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What Is Purified Water (PW), and Water for Injection (WFI)?

Water is the most critical ingredient in any pharmaceutical plant and, when used for production at any volume, is highly regulated. All pharmaceutical waters in the United States are subject to Food and Drug Administration (FDA) and current Good Manufacturing Practice (cGMP) guidelines for the removal of minerals, organics, and microbes, even when water does not remain in the finished product.

Regulatory bodies, such as the United States Pharmacopeia (USP), European Pharmacopeia (PhEur or EP), and Japanese Pharmacopeia (JP), write and regularly update 'Monographs' that outline the standards for identity, quality, purity, and handling of water and other ingredients used for pharmaceutical production. Waters that are compliant with monographs are described as "Compendial" and currently fall into two broad categories; "Purified Water" (PW) when produced for oral or external use and "Water for Injection" (WFI) when produced for parenteral (injectable) use.

Compendial water treatment must always begin with a potable water source before one or more treatment steps remove minerals, organics, and microbes to defined levels. The specifications for WFI are more stringent than PW, and some manufacturing sites add additional requirements that exceed that of their local regulatory body. The equipment used for water production must be carefully validated to confirm proper installation and operation and is rigorously monitored for performance and adherence to quality specifications.

Compendial Water Standards

	Purified Water (PW)		Water for Injection (WFI)	
MONOGRAPH	USP 29 <1231>	PhEur 9.1 <0169>	USP 29 <1231>	PhEur 9.1 <0169>
PROCESS*	Distillation, RO and any other suitable process	Distillation, ion exchange, RO & other suitable process	Distillation or RO	Distillation or a Purification Process Equivalent to Distillation
CONDUCTIVITY	< 1.3 µS/cm² @ 25°C	< 4.3 µS/cm² @ 20°C	< 1.3 µS/cm² @ 25°C	< 1.1 µS/cm² @ 20°C
AEROBIC BACTERIA	100 cfu/ml (suggested)	< 100 cfu/ml	< 10 cfu/100 ml (suggested)	< 10 cfu/100 ml
BACTERIAL ENDOTOXIN	N/A	< 0.25 IU/ml (bulk water for dialysis)	< 0.25 EU / ml	< 0.25 IU / ml
TOC	500 ppb	< 0.5 mg/l	500 ppb	< 0.5 mg/l
PH	5.0 - 7.0	5.0 - 7.0	5.0 - 7.0	5.0 - 7.0
NITRATES	N/A	< 0.2 ppm	N/A	< 0.2 ppm
HEAVY METALS	N/A	< 0.1 ppm	N/A	< 0.1 ppm
ALUMINUM	N/A	< 10 ppb (dialysis solutions)	N/A	< 10 ppb (dialysis solutions)

** The water source used for treatment / production must be obtained from potable waters complying with the "U.S. Environmental Protection Agency National Primary Drinking Water Regulations" or equivalent regulations of the European Union or Japan.*

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Purified Water (PW)

PW can be produced using any suitable single or multi-step water treatment method including reverse osmosis (RO), ion exchange (IX), and distillation. RO membrane process systems are effective at removing up to 99% of the minerals, organics, and bacteria contaminants from the source water supply and, despite greater wastewater volume, sanitization downtime, and process complexity, are more common than thermal processes due to lower capital and energy costs.

A typical RO PW process includes sediment filtration, water softening, and activated carbon filtration upstream of the RO system to prevent fouling from particulates and mineral scale and to remove municipally-added chlorine which irreversibly damages most RO membrane elements. A second-pass of RO membranes or ion exchange is often used to 'polish' the water to well beyond the required product specifications. Systems are periodically taken out of service for chemical or hot water sanitization which is used to prevent and control bacteria growth in the equipment. Other treatment steps such as online UV disinfection, pH correction, and final filtration are used to increase product safety margins or to compensate for site specific conditions like alkalinity, temperature, chloramines, etc.

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Water For Injection (WFI)

In April 2017 the PhEur 9.1 monograph 0169 was revised to allow WFI production with a purification process equivalent to distillation, harmonizing its rules with USP and JP methods. This change allowed membrane-based processes to be qualified for WFI production with special considerations for microbial control safety assurances requested in follow-up European Medicines Agency (EMA) Q&A and GMP Annex 1 guidelines.

Membrane based production is known as "Membrane WFI" or "Ambient WFI". While there is no defined ambient WFI process, a two-pass RO, ion exchange, and ultrafiltration (UF) approach is becoming common.

From back-to-front:

• UF is used for up to 4-log retention of endotoxins/pyrogens. Pharmaceutical UFs are commonly sized for a 10,000-20,000 Dalton molecular cut-off weight (MWCO) with 6,000 Da MWCO required for certain applications.

• Continuous electrodeionization (CEDI) is an ion exchange process that uses DC electric current for online regeneration of the resins and is normally used instead of replaceable or chemically regenerated systems which introduce a contamination risk. CEDI is a polishing technology that reduces any residual minerals, CO_2, NH_4, SiO_2, and TOC remaining from the RO process.

• While single-pass RO is permitted, two-pass RO provides "added assurance of the maintenance of the quality of the water produced" according to the EMA Q&A document as the second membrane provides a barrier to any microorganisms that find their way through membrane or o-ring defects or grow on the back side of the first-pass. Additionally, pH adjustment is often used in conjunction with the second-pass to reject excess CO_2 and ensure reliable operation of downstream CEDI modules.