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Best Practice

Compliance by Design

in Pharmaceutical Water Systems

METTLER TOLEDO

Contents

This guide is designed to provide a valuable and convenient information resource to aid in the design of pharma water systems that are compliant with the requirements of global pharmacopeias. It offers vital information on topics including requirements for source bulk waters, control of biofilms, and the three stages of water systems.

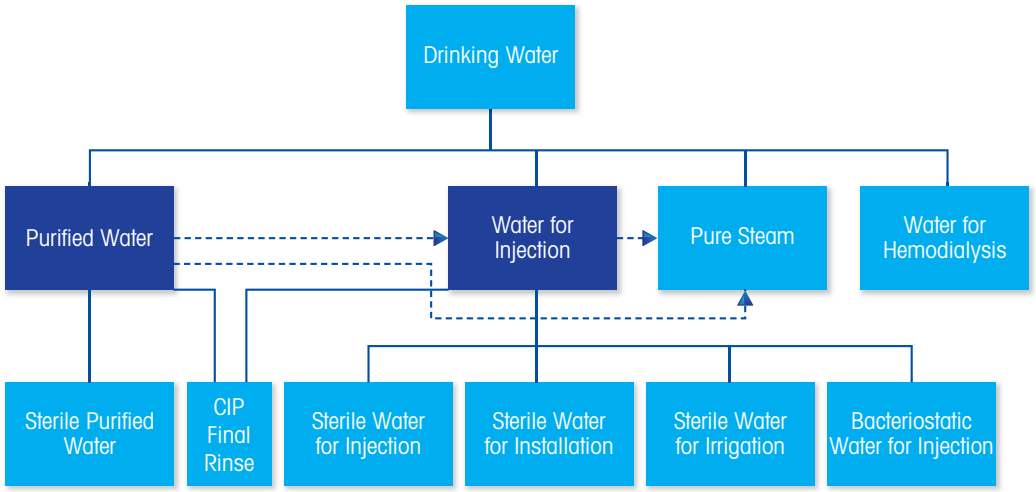
1 Initial Design Considerations

For the production of pharmaceutical waters, source water must be treated using a combination of purification steps that are designed to remove specific types of impurities. The combination and order of purification steps varies for every system, and several aspects need to be considered when designing a pharmaceutical water system:

- Source water
  - Quality
  - Seasonal changes
  - Microbial control methods
- Green engineering
- Risk factors to the end product
- Cost
  - Capital
  - Available resources
  - Operating costs
- Required volume and quality of water
  - Peak, average, shutdown volumes
  - Types of water, compendial requirements
  - Temperature
- Uses of water
  - Compendial ingredient
  - Cleaning/rinsing/washing
  - Humidification
- Redundancy
- Future capacity

No single design will meet every requirement or is guaranteed to produce the appropriate water quality. A pharmaceutical water system must have the capability to deliver safe water consistently and confidently, based on knowledge of source water and produced water, good engineering practices and water system design, good monitoring/control programs, and proper sanitization/maintenance.

Figure 1: Sources of pharmaceutical waters



2. General Information on Water Sources and Contaminants

The water supply to a municipality for the production of drinking water can vary substantially depending on whether it is ground or surface water and if it is in an area that is subject to seasonal variations or drought/monsoon conditions. This guide considers ground and surface water and the contaminants that can be found in those waters.

Table 1: Water sources for production of potable (drinking) water:

Ground waters	Surface waters
Higher mineral content Low organic levels Higher hardness levels Less temperature variation	Lower mineral content Higher organic levels Higher TDS levels Wide temperature variations Seasonal fluctuations

2.1 Contaminants in water

Due to wide variations in source waters and because of water's unique chemical properties, there is no pure water in nature. Water has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that could react with the intended solution, drug or product. There are more than 90 possible unacceptable contaminants in potable water which are listed by government health authorities.

- Total dissolved solids (TDS)
- Total ionized solids and gases
- Total solids
- Microbial
- Particulates
- Organics

Currently available purification processes and technologies effectively remove certain of the above contaminants at varying rates and efficiencies. The table below (Table 3) details the different purification technologies and the ability of each to remove specific contaminants and whether they are excellent, good or poor at removing that contaminant.

Table 2: Major classes of contaminants in water.

E = Excellent (capable of complete or near total removal) G = Good (capable of removing large percentages) P = Poor (little or no removal)	**Dissolved Ionized Solids**	**Dissolved Ionized Gases**	**Dissolved Organics**	**Particulates**	**Bacteria/ Algae**	**Pyrogens/ Endotoxins/ Viruses**
Purification Process						
Distillation	E	G/E (1)	E	E	E	E
Deionization (EDI)	E	E	P	P	P	P
Reverse Osmosis	G (2)	P	G	E	E	E
Carbon Adsorption	P	P (3)	E/G (4)	P	P	P
Micron Filtration	P	P	P	E	P	P
Sub Micron Filtration	P	P	P	E	E	P
Ultrafiltration	P	P	G (5)	E	E	E
U.V. Oxidation	P	P	E/G (6)	P	G (7)	P

(1) The resistivity of the water is dependent on the absorption of CO_2.
(2) The concentration is dependent on the original concentration in the feedwater.
(3) Activated carbon will remove chlorine by adsorption.
(4) When used in combination with other purification processes special grades of carbon exhibit excellent capabilities for removing organic contaminants.
(5) Ultrafilters, being molecular sieves, have demonstrated usefulness in reducing specific feedwater organic contaminants based on the rated molecular weight cut-off of the membrane.
(6) 185 nm UV oxidation has been shown to be effective in removing trace organic contaminants when used post-treatment.
(7) 254 nm UV sterilizers, while not physically removing bacteria, have bactericidal or bacteriostatic capabilities limited by intensity, contact time and flow rate.

2.2 Pharmacopeia requirements for source water

The production of water for pharmaceutical use requires the source water used for purification to be "water safe for human consumption as deemed by a competent authority".

Source water requirements by pharmacopeia:
- USP: "It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union, Japan, or with the World Health Organization's Guidelines for Drinking Water Quality."
- EP: "…from water that complies with the regulations on water intended for human consumption laid down by the competent authority."
- JP: "prepared from Water."
- ChP: "prepared from water complying with National Standard of the People's Republic of China."
- IP: "…prepared from water meeting all statutory requirements for drinking water."

3. Production Requirements for Bulk Waters

In addition to the water types as discussed above, bulk waters (PW, HPW, WFI) are the primary starting point for all other waters. A facility must determine the type of bulk water they require and design the system such that it will be compliant at all times. To ensure continuous compliance, the performance of a pharmaceutical water purification, storage, and distribution system must be monitored.

The type of bulk water being produced determines the purification technologies that should be incorporated into a system. For PW the system can incorporate any combination of technologies, but specific water quality requirements must be met. For example, WFI should use distillation as the final purification step. The one exception is for WFI for use in Japan only, where a combination of reverse osmosis and ultrafiltration when fed PW can be the final purification step. HPW is a Europe only water type which can be used for very limited pharmaceutical applications.

3.1 Basic water system monitoring requirements

- Monitoring of water sources regularly
  - chemical and microbiological
  - endotoxin (pyrogen) level where relevant
- Monitoring of system performance, storage, and distribution systems
- Records of results, and any actions taken
- Validated sanitization procedures followed on a routine basis

The storage and distribution system should be considered as a key part of the whole system, and must be designed to be fully integrated with the water purification modules of the system. Once water has been purified using an appropriate method, it can either be used directly or transferred into a storage vessel for subsequent distribution to points of use. The storage and distribution system should be configured to prevent recontamination of the water after treatment and be subjected to a combination of on-line and off-line monitoring to ensure that the water is suitable for intended use and that the quality is maintained. The final validation and the ongoing control of the water system must include all aspects of the process, but special attention must be paid to the purification and storage and distribution sections.

3.2 Purified Water (PW) - USP37 – NF32

PW is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union or of Japan, or with the World Health Organization's Guidelines for Drinking Water Quality. It contains no added substance.

3.3 Water for Injection (WFI) – USP37 – NF32

WFI is characterized by superior distillation in the removal of chemicals and microorganisms. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union or of Japan or with the World Health Organization's Guidelines for Drinking Water Quality. It contains no added substance.

Table 3: Requirements for bulk Purified Water and Water for Injection by pharmacopeia.

Attribute	USP	EP	JP	ChP	IP
Source Water for PW and WFI	US, EU, Japan, WHO drinking water	Human consumption	JP water specification	Potable water or Purified Water	Potable water or Purified Water
PURIFIED WATER					
Production Method	Suitable process	Suitable process	Distillation, ion-exchange, UF, or combination	Distillation, ion-exchange, or suitable process	Distillation, ion-exchange, or suitable process
Total Aerobic (microbial) (cfu/mL)	100	100	100	100	100
Conductivity (µS/cm at 25°C)	1.3 (3 stage)	5.1 (1 stage)	1.3 on-line or 2.1 off-line	5.1 (1 stage)	1.3 (3 stage)
TOC (mg/L)	0.5	0.5 (optional)	0.5 (0.3 for control)	0.5	0.5
Nitrates (ppm)		0.2		0.2	Required
Acidity/Alkalinity					Required
Ammonium (ppm)				0.2	Required
Oxidizable Substances		Required			
WATER FOR INJECTION					
Production Method	Distillation or suitable process	Distillation or RO with additional technology	Distillation or RO with UF, from Purified Water	Distillation	Distillation
Total Aerobic (microbial) (cfu/100 mL)	10	10	10	10	10
Conductivity (µS/cm at 25°C)	1.3 (3 stage)	1.3 (3 stage)	1.3 on-line or 2.1 off-line	1.3 (3 stage)	1.3 (3 stage)
TOC (mg/L)	0.5	0.5	0.5 (0.3 for control)	0.5	0.5
Bacterial Endotoxins (EU/mL)	0.25	0.25	0.25	0.25	0.25
Nitrates (ppm)		0.2		0.2	Required
Heavy Metals				Required	
Acidity/Alkalinity				Required	
Ammonium (ppm)				0.2	

* Shaded boxes – no test required

4. Biofilm

Free-swimming aquatic bacteria use polymucosaccharides as a glue to colonize surfaces and form a biofilm. Biofilm is composed of cellular debris, organic material and a small number of vegetative cells. Complex communities evolve which, when mature, shed micro-colonies and bacteria. This gives rise to sporadic high counts in bacteria levels. The major groups of water borne contaminants are algae, protozoa and bacteria.

Water treatment equipment, storage, and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, and incorporate techniques for sanitizing or sterilizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualification activities.

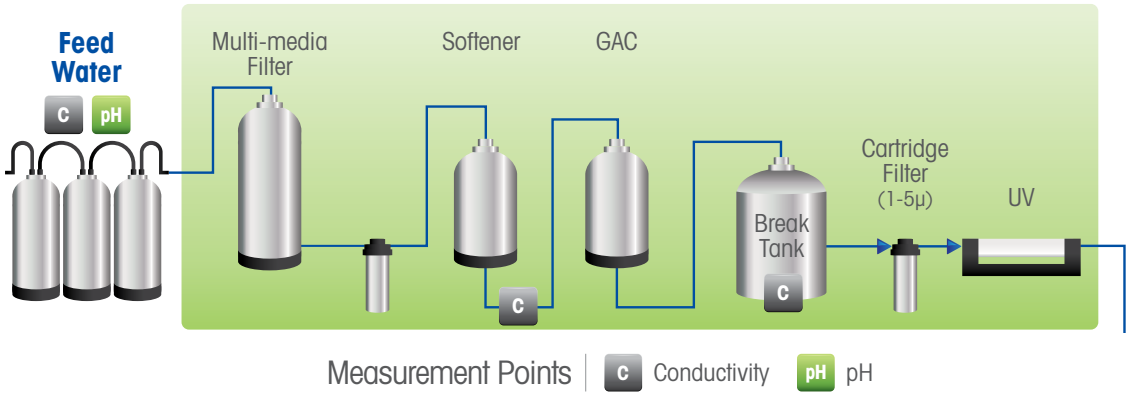
5. Designing and Engineering Pharmaceutical Water Systems

A pharmaceutical water system that it is in compliance at all times and produces the intended quality of water, should be properly monitored and controlled with a variety of parameters and instruments. When planning the system, breaking it into three sections – pre-treatment, purification, storage and distribution – simplifies the design process and will allow the system to be engineered to meet the facility's demands.

5.1 Pre-treatment

The source water is a significant determining factor in what pre-treatment technologies will be utilized. While the pharmacopeia requires, at a minimum, that the source water be safe for human consumption, the ionic and organic profile of that water will vary depending on the source used, ground water or surface water. This should be known and taken into consideration when deciding on the pre-treatment system. A typical pre-treatment system incorporating several removal technologies and the parameters that should be incorporated into the system to monitor performance and contaminant removal is shown in (Figure 2).

Figure 2: Schematic of pre-treatment system.



This system includes filtration (multi-media and cartridge filters), softener (to reduce hardness), Granular Activated Carbon (GAC - for organic removal) followed by additional filtration at a smaller micron rating, UV treatment (for inactivation of microbial contaminants) and then the addition of acid, alkali or sodium bisulfite to adjust the pH and remove chlorine.

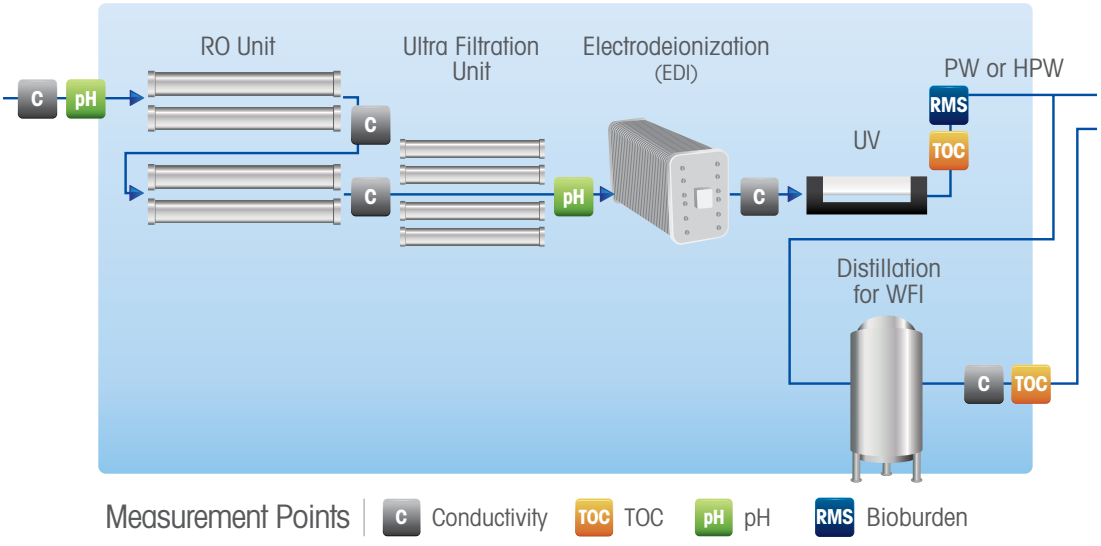
Many of the pre-treatment processes involve the physical removal of contaminants so monitoring will utilize pressure and flow to determine maintenance and replacement schedules. Further in the pre-treatment module, pH and ORP are the controlling parameters for the adjustment of pH and determining the removal of chlorine or other oxidants.

5.2 Purification

The purification section will vary depending on the water type being produced for the specific pharmaceutical applications and the capacity required, plus any future expansion requirements. In general, if the intention is to produce WFI the purification will include reverse osmosis and either deionization or electrodeionization followed by distillation. The inclusion of UV oxidation is for inactivation of bacteria, and in some systems there may be ultrafiltration, but it would only be installed before the last purification process. Filtration after the water has been treated is strongly discouraged by the regulators as it may be a potential site for microbial growth.

The entire purification process is shown with the parameters that should be incorporated in the system (Figure 3). The purification process is the part of the pharmaceutical water system that determines the quality of the water and the type of water that is being produced. This is also an area of a pharmaceutical facility that will be audited by regulators and inspectors (the water system is one of the most audited aspects of a pharmaceutical facility).

Figure 3: Schematic of entire purification system.



The measurement parameters utilized in the purification process are not only used to control the performance of the system, but are also the measurements that must be reported to confirm the quality of the water being produced. Control and system monitoring of the process will or should include; flow, pressure, temperature, bioburden, pH and ORP. However, these parameters are not part of the required tests for the pharmacopeia, but they are critical to the proper control of the purification system. In addition, there will be conductivity and TOC measurements installed on the system, not only for control and monitoring, but also as regulatory control

points. For WFI and PW there are conductivity, TOC and microbial contamination limits that must be monitored and reported. While off-line testing is still permitted, the pharmacopeias are encouraging the use of on-line testing and cautioning that off-line testing can be a source of false test results.

"Online conductivity testing provides real-time measurements and opportunities for real-time process control, decision, and intervention. Precaution should be taken while collecting water samples for off-line conductivity measurements. The sample may be affected by the sampling method, the sampling container, and environmental factors such as ambient carbon dioxide concentration and organic vapors."

USP ‹645›

The pharmacopeias require that the conductivity, TOC and microbial contamination be tested and reported from a point that demonstrates the quality of water used in production. This reporting point is usually after the last point-of-use.

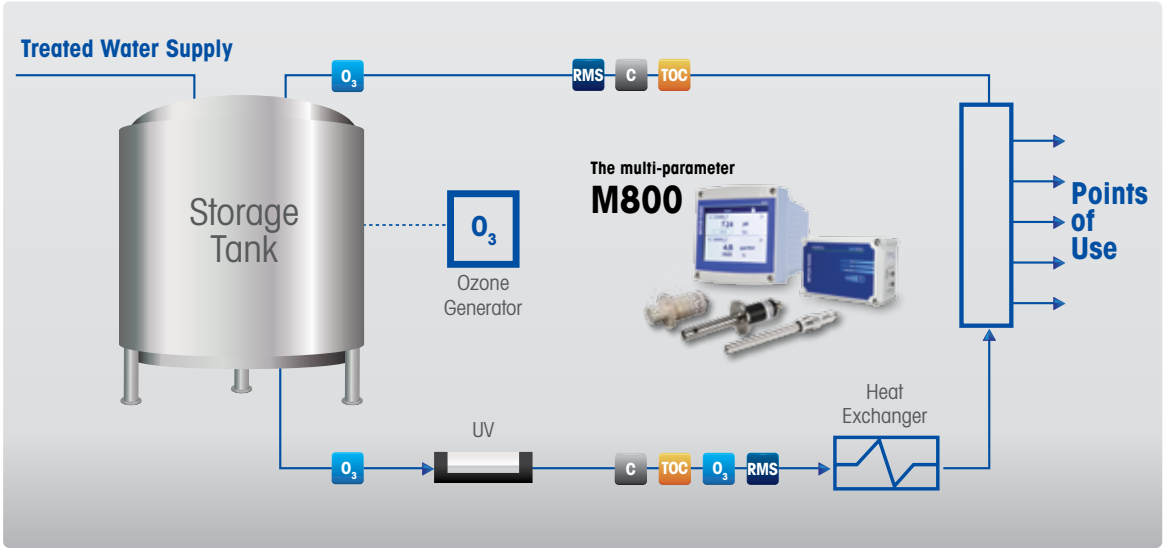
5.3 Storage and distribution

The storage and distribution section must take into consideration the on-demand requirements for water, the peak demand, sanitization and distribution piping. Shown below is a system layout for storage and distribution with the parameters that should be included as part of the system design.

Measurement parameters that must be included in the storage and distribution section are flow, pressure and temperature. In addition, conductivity, TOC and microbial contamination are also included because these are the reportable measurements to determine if the water quality meets the requirements for PW or WFI. If the storage and distribution system utilizes ozone for sanitization then the loop will require multiple ozone measurements to verify ozone destruction and therefore comply with the "no added substance" requirement.

Piping, tanks, tank liners, and all materials of construction – including fittings, pumps and valves are all in direct contact with pharmaceutical waters and all are potential risks for degradation of the purified water. Therefore, these water system components must be selected carefully to ensure that they are sanitary in nature and that none will leach any potential contaminants into the water, degrading water quality and risking compliance.

Figure 4: Schematic of storage and distribution system.



Suitable materials include:

- stainless steel Grade 316 L (low carbon)
- polypropylene (PP)
- polyvinylidenedifluoride (PVDF)
- perfluoroalkoxy (PFA)
- unplasticized polyvinylchloride (uPVC) used for non-hygienic designed water treatment equipment such as ion exchangers and softeners

6. Instrumentation Recommendations for Pharmaceutical Water Systems

For every section of the water system there are three measurement types that are monitored and controlled, which are: chemical, physical and biological.

The control of each section of the water system depends on the inclusion of the proper controls for every area of purification. Additional measurements will not produce better water but will give better control and monitoring. Shown below in Table 6 are the measurement parameters for a water system which provides some monitoring guidelines for different purification technologies.

Table 4: Overview of recommended parameters for different unit processes.

Unit Process	Parameters								
	Cond/ Res	Temp	Bioburden	TOC	pH/ ORP	O_3	Press	Level	Flow
Media Filters, Depth and Sand Filters	•	•					•		•
Softeners	•	•					•		•
Carbon (GAC) **Filters**				•	•		•		•
pH Adjust (Acid/Caustic Injection) ***PID Control**	•				*				
Reverse Osmosis	•	•		•	•		•		•
Ion-Exchange (Mixed-Bed)	•			•			•		•
Electrodeionization	•	•		•			•		
Distillation	•	•		•					
Ozone (injection, destruction, sanitization)						•			
Storage Tank		•	•			•		•	•
Distribution Loop	•	•	•	•		•	•		•

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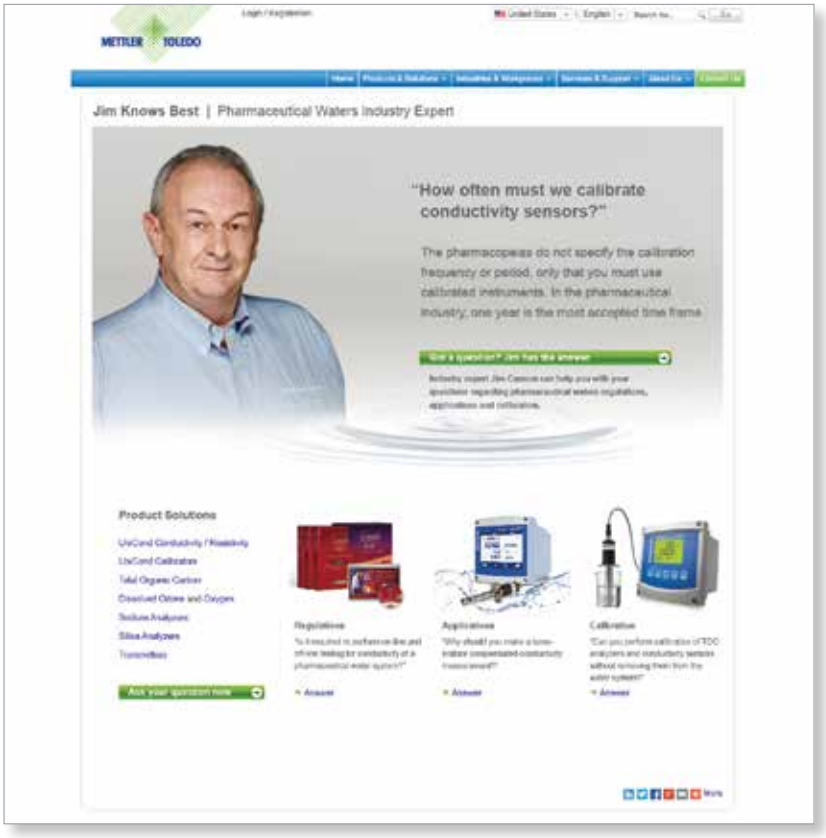

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