be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water.**

Purified Water, **must also be used for rinsing equipment and utensils.**

In those cases when a water is used to prepare a sterile preparation,*Water for Injection, Sterile Water for Injection,* or *Bacteriostatic Water for Injection* must be used to prepare sterile preparations

Water

- **USP 29**

Bacteriostatic Water for Injection

like sterile water for injection, 30 ml, glass I or II,

Bacteriostatic Water for Injection—Bacteriostatic Water for Injection is sterile *Water for Injection* to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products. It may be packaged in single-dose or multiple-dose containers not larger than 30 mL.

Water

- **USP 29 monograph**

Sterile Water for Irrigation

sterile, bacterial endotoxins, glass I or II

Sterile Water for Irrigation—Sterile Water for Irrigation is *Water for Injection,* packaged in single-dose containers of larger than 1 liter in size, that is intended to be delivered rapidly and is rendered sterile.
It need not meet the requirement for small-volume injections under *Particulate Matter* <788>.

Water

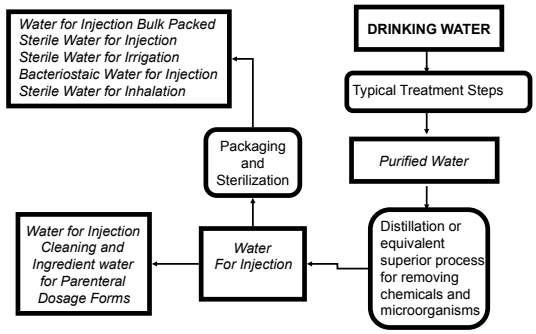
- **USP 29**

Sterile Water for Inhalation

sterile, bacterial endotoxins, glass I or II

Sterile Water for Inhalation—Sterile Water for Inhalation is *Water for Injection* that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions.

Pharmaceutical Waters USP

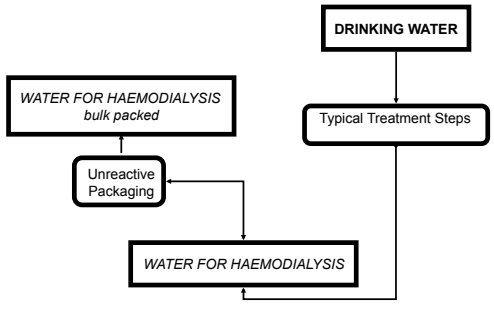


USP Monograph: Water for Hemodialysis

- Water for Hemodialysis is water that complies with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations and that has been subjected to further treatment, using a suitable process, to reduce chemical and microbiological components.
- It is produced and used onsite under the direction of qualified personnel.
- It contains no added antimicrobials and is not intended for injection.

QC: endotoxins, water conductivity, microbiological limit

Pharmaceutical Waters USP



European Pharmacopeia

European Pharmacopoeia (Ph Eur) Fifth Edition, official from July 1, 2005 and published by the European Directorate for the Quality of Medicines (EDQM).

This is mandatory in 30 member states including the European Union (EU) countries.

Sixteen countries and the World Health Organization (WHO) are observers at the EDQM.

Certain observer states officially implement in whole or in part the standards of the Ph Eur.

The requirements of the Ph Eur provides standards for the following grades of water:

-Water For Injection
-Purified Water
-Highly Purified Water

645 WATER CONDUCTIVITY

- Electrical conductivity in water is a measure of the ion-facilitated electron flow through it.
- Water molecules dissociate into ions as a function of pH and temperature and result in a very predictable conductivity.
- Some gases, most notably carbon dioxide, readily dissolve in water and interact to form ions, which predictably affect conductivity as well as pH.
- These ions and their resulting conductivity can be considered intrinsic to the water.

645 WATER CONDUCTIVITY

- Water conductivity is also affected by the presence of extraneous ions.
- The extraneous ions used in modeling the conductivity specifications described below are the chloride and sodium ions.
- The conductivity of the ubiquitous chloride ion and the ammonium ion at the limit of 0.3 ppm represents a major portion of the allowed water impurity level.
- A balancing quantity of cations, such as sodium ion, is included in this allowed impurity level to maintain electroneutrality.
- Extraneous ions such as these may have significant impact on the water's chemical purity and suitability for use in pharmaceutical applications.
- The combined conductivities of the intrinsic and extraneous ions vary as a function of pH and are the basis for the conductivity specifications.