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Pharmaceutical Waters Guide

for Regulatory Compliance, Analysis and Real-Time Release

METTLER TOLEDO

Contents

The METTLER TOLEDO Pharmaceutical Waters Guide provides you with a valuable and convenient informational resource for Pharmaceutical Water production, with insights into the applications integral to producing these waters. This booklet offers vital information on topics including water purification technologies and system capabilities, critical measurements, global pharmacopeia regulations, and the latest technologies to assist you in the design, operation, control, validation, and compliance of your water systems.

METTLER TOLEDO is dedicated to providing our pharmaceutical industry customers with solutions for measurement, monitoring, and control while assuring regulatory compliance, for all liquid analytics measurements. Decades of industry leadership in the process analytics environment ensure that METTLER TOLEDO can provide accurate and reliable measurements with robust solutions that meet the demanding needs of this innovative industry.

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The Preparation of Pharmaceutical Waters

While the public considers municipal water to be "pure", the pharmaceutical market considers municipal water (feedwater) just the starting point in producing pure water. Water is the most widely used excipient in pharmaceutical manufacturing, and pharmaceutical water is a multi-functional resource, crossing all disciplines in the pharmaceutical industry. Water is used as a raw material, solvent, ingredient, reagent, and clean-ing agent, and is produced in a variety of "pure" forms.

Purified Water (PW), Highly Purified Water (HPW), and Water for Injection (WFI) used in pharmaceutical processes are produced on site from the local potable water, which has been produced by the treatment of the feedwater.

Today's pharmaceutical companies have invested considerable capital in state-of-the-art instrumentation, purification equipment, storage and distribution loops, and importantly in the calibration and certification of their water systems. By understanding water, its sources and impurities, and the capabilities and limitations of purification methods, a water system can be designed to meet not only pharmaceutical companies' requirements but to meet global pharmacopeia regulations.

Global pharmacopeia requirements for PW, HPW, and WFI

1. Source water requirements
2. Method of Manufacture requirements:
    a. PW – any method but must meet quality standards
    b. WFI – USP, EP, ChP, IP – distillation only, JP – distillation or combination of RO/UF
3. Microbiology requirements
4. Endotoxin requirements (WFI only)
5. <645> Conductivity
6. <643> TOC
7. No Added Substance rule

The purpose of this chapter is to provide a synopsis of source waters, purification methods, and measurement technologies to maintain quality and certification of a pharmaceutical water system.

Source water requirements

"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." USP 35
The feedwater source for a municipality can be from a surface water or a ground water supply. The impurities vary in each source and some of the primary differences are shown below;

Ground waters	Surface waters
High mineral content	Lower mineral content
Low organic level	High organic level
High hardness level	High total dissolved solids level
Less temperature variation	Wide temperature variation

Because the quality and characteristics of the feedwater supply have an important bearing on the purification, the pharmacopeias define the source water for the production of PW, HPW, and WFI. The pharmaceutical facility should communicate regularly with their water provider and request an annual water test report for the feedwater. To further the understanding of the feedwater and what technologies are required to purify it, below are the categories of contaminants found in a water supply.

Contaminants in feedwater
The impurities found in water can be categorized into six major classes: dissolved ionized solids, dissolved ionized gases, dissolved non-ionized solids (organics), particulate matter, bacteria/algae, and pyrogens. Feedwater varies significantly in purity both from one geographical region to another, and from season to season.

Total dissolved solids (TDS)
A measure of the total of organic and inorganic salts dissolved in water, obtained by drying residue at 180°C. The sum of all ions in a solution is often approximated by means of electrical conductivity or resistivity measurements. TDS measurements are commonly used to assess reverse osmosis unit performance.

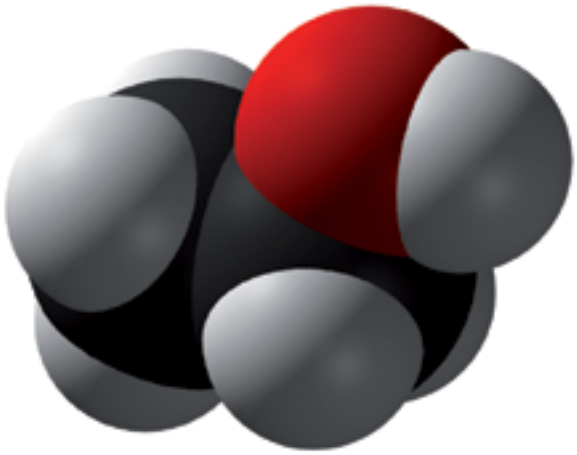
Total ionized solids and gases
Concentration of dissolved ions in solution, expressed in concentration units of NaCl (sodium chloride). This determines the operating life of ion exchange resins used in water purification, and is calculated from measurements of specific resistance. Gases (carbon dioxide and oxygen) affect the water quality and system performance.

Total solids
Total solids in water include both dissolved and suspended solids. The quantity of total solids is determined by weighing a sample of the feedwater before and after evaporation.

Microbial
Bacteria, viruses, and pyrogens (endotoxins).

Particulates
Sand, dirt, and decay material.

Organics
Organic matter is a broad category that includes both natural and man-made molecules containing carbon and hydrogen. All living matter in water is made up of organic molecules. The most common are by-products of vegetative decay such as tannins, lignins, and humic acid. By knowing the variety of contaminants in the water and the removal capabilities of the different available purification processes, a system can be designed that will produce the water quality required for a pharmaceutical facility. There are a range of purification technologies and we have provided below a brief description of the major purification techniques.



Organic molecule

Major water purification technologies
The chart shown below is a summary of the removal capabilities of different purification technologies versus the contaminants commonly found in water.

PW, HPW, and WFI for pharmaceutical use are produced via a combination of different purification technologies. As with the source water, each pharmacopeia defines the methods of production, but for PW and HPW the technologies utilized is the decision of the system designer, with the only requirement being that the water meets the pharmacopeia regulations for quality. For WFI, to meet the pharmacopeia requirements (all pharmacopeias except Japan), the final purification process must be distillation.

E = Excellent (capable of complete or near total removal) G = Good (capable of removing large percentages) P = Poor (little or no removal)	Major Classes of Contaminants					
	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) Activaled 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.

Purifying the feedwater for use in the pharmaceutical industry requires a series of steps. The objective is to remove the impurities in the feedwater while minimizing additional contamination from the components of the purification system, the storage tanks, the distribution system, and from possible biofilm growth. Selection of the correct purification technologies and the instrumentation to monitor the system are critical to success.

Reverse osmosis

Reverse osmosis is best understood when related to osmosis itself. In one of the experiments performed by everyone in first year chemistry, a semi-permeable membrane (a membrane that is permeable to water but not to salt) is used to separate two solutions; a saline solution and pure water. The pure water will flow through the membrane to dilute the saline solution. This is osmosis. When pressure is applied to the saline solution, the natural process of osmosis can be overcome and even reversed. With sufficient pressure, pure water can be forced out of the saline solution through the membrane and into the pure water side of the vessel. This is reverse osmosis.

In reverse osmosis for pharmaceutical water production, a membrane is also used for the separation of contaminated water. Membranes can be made from cellulose acetate, polyamide, polysulfone, or a variety of proprietary formulations. Two configurations are common: "hollow fiber" and "spiral wound". Hollow fiber membranes look like a group of drinking straws gathered into a bunch, the spiral wound resemble a helix.

Because the quality of water produced by a reverse osmosis apparatus is directly dependent upon the quality of the input water and because effective removal of ions rarely exceeds 97%, reverse osmosis is widely used as a pretreatment process to purify feedwater before introduction into an ion exchange unit or a distillation system.

Distillation

Distillation is the oldest form of water purification and has been utilized by humans since we first boiled water in a cave. It is a unique process because it removes the water via a phase change and leaves behind the impurities. In distillation, water is heated to its

boiling point and undergoes the first of two phase changes, from a liquid to a vapor. The solid ionic materials, the particulates, the microbials, endotoxins, and most of the dissolved organic contaminants are left behind in the boiler. The pure steam is then passed through a cooling coil where it undergoes a second phase change from a vapor back to a liquid. For the production of WFI, the pharmaceutical distillation system is normally fed water that has been pretreated by a variety of other technologies. The pretreatment is used to reduce the costs of maintenance on the distillation system and to ensure the quality of the distillate. Distillation is the only purification method that removes 100 percent of biological materials whether bacterial, viral, or pyrogenic.

Deionization

Deionization or ion exchange is a process also mistakenly called demineralization. The Encyclopedia of Chemical Technology defines deionization as:

"The reversible interchange of ions between a solid and a liquid phase in which there is no permanent change in the structure of the solid."

Ion exchange involves the use of a resin composed of small spherical beads of a styrene polymer, cross-linked with divinylbenzene with chemically bonded functional groups on the surface. For exchange of positive ions (cations), a resin called strong acid cation is used. This resin makes available a hydrogen ion (H^+) for exchange purposes. The exchange of negative ions (anions) uses strong base anion resin. Here, a hydroxyl ion (OH^-) is available for exchange.

Deionizers are generally available in two forms: a two-bed and a mixed-bed configuration. In the two-bed configuration, the cation and anion resins are in two discrete columns or in two discrete layers in the same column. The advantage of the two-bed deionizer is that it can purify a greater volume of water than a comparable mixed-bed system; however, they produce lower quality water.

The mixed-bed deionizer contains an integral mixture of anion and cation resins packed in a single column. Only mixed-bed deionization can produce water with a resistivity of 18.178 million ohms, which is theoretically ionically pure.

Ion exchange technology is designed to remove ionized or charged material from water. Even though water will be ionically pure after the deionization process, the water will still contain non-ionized solid and gaseous materials (organics), bacteria, viruses, and pyrogens. These are not ionically charged species and cannot be removed by ion exchange processes.

Electrodeionization

Electrodeionization (EDI, also known as EDR, CDI, and CEDI) is a technology that combines ion exchange resins, ion-selective membranes and an electrical current to remove ionized contaminants from the water. Reverse osmosis is typically used before EDI to ensure that the EDI stack is not overloaded with high levels of salts. Usually, reverse osmosis removes about 97% of ions. EDI will remove 99% of the remaining ions as well as carbon dioxide, organics, and silica. In electrodeionization, the water passes through multiple

chambers filled with ion exchange resins held between cation or anion selective membranes. Under the influence of an electrical field, the anions and cations migrate across the membranes to the anode and cathode. Typically, EDI product water has a resistivity of 11 to 18.2 MΩ-cm (at 25°C) and a total organic carbon (TOC) content below 20 ppb. Bacterial levels are minimized because the electrical conditions within the system inhibit the growth of microorganisms.

Carbon adsorption

In adsorption, the organic impurities in water form a low-energy chemical bond with the surface of activated carbon. Because adsorption is a technique for removing only organics and chlorine, it is most often used as a pretreatment to remove large amounts of organic impurities prior to other purification processes. Activated carbon is very effective at removing chlorine and other oxidants at rates of 2 to 4 times the chemical weight of the oxidant. By removing the oxidants, the opportunity for microbial growth is increased and must be controlled and monitored.

Ultraviolet light

Ultraviolet light at the 254nm wavelength is used as a bactericide. This wavelength disrupts the ability of bacteria to reproduce. UV at 185nm will break down organic contaminants to CO_2 and water for subsequent removal by ion exchange.

Filtration

Filtration can be performed by one of two methodologies, either depth filtration or membrane filtration. Depth filters can be made of sand in a container or of fiber wound around a core. Both methods mechanically strain out sediment and particulate matter.

Membrane filtration, on the other hand, is physical straining by a single layer of membrane material. The membrane material is produced from man-made resins and can be either hydrophobic or hydrophillic. The pore size is tightly controlled and therefore absolute removal of particulates with diameters larger than the pore size can be achieved. In pharmaceutical systems, filtration is normally limited to the pretreatment section because although filters trap contaminants, it is possible for bacteria to pass through a membrane filter.

Controlling and monitoring the water purification system

Once the feedwater source is known and the purification technologies have been selected, knowing what

parameters need to be utilized to control and monitor the system are critical.

Conductivity/resistivity is an electrical measurement of the number of ions in water and is presented as either a conductance or resistance measurement. The pharmaceutical industry is required to report the conductance of their PW, HPW or WFI. TOC is the determination of the total organic carbon level of the water and is also a required measurement by international pharmacopeia regulations. The chart on the next page provides some guidance for the parameters that should be used for control and monitoring of a pharmaceutical water system.

Calibration and maintenance of the pharmaceutical water purification system

Once the water system is installed, qualified, and validated a preventative maintenance and calibration program must be developed and executed. Calibration of the measurement parameters is required by the pharmacopeia. Periodically, the local or international inspecting authorities will inspect all pharmaceutical water treatment systems to ensure that the pharmaceutical facility complies with local or international regulations. Ultimately, the pharmaceutical company is responsible for validation and ongoing calibration of the water system to make sure that it meets pharmacopeia requirements and passes the inspector's audit.

Summary

This chapter discussed the impurities commonly found in water. We have also detailed water purification technologies and the measurement parameters required for monitoring a water system. By understanding feedwater and the water purification system, a consistent supply of Purified Water, Highly Purified Water or Water for Injection can be ensured.

Unit Process	Parameters													
	Cond Resist	% Rej.	Temp	TOC	pH	ORP	Flow	% Rec	Press, Level	DO	O_3	Turbidity	Volt. (VDC)	Amps (mA)
Particle Filtration			•				•		•					
Catridge Filters	•		•				•		•					
Softeners	•		•				•		•					
Dechlorination							•							
Carbon (GAC) Filters	•			•		•	•		•					
SB S, SMB S Inj.						*								
Break Tank			•						•					
Chemical Addition														
pH Adj. (Acid/Caustic Inj.)					*	•								
Neutralization Tank					*	*	•							
Nano and Ultra Filtration							•		•					
Reverse Osmosis														
Single Pass	•	•	•	•	•	•	•	•	•					
Two/Three Pass	•	•	•	•	•	•	•	•	•					
Desalination	•	•	•	•	•		•	•	•			•		
Ion Exchange														
MB (Auto, Service)	•			•			•		•	•				
CEDI, EDI, EDR, CDI	•	•		•			•	•					•	•
Distillation	•		•	•						•				
Ozone (Injection or destruction)											•			
UV 254 (Microbial control)/ (ozone destruction)											•			
UV 185 (TOC destruct)				•										
Degasifier	•		•							•				
Final Filtration							•		•					
DI Storage Tank	•		•	•					•		•			
Storage Tank	•		•	•					•		•			
Distribution Loop	•		•	•			•		•	•	•			

*Only available with PID control.

Overview of recommended parameters for different unit processes.

Pharmacopeia Overview

The United States Pharmacopeia (USP) defines several types of water for pharmaceutical use, as follows:

- Purified Water (PW)
- Sterile Purified Water (SPW)
- Water for Injection (WFI)
- Sterile Water for Injection (SWFI)
- Bacteriostatic Water for Injection
- Sterile Water for Inhalation
- Sterile Water for Irrigation
- Sterile Water for Pure Steam

In addition to these waters which are common to most pharmacopeia, the European Pharmacopoeia (EP) has also defined Highly Purified Water which meets all the requirements of WFI but may be produced by means other than distillation.

The two commonly used grades of pharmaceutical water are PW and WFI. The requirements are very similar; however, WFI has some additional preparation and microbiological requirements:

- WFI is usually prepared by distillation, although other final purification steps are possible depending on the pharmacopeia.
- WFI meets all the requirements for PW, and includes a specification for bacterial endotoxins (pyrogens).
- Also, the microbial limits (or recommended levels) are lower for WFI than for PW by a factor of 1,000.

The production of Purified Water (PW) and its requirements defined by different Pharmacopeia

"Purified Water is…"	
US Pharmacopeia (USP):	"… obtained by a suitable process"
European Pharmacopoeia (EP):	"… prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method"
Japanese Pharmacopoeia (JP):	"… purified by ion exchange, distillation, reverse osmosis, ultra filtration or by a combination of these methods"
Chinese Pharmacopoeia (CP):	"… obtained by distillation, by ion exchange or by reverse osmosis"
Indian Pharmacopoeia (IP):	"… prepared by distillation, by means of ion exchange or by any other appropriate means"

Pharmacopeia Requirements for Purified Water					
	USP	**EP**	**JP**	**CP**	**IP******
Conductivity (µS/cm)	<1.3*	<5.1*	<2.1*	<5.1*	
TOC (µg C/L, ppb)	<500	<500**	<500	<500	
Bacteria (cfu/mL)	<100	<100	<100	<100	<100
Nitrates (ppm)	NR	<0.2	ND	NH_3 (2 ppm)	
Heavy Metals (ppm)	NR	<0.1***	NR	<0.1	<0.1
pH	NR	NR	NR	5.0-7.0	

* Limit is for 25°C. Stage 1 limits are temperature dependent. See table below.
** Test is optional. May be replaced by Oxidizable Substances Test.
*** Not required if the WFI conductivity requirements are met.
**** India Pharmacopoeia requirements are in process of changing from chemical test to conductivity.
ND – Not detectable
NR – Not required

USP <645> Stage 1 Requirements For non-temperature compensated conductivity measurements			
Temperature °C	**Maximum Conductivity µS/cm**	**Temperature °C**	**Maximum 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		

The production of Water for Injection (WFI) and its requirements defined by different Pharmacopeia

"Water for Injection is…"	
US Pharmacopeia (USP):	"…distillation or a purification process that is equivalent or superior to distillation"
European Pharmacopoeia (EP):	"… prepared by distillation"
Japanese Pharmacopoeia (JP):	"… prepared by distillation or by a combination of reverse osmosis and ultrafiltration"
Chinese Pharmacopoeia (CP):	"… prepared by distillation"
Indian Pharmacopoeia (IP):	"… obtained by distilling"

Pharmacopeia Requirements for Water for Injection					
	USP	**EP**	**JP**	**CP**	**IP**
Conductivity (µS/cm)	<1.3*	<1.3*	2.1	<1.3*	<1.3*
TOC (µg C/L, ppb)	<500	<500	<500	<500	<500
Bacteria (cfu/100 mL)	<10	<10	<10	<10	<10
Endotoxin (EU/mL)	0.25	0.25	0.25	0.25	0.25
Nitrates (ppm)	NR	<0.2	ND	NH_3 (2 ppm)	NH_3 (2 ppm)
Heavy Metals (ppm)	NR	NR	NR	<0.1	<0.1
pH	NR	NR	NR	5.0-7.0	NR

* Limit is for 25°C. Stage 1 limits are temperature dependent.
ND – Not detectable
NR – Not required

Industry Trends for Pharmaceutical Waters

The high purity water treatment industry has progressed and changed significantly in recent years.

Major trends include:

- Establishment and global harmonization of pharmacopeia water regulations
- Increased industrial safety and environmental regulations
- Industrial multi-national companies (MNC) seek international integrated supply solutions
- Green engineering has improved energy efficiency and significantly increased demand for reclaimed and recycled water
- There is a shift from chemical treatment (except ozone) to physical treatment
- Ozone (gas) is increasingly being used to sanitize water systems
- Process engineers prefer total solutions from a single source
- Installation of new systems outweigh replacements and upgrades of existing systems
- Added regulatory emphasis on on-line measurements for "real-time process control, decision and intervention"
- Increased emphasis on proactive and preventive maintenance instead of reactive and hurried repairs
- Single-use components and systems utilization is increasing with low cost disposable technologies.

Trend requirements for measurement components and systems will be met by METTLER TOLEDO Thornton with progress in instrumentation technology, innovative Intelligent Sensor Management (ISM®) and real-time control.

Ensuring Pharmaceutical Water Compliance in a PAT Environment

The quality and safety of pharmaceuticals and biologics rely on the purity of water used in their production. Increasingly stringent pharmacopeial requirements and the introduction of new initiatives such as Process Analytical Technology (PAT) and Quality by Design (QbD) places added challenges to life sciences companies. A new analytical sensor technology, Intelligent Sensor Management (ISM), offers advanced process control to simplify the achievement of PAT goals, and to ensure the quality of pharmaceutical waters at all times.

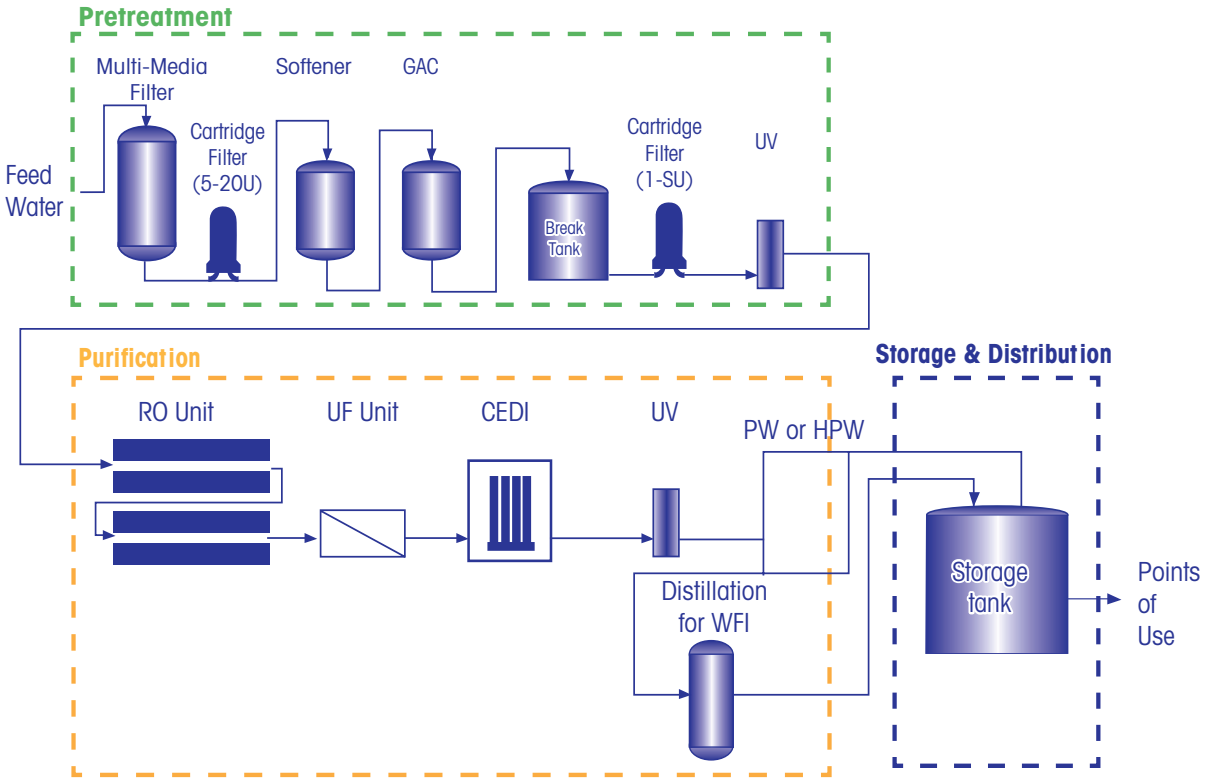
Water for Injection, Purified Water, Highly Purified Water, Pure Steam Condensate, Water for Hemodialysis, Sterile Water for Injection, etc…: the variety of pharmaceutical waters and water systems means their production is becoming an increasingly specialized process that requires highly dependable instrumentation.

In 2002, the FDA launched a new initiative called "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach." This scheme has led to the FDA encouraging the adoption of Process Analytical Technology (PAT) tools as a mechanism for designing, analyzing, and controlling pharmaceutical manufacturing processes for the purpose of making safer, compliant products more efficiently with less dependence on end-product testing. PAT encourages manufacturers to develop a complete understanding of the process by determining and defining the Critical Process Parameters (CPPs), and monitoring them accordingly in a timely manner, preferably with at-line or in-line instrumentation. This concept is particularly critical for water production as water is the most widely used raw material and excipient by every producer worldwide. In addition, water production is a 24/7/365 operation and the water is a continuously manufactured material, not typically produced in batches that can be sequestered, so constant monitoring is essential for continuous manufacturing operations.

Process control vs. product control

The importance of water monitoring and analysis during and after production is not in doubt; however, the viewpoints on the merits of end product water testing and water system process control vary according to function. The owner of the water system (Production or Engineering) has process analytics measurements and physical measurements throughout the water system from the incoming feedwater to pretreatment to purification to final distribution, in order to measure and control water production and quality. Some of these in-process measurements include conductivity, TOC, dissolved ozone, pH, ORP, silica, turbidity, flow rate, % rejection, tank level, temperature, and pressure.

When a water system is designed, these measurements are required for the water system to verify functionality and performance of each purification step (IQ and OQ). During water system production, the process owners monitor these various measurements throughout the purification process to ensure that each step in the process is working properly. An example of the dozens of measurements throughout a purification system is shown below. For example, temperature is a CPP to demonstrate proper thermal sanitization (in a hot loop), or differential pressure across a filter is a key



Schematic of a Pharmaceutical Water Preparation System

measurement to determine the proper time to change the filter.

The purpose of end product quality testing is to make certain that a sample of the batch/lot is safe, meets compendial standards, and is of a consistent and acceptable quality. The term "quality" is often used but not defined. In the case of high purity waters such as Purified Water and WFI, "quality" usually means that specific requirements for conductivity, TOC, microbial count, and endotoxins (WFI only) are met and found to be acceptable to ensure water quality and consistency, as water is a key ingredient. Depending on the local pharmacopeia, other chemical tests may be required.

The Quality Assurance group, responsible for end product quality testing, will test the water according to general test chapters USP <643> Total Organic Carbon, USP <645> Water Conductivity, and other specific tests that have traditionally been performed in the laboratory. This is where water differs from other pharmaceutical products. Most pharmaceutical products are produced, inspected, tested, and released in a batch/lot process. Water production is not a batch process. Water is produced continuously, it is re-circulating constantly, and it is often consumed 24/7. There is no opportunity or desire to quarantine the water while QA testing is being conducted. As a result, the water is used in production, at some risk, while (or before) the testing is completed.

The challenge to Quality Assurance is to test the water frequently enough to have confidence that the water being used (or has already been used) in production is safe and meets specifications at the time of use. A traditional method of achieving this has been to sample the water system at all use points on a timely basis. Depending on the size and design of the water system, and the risk to the final drug product, Quality Assurance collect samples from use points 1-3 times/day, possibly more or less frequently. For a facility with 50-100 use points, this requires significant resources to accomplish TOC and conductivity testing. Testing more samples per day assumes more cost and resources and additional delays, but the user feels at less risk. Testing fewer samples or use points lowers costs, but carries more risk.

Physicochemistry of measurements in high purity pharmaceutical waters

The challenges with measuring high purity pharmaceutical waters are not confined to frequency and costs of lab testing. The waters themselves pose exceptional analytical problems when trying to measure the "quality" of the water in a lab environment, especially for conductivity and TOC measurements. The typical conductivity of Purified Water or WFI may be anywhere from 2.0 µS/cm down to 0.055 µS/cm (0.5 - 18.2 MΩ-cm) as measured in the water system piping or tank. However, when that water is removed

from the distribution system, collected in a clean container, and transported to the laboratory, the conductivity of the cleanest water increases to ~0.8-1.2 µS/cm with exposure to air, even in the cleanest environments.

This increase is due to the immediate reaction of ambient CO_2 with water to make carbonic acid (H_2CO_3). H_2CO_3 is a weak acid which partially dissociates to H^+ and HCO_3^- ions, and the immediate creation of these ions causes the conductivity to increase to ~1 µS/cm. You cannot control or prevent this reaction with a naturally-occurring molecule such as CO_2. In addition, there are risks of organic vapors (perfume, human breath, soaps) and contamination from all components used to transport samples. Any miniscule residue of cleaning reagent or fingerprints on the container will adversely affect the sample.

But the increase in the conductivity due to CO_2 also obscures the true quality of the water as measured by conductivity. An example of this is based on a METTLER TOLEDO Thornton R&D study of two types of water (on-line 1 and on-line 2, see Figure 1). Both are high purity

there is a loss of information about the water quality under these conditions. While there remains a clear distinction in the conductivities of the two on-line data sets, the two off-line data sets are indistinguishable from each other. The off-line samples have a wider degree of variability (not measurement noise, but impurity noise) when going from on-line to off-line, resulting from variable amounts of ambient CO_2.

Also, the small increase in conductivity in on-line 1 at sample 35, from 0.055 µS/cm to ~0.07 µS/cm is completely undetectable in the off-line sample. In applications where ultra-low ionic control is critical to the process, an on-line measurement is the only approach for detecting small changes.

Similar results are observed for TOC measurements. Samples of water collected in a container, after exposure to the environment, always have a higher TOC measurement than those measured in the on-line pipe. In this case, it is not CO_2 that causes the increase: the water is so pure under these circumstances (typically <50 ppb, often <10 ppb) that it is the container clean-

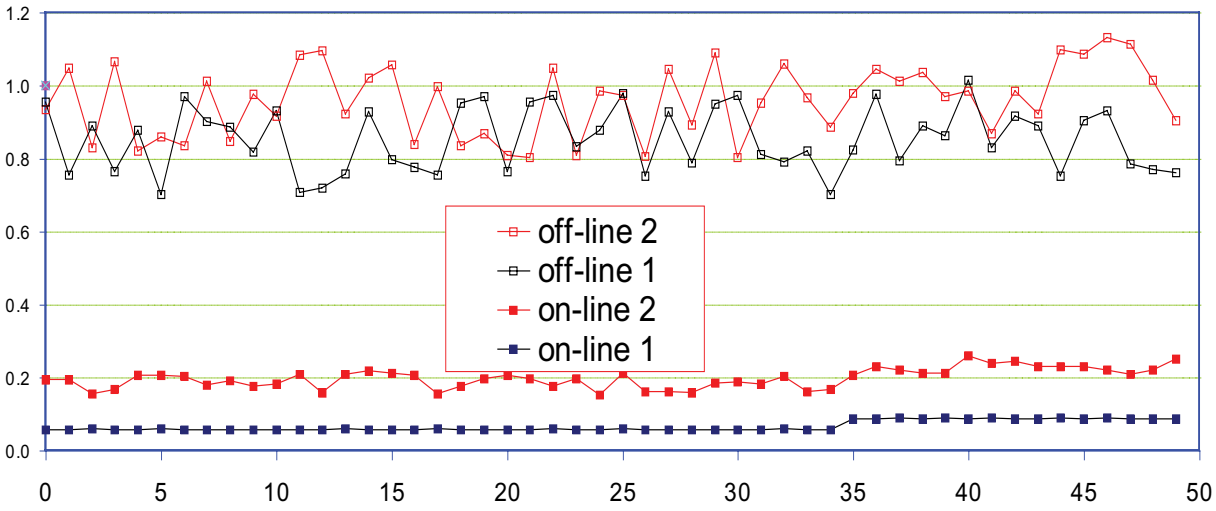


Fig. 1: Comparison of on-line and off-line conductivity measurements of two high purity water samples

samples <0.2 µS/cm (>5 MΩ-cm), but there is a clear distinction between on-line 1 and on-line 2. Further, a very small increase in conductivity of on-line 1 is detected at sample 35. Both of these samples are measured in real time, inside the on-line water system distribution loop, without exposure to air, using the same instrumentation.

The other two samples of water (off-line 1 and off-line 2) are the same waters as measured on-line, and measured with the same sensor and transmitter, except that they are measured 5 minutes after dispensing into a clean container. The increase in conductivity for both sample types is completely understood since this is a result of the ambient CO_2 in the environment. However,

liness (soap residue, fingerprints, etc.), organic vapors in the air, technician's breath, perfumes, etc. that always result in a higher reading from the off-line sample.

With regard to conductivity and TOC measurements in high purity waters, there is not a problem with the laboratory instrumentation or procedures; it is the sample that has changed.

Benefits of "intelligent" on-line process analytics for compendial high purity waters

While many measurements described above are used to control the water system, conductivity and TOC measurements are the most closely monitored attributes

that indicate the water purification system is under control for ionic and organic impurities. For process control benefits, water system engineers insist that these be on-line, real-time measurements. Measurements made an hour or a day later do little to control a continuously operating water purification system. Since conductivity is a highly temperature-dependent measurement, these conductivity measurements should also be temperature-compensated for the best process control practices (and according to USP <1644> Theory and Practice of Electrical Conductivity Measurements of Solutions).

Intelligent Sensor Management (ISM®) is an exclusive METTLER TOLEDO innovation in process measurement, which supports regulatory initiatives such as PAT by improving in-line and on-line process control with intelligent digital sensing and communications and real-time process analysis.

ISM is an advanced digital sensor technology that includes predictive diagnostics, sensor calibration away from (or as part of) the process, Plug and Measure start up, and electronic documentation. These features provide users with a better understanding of their process with greater reliability, process safety and efficiency; lower cost of ownership; and improved traceability.

For conductivity and associated temperature measurements, UniCond® sensors with ISM technology store unique factory and user sensor calibration information and increase measurement accuracy with in-line calibratable electronic circuitry within the sensor and digital communication to the transmitter. Total organic carbon (TOC) sensors with embedded digital conductivity sensors with ISM save previous calibration and system suitability records, while displaying time to calibration and time to maintenance reminders.

ISM technology permits TOC sensors to display long-term Peak and Average readings from the water system, simplifying compliance record keeping by identifying two measurement points, peak and average, which are configurable for up to 24 hours of data. In addition, continuous measurements are monitored and displayed. This combination of Peak and Average and continuous TOC measurements support the PAT initiative and facilitate real-time control of CPPs.

In addition, an ISM sensor's individual performance is monitored continuously during operation to predict maintenance requirements, including calibration schedules, to avoid costly unplanned process downtime. Consumable sensors such as pH electrodes benefit from ISM predictive indicators which identify sensor life status (aging) and time until maintenance. Service and calibration intervals for the exchange of consumables can be scheduled in advance, saving time and money.

ISM addresses limitations of traditional analog sensors

Intelligent Sensor Management helps to eliminate issues for maintaining water system compliance. For example:

- Sensor failure: The Dynamic Lifetime Indicator (DLI) and Time to Maintenance (TTM) tools offer specific data warnings that a sensor is aging or needs maintenance.
- Calibration date planning: ISM sensors inform in advance of an upcoming calibration to avoid missed or late calibration.
- Provide critical regulatory information: Electronic documentation demonstrates that required tests have been performed with data to support regulatory compliance.
- System calibration: The METTLER TOLEDO Thornton UniCond Calibrator and Pharma Waters Verifier are the only tools that permit calibration of both the digital sensor and the measurement circuit to ensure the measurement system is in compliance with global pharmacopeia standards.

Plug and Measure – swiftly exchange pre-calibrated sensors to save time and cost

One of the unique features of ISM technology is the ability of each sensor to maintain its own calibration dataset, allowing the user to perform a calibration at a location other than where the sensor is installed, if necessary. With this feature comes the ability to pre-calibrate sensors in a controlled environment rather that at the actual process. Pre-calibrated sensors may then be exchanged at the measurement point in minimal time. Sensors can be calibrated in batches and stored with their fresh calibration data until needed in the process environment.

With real-time sensor status data available at any time, the process can run more efficiently and critical measurement loops can be monitored for potential faults. ISM can also help to identify those sensors that could possibly become the cause of the next unscheduled downtime. Sensor status information, such as sensor aging, helps optimize maintenance intervals;

thus, the operator need intervene only when action is required.

ISM provides a built-in counter to track CIP and SIP cycles

Digital ISM sensors have a built-in Clean-in-Place (CIP) and Steam-in-Place (SIP) counter, which detects when the sensor is exposed to thermal cycles. Upon connection to an ISM transmitter, the status data from the digital sensor is automatically loaded into the transmitter. When the maximum limit of thermal cycles allowed at this particular measurement point is exceeded, an alarm condition is raised. As a result, a sensor that could potentially fail in the process is identified and cannot be utilized. Additionally, there is no need to manually record each sensor's CIP/SIP history, as the number of cycles is stored in the sensor itself.

M800 ISM iMonitor displays sensor status

Multi-parameter ISM transmitters provide simultaneous measurement parameters

METTLER TOLEDO Thornton offers a complete array of digital sensors, and a broad combination of process control sensors can be utilized on a single multi-channel instrument, thereby reducing the need for multiple types of transmitters, multiple spare parts, multiple control panel installations, and differing user interfaces. All METTLER TOLEDO ISM sensors provide enhanced measurement performance while communicating vital information for process management and control in real time.

ISM sensors are available for the following parameters:

- conductivity (temperature)
- TOC
- pH
- ozone

Transmitters and sensors with ISM capabilities provide the tools necessary to take full advantage of the benefits of digital on-line measurements. Critical points throughout a system are monitored and controlled on-line with data provided locally at point of use, or remotely.

Conclusion

From a total cost of ownership perspective, the application of on-line measurement systems in pharmaceutical waters production represents a different cost allocation than laboratory sampling. The cost basis for laboratory sampling includes the cost of sampling materials, clean containers (utilities cost for hot clean water), and labor (for documenting sampling locations, and collecting and measuring samples). Typical sampling regimens may include 1-3 samples/day for all use points. Even when there are few samples and use points this still needs to be done consistently every operating day. However, after the cost of installation of the online transmitters, the data is transmitted for free thereafter via a data collection system. Therefore, with on-line measurements there are significant labor/time savings that can be used for more critical operations.

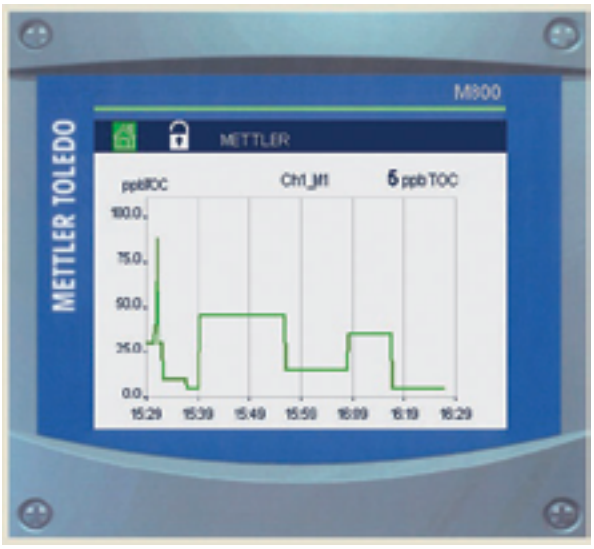
On-line measuring allows for continuous measurements at selected critical points, and especially at point of use (POU) locations. End product analysis ensures product quality in real time. According to USP <645>: "The selected sampling instrument location(s) must reflect the quality of the water used." In this case, the measurement point may be on the return to the storage tank after the last POU. If the water quality meets regulatory requirements on the return, it is within specification at the previous POUs.

The single greatest advantage of on-line measurements is removal of uncertainty about product quality. For the off-line QA systems, these end-control measurements are made an hour, a day or longer after the samples are collected. When there is an out-of-specification result for TOC, for example, costly investigations commence and multiple decisions need to be made

regarding the water and the product that came in contact with the water since it was last tested.

A low risk, simple, cost-effective alternative is to use continuous on-line measuring instruments with the predictive diagnostic abilities of Intelligent Sensor Management. Such systems produce measurement results every second to monitor the whole water system for real-time process control, a goal of PAT, and in addition, monitor sensor "health" for significantly improved production safety.

M800 transmitter monitors multiple ISM sensors



M800 transmitter displays real-time trending, peak and average TOC

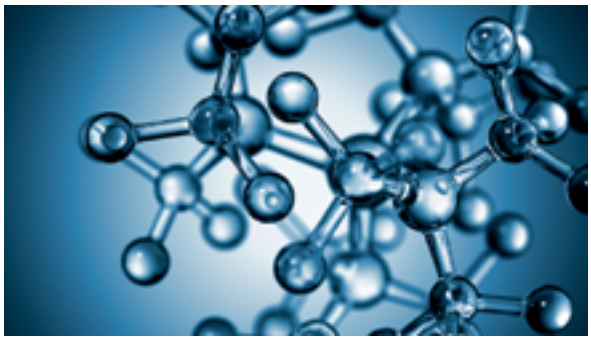
Total Organic Carbon Measurement
is a Key Control Point for Pharmaceutical Water Systems

The control of organic impurities in pharmaceutical water systems is often misunderstood. The waters produced in these systems come into contact with humans (and animals) through ingestion, injection, transplants, transdermally, and via other medical processes. It is often thought that the organic impurities in the water must be kept low to protect the patient. In fact, we ingest (and inject, transplant, etc.) organics all the time through food, drink, and organic medicines. Any residual organics in pharmaceutical waters are miniscule relative to the amount we eat, drink, or take as medicines.

There are two principal reasons why the pharmacopeias require total organic carbon (TOC) measurement and control in PW and WFI systems. Firstly, the quantity and trending of TOC are key indicators of the overall purification process control. Secondly, TOC is a vital food source for bacteria, and there can be a qualitative relationship between TOC and bacterial counts.

A water purification system starts with drinking water as a raw material (which is often an unknown quantity) and produces a compendial water (PW, HWP, WFI) in a continuously-operating series of purification processes (see "Pharma Waters Overview"). Each purification process is designed to remove a specific type(s) of impurity such as particles, hardness (Ca^{2+} and Mg^{2+}), free chlorine, organics, metals, gases, microbes, etc. in order to generate a water that is safe and proper to use in pharmaceutical tests, processes, and products. Measurements such as differential pressure and % Recovery indicate the efficiency and performance of an RO system. In this regulated environment TOC measurement is not just a required measurement of the finished water, the TOC value is a key indicator of the overall system purification process. A low and stable TOC is a signal that the carbon bed, reverse osmosis, downstream filters, electrodeionization, and other individual purification steps are properly purifying the water. Not only does the TOC measurement indicate a low TOC value for the water, it also indicates a level of process control of the manufacturing (purification) system.

Another misunderstood reason for TOC measurement is that they are related to microbial counts. A question



Organic structure

that is regularly discussed at science meetings (and that USP used to regularly receive from end-users) is, "I perform on-line TOC measurements – can I stop doing microbial testing?" The answer is "no". Since 2008, USP has been very precise in the chapter (643) Total Organic Carbon.

"A TOC measurement is not a replacement test for endotoxin or microbiological control. While there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation."

At best, TOC measurement is an indicator of the microbial and endotoxin control, but it is not a replacement for those tests.

For example, assume that 0.5 µm spherical microbes consist of ~10% carbon and has a density of 1 g/mL. If the water has 500 ppb TOC and all of the TOC is bacteria, this would be ~10^6 microbes/mL, or approximately 10,000x the WFI limit for control of microbes! Another way to state this is the following: at the 10 cfu/100 mL limit for WFI, the amount of TOC in that sample is 0.00005 ppb! In other words, TOC measurements cannot be used to count bacteria, but they can be used to monitor and control the total water purification process.

This philosophy can also be adapted to processes that utilize water for cleaning. While a variety of acid and caustic solutions are often used to rinse piping and vessels for Clean-in-Place (CIP) application, the typical final rinses of the hardware is with PW or WFI. Historical methods for validating the piping/vessel cleanliness and health are the use of swab samples to

collect residue and then perform HPLC analysis. These results take hours or days if extensive sample preparation is required. But the motivation to reduce costs by reducing system downtime has caused the industry to ask, "Can I determine if the system is clean in a more efficient manner?" A common approach is the use of TOC and conductivity measurements as the final water rinses are occurring. If the TOC and conductivity of the effluent (water leaving the system) is equal or similar to the quality of water entering the system, then the bulk effluent and vessel is clean. [Note – This approach does not ensure that some chemicals have not adhered to the walls of the system. However, the regular acid/caustic cleaning and sanitary designs do confirm that there are no residual chemicals.]

Meet USP <643> and EP Regulatory Requirements with METTLER TOLEDO Products		
Pharmacopeia Requirement	**USP <643> / EP/JP Specifications**	**METTLER TOLEDO Product Performance** 4000TOC Sensor 5000TOCi 5000TOC Analyzer
Limit of detection	0.050 mg/L	<0.001 mg/L
Calibration	Required	NIST traceable
Distinguish inorganic carbon from TOC	Required	Measures initial conductivity
Meet system suitability	85 – 115%	Typical performance is 95-100%
On-line or off-line measurements	Either	Capable of on-line and off-line

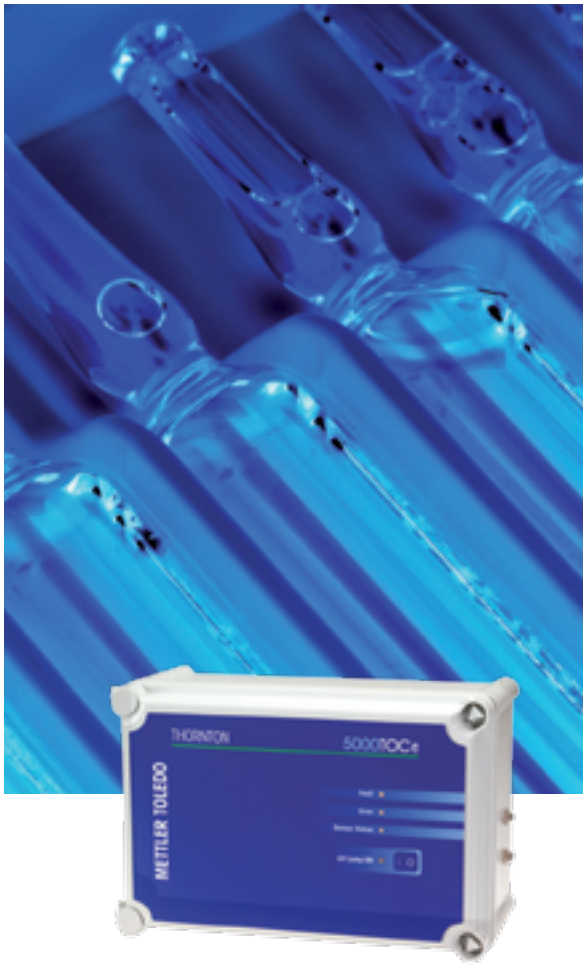
Improving Water System Performance
Continuous Real-Time TOC Measurements

Safeguarding water quality at points of use necessitates rapid identification of total organic carbon excursions. On-line, continuous flow TOC sensors ensure that even brief excursions will not be missed.

Organics are introduced into natural water systems by leachates in soil, typically from the decomposition of vegetation, animal waste, and soil runoff. Organic compounds in water are a concern at all levels of water purity from potable water to pure waters used in the manufacture of pharmaceuticals.

The source water used for the production of Purified Water and Water for Injection is drinking water as indicated in the major pharmacopeia. Potable water quality can vary seasonally according to climatic changes and municipal treatment strategies, which results in varying TOC concentrations. In pharmaceutical manufacturing, organics are a contaminant that needs to be controlled as they are a food source for bacteria in the water purification system and can contaminate the final product.

A change in the TOC load in the water system can be the result of fluctuating TOC in the source water, degradation in the water system components, a drop in the efficiency of the water purification system or development of bio-film. This change can potentially influence microbiological control. Because variations within a water system can often occur both suddenly and unexpectedly, rapid detection of deviations in system performance is critical for the purpose of minimizing TOC load impact.



Continuous measurements

For this discussion, a continuous measurement is defined as one that monitors a physical, chemical or biological property of a process, and the measurement is followed by another measurement within seconds. This continuous measurement technology is based on a constant flow of sample through the sensor and the ability to measure the process change in a brief time period. An excursion can be rapidly identified with this type of TOC sensor. Fast identification allows an immediate response and intervention to prevent non-compliant water from being used in the production or from reaching the UPW water storage tank. This rapid response capability can result in significant cost savings through quick detection and isolation of system faults. Continuous flow TOC sensors provide real-time measurements that minimize the effect of excursions on pharmaceutical waters.

Excursions and real-time recovery

In addition to measurement and control, TOC sensors are used to monitor deviations, sometimes rapid or intermittent, from a baseline measurement. These excursions are caused by the introduction or release of contaminants into the purification process. It may be a brief disruption with duration of seconds or minutes caused by a valve opening and closing for example, followed by a return to baseline reading. Alternatively, it may be a longer disruption which results in a long

term baseline drift or change such as an RO membrane defect. It can also be normal cyclical behavior due to water consumption or sanitization cycles. For these types of excursions, rapid, continuous, and real-time measurement technology is an invaluable tool for TOC measurements.

When the disruption is brief or intermittent, a fast update rate allows the excursion to be detected, whereas a slow sample rate measurement is likely not to detect the intermittent failure. If there is a significant baseline shift, a slow sampling frequency measurement system is similar in terms of its detectability to a continuous measurement system. Both fast and slow technologies will see the shift. In the case of a measurement technology where there is a combination of fast response time and continuous measurement, a close and rapid (real time) inspection of the process is possible. This combination of speed and continuous measurements provides an immediate opportunity for non-compliant water to be directed to drain or recirculated, rather than inadvertently used for product contact directly or indirectly, such as a cleaning/rinsing process.

In a series of real-time recovery tests, three conductivity based TOC systems (CF-TOC, TOC A and TOC B) were compared by performing testing on select typical organic chemicals. All chemicals were prepared at concentrations of 10 ppb carbon. High purity water (TOC <5 ppb) was flushed through each analyzer for 30 minutes. An organic solution was pumped into each of the units for 5 minutes and the TOC data observed for up to 1 hour to track the response. The delay from a common manifold was calculated to be 21 ± 5 seconds for all systems tested. The continuous flow TOC technology (CF-TOC) and two other technologies were evaluated under these test conditions.

A test was performed with 10ppb TOC 2-propanol (isopropyl alcohol or IPA). The CF-TOC sensor responds in less than a minute of the injection time to IPA with a proportional response (Figure 1). By comparison, TOC A responds similarly, but 5 minutes after the beginning of the excursion. In a similar test (Figure 2), TOC B responds proportionally to the TOC disturbance, but 8 minutes after the IPA is injected. Again, in both cases (Fig 1 and 2), the 5 minute excursion is over before TOC A and TOC B detect it. The CF-TOC technology responds to the excursion within 2 minutes after its appearance, and it also detects the disappearance of the excursion in real time. When discrete batch measurements in the laboratory were more common, sampling 1 liter of water which took about 5 seconds

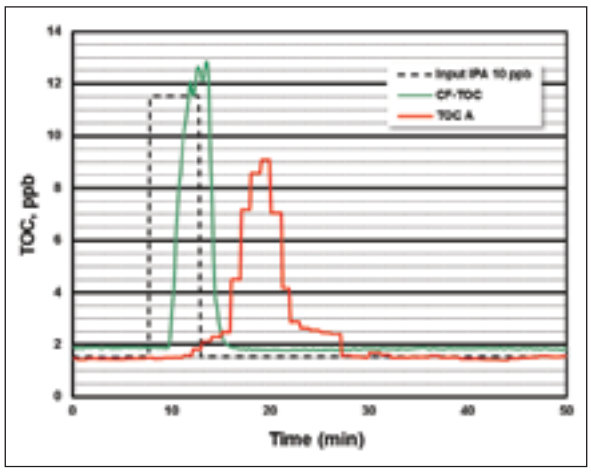


Figure 1: IPA response curves. CF TOC vs TOC A.

to produce (out of a 10 hours day, this represents sampling of <0.014% of the time) means that the water is not being monitored >99.98 % of the time. Since water production is a continuous purification and consumption process, a water system can be enhanced by real-time detection and analysis.

When an excursion occurs, it is essential to relate the accuracy of a TOC sensor to its ability to respond and identify the upset condition in a timely manner. Directly stated, if the duty cycle of the measurement system is low, the ability to detect an event is low. If the duty cycle is high, the ability to detect is high. Unless an event is being monitored, it will not be detected.

If the excursion duration is regarded as an integration window over which we determine the response factor from a TOC sensor, a sensor with continuous measurement technology would respond immediately and be more accurate because the response is within the time that the excursion was occurring. Conversely, if a sensor's main response is after the upset condition due to a slow response time, then its integrated error is

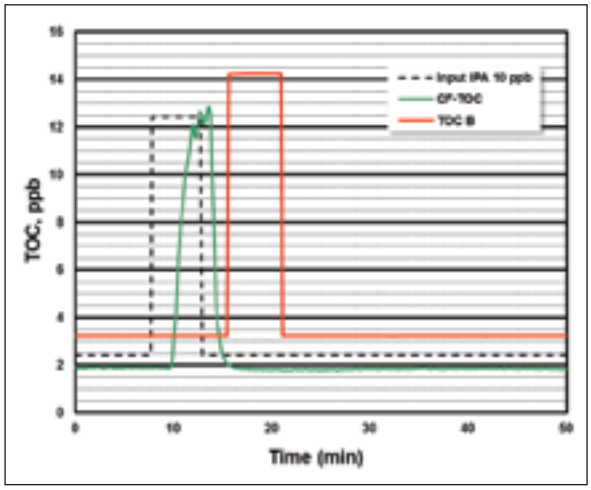


Figure 2: IPA response curves. CF TOC vs TOC B.

higher, and it exhibits a greater response error. A real-time recovery error would incorporate both speed of response and the percentage recovery or sensor response. Then the definition of the real-time error would be:

$$\text{Real Time Recovery Error \%} = 100 \times \left(\frac{\text{Abs}\,[R(t) - I(t)]}{I(t)} \right)$$

Where I(t) is the input disturbance at time t, R(t) would be the sensor measurement in response to I(t) at time t, and Abs is the absolute value. A perfect response would be when R(t) = I(t) at all times because the response is instantaneous and equivalent to the disturbance. The total recovery error for a perfect sensor would then be the sum of all the real-time recovery errors and would be equivalent to zero, i.e.

$$\text{Total Recovery Error for a perfect Sensor} = \sum_{t=0}^{t} \text{Real Time Recovery Error } (1) = \text{Zero}$$

In actuality, these equations are relative errors as they are calculated as deviations from a baseline response which can vary from one type of sensor to the other.

If the total recovery error for all the tested sensors was calculated for IPA using data collected from response curves in Figures 1 and 2, the plot in Figure 3 would be the result. Figure 3 shows that the longer the delay in the response from the TOC sensor after an excursion, the greater the accumulated error. The total error for the CF-TOC is lower because of the accuracy and the response within 2 minutes of the beginning of the disturbance.

Figure 4 shows the final value of the total recovery error at the end of the experiment. As shown in the bar graphs, the total recovery error is dependent on the organic compound and the sensor being used. The bar graphs represent the total recovery error for a TOC measurement system grouped by organic compound. The lower the bar graph value, the closer that sensor responded to a perfect response for the organic compound injected. The varying errors show that none of the sensors responded perfectly for all tested organic compounds. Where NR is shown, this indicates that there was No Response or a less than 1ppb shift from the baseline was observed during the measurement.

Each instrument has a variable real-time recovery error depending on the organic compound injected. Each of these compounds represents one of thousands that may be present in a water purification system that makes up the TOC measurement.

In real water systems, both speed of response to an excursion as well as recovery of response back to normal conditions are important in real-time monitoring. A TOC measuring system needs to respond rapidly to an excursion and then just as quickly recover when the excursion has passed.

Conclusion

A Real Time Release, continuous flow TOC sensor provides rapid response to an excursion with an opportunity in real time to respond to and divert contaminated water. This reduces downtime associated with excursions, maximizes efficiency, and reduces cost associated with product loss, manpower, and equipment. In brief, it allows closer control of the entire water purification process through the understanding of the UPW system characteristics. It ensures that end users are receiving reliable good quality water for the various uses in production.

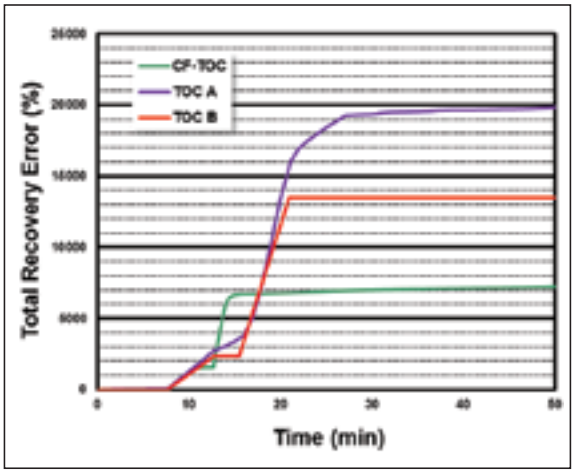


Figure 3. Total error accumulated over time

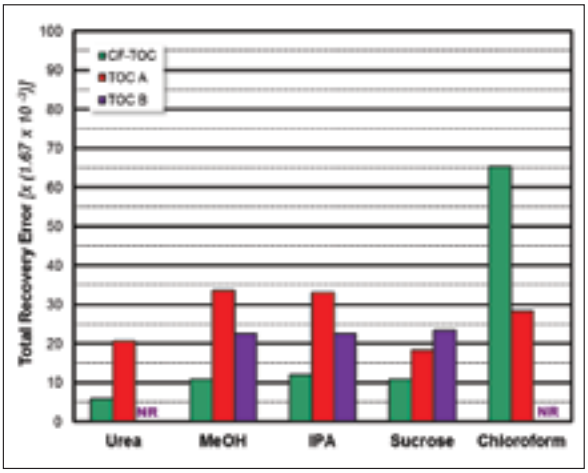


Figure 4. Summary of Total Recovery Error – NR is no response

Real-time TOC Analysis
Safeguards Water Purity

Case Study

To prevent bacterial growth, pharmaceutical-grade water systems require precise monitoring and control of TOC. A European producer of pure water systems trusts in-line Thornton instrumentation for ensuring customers of consistent water quality.

USF Water Purification GmbH designs, manufactures, and maintains reverse osmosis and continuous electrical deionization Purified Water (PW) and Highly Purified Water treatment systems. The company serves pharmaceutical industry customers throughout Austria and Eastern Europe. The team has its roots in the early 1990s (at one time the team was part of US Filter, which was acquired by Vivendi and subsequently by Siemens Water). USF produces systems which sanitize using hot water at 80 °C employing a fully automated process. The company offers instrument calibration service and maintenance programs as a convenience for its customers, which include Actavis, Teva, Pfizer, Novartis, Boehringer Ingelheim, Baxter, Fresenius, Ebewe and GL Pharma.

In-line process monitoring offers real-time analysis
METTLER TOLEDO Thornton measurement systems have been specified by USF engineers for nearly two decades. The innovative features, technical capabilities and robust solutions of Thornton products have helped USF to develop and preserve a long standing reputation for providing high quality water systems to leading pharmaceutical companies in the European marketplace.

The Thornton 5000TOC Sensor, in combination with the multi-channel 770MAX multi-parameter transmitter, is a high-performance system for determination of TOC levels in pharmaceutical-grade water, while satisfying requirements of international pharmaceutical regulations. The Thornton sensor provides accurate TOC measurement and response in less than a minute. Managing Director, Walter Lintner stated, "Alternative batch-style systems require significantly more time to generate a response, which may result in lost production in cases of serious TOC contamination."

TOC testing is required by the USP and EP
In 1996, in USP 23 Supplement 5, conductivity and TOC measurements were officially recognized as the best means to ensure ionic and organic impurity control in PW and Water for Injection (WFI). The advent of USP < 645 > Water Conductivity and USP < 643 > Total Organic Carbon introduced test methods that 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 regulations for the measuring instrumentation used for TOC and conductivity measurements such as system suitability, limit of detection, instrument resolution, and calibration requirements for sensors and transmitters. Concurrently, all of the USP wet chemistry tests for bulk waters were deleted, with the exception of microorganisms and endotoxins (for WFI only). The EP TOC test, listed as 2.2.44, is identical to USP < 643 > in terms of limits and methods. Subsequent updates to global pharmacopeias have continued to emphasize TOC and conductivity measurements for regulatory oversight.

Why use TOC sensors for the PAT initiative?
TOC sensors are used to quantify the concentration of organic impurities in water. To ensure water quality and water purification system performance, constant monitoring is critical to allow action to be taken in a timely manner, especially in the case of organic excursions. It is this approach that is embodied in the FDA's Process Analytical Technology (PAT) initiative. The PAT initiative promotes the use of real-time measurements with the objective of ensuring good product quality. This allows Real Time Release of product and leads to a more efficient operation. In cases where a TOC instrument will be used for the USP / EP-relevant

TOC measurements in PW or WFI, the selected technology should comply with the current monographs in USP < 643 > and / or EP 2.2.44. (See "Improving Water System Performance – Continuous Real-Time TOC Measurements").

Service and support are paramount

Mr. Lintner states, "From the point of view of price, performance, and ease of use, the Thornton 5000TOC Sensor with 770MAX transmitter is the system of choice for on-line measurement of TOC. Our purification systems typically show TOC levels down to 5 ppb in the product water. Low TOC levels do not support growth of bacteria, thus yielding better control for our pharmaceutical customers."

Thornton TOC sensor and monitoring systems are robust and easy to maintain. Mr. Lintner continues, "One of the positive aspects of Thornton instruments is the software – it is straightforward to use and allows us to calibrate quickly and efficiently. We use Thornton instruments because the product, value, and applications support all benefit the customer."

M800 transmitter

5000TOCi ISM TOC sensor

In-line TOC Monitoring
Reduces Production Downtime

Case Study

Off-line TOC monitoring missed critical diagnosis in a newly installed Water for Injection (WFI) storage tank. After installation of Thornton's on-line 5000TOC sensor, the cause of the problem was found, avoiding costly production downtime.

TOC analysis in pharmaceutical-grade waters is used to detect organic contaminants. For a pharmaceutical water system, the most critical performance qualities in TOC instruments are fast response and high accuracy. The consequence of an excessive TOC level is that the production line must be stopped and the water system thoroughly inspected, a process that may require up to a week's lost production. Real-time determination of TOC can signal an upset that may be symptomatic of an impending failure in the pure water system.

TOC system meets international requirements

The Thornton 5000TOC[1] sensor in combination with the multi-parameter, multi-channel 770MAX transmitter is a high-performance system for determination of TOC in pharmaceutical-grade waters. The system satisfies the international requirements of pharmaceutical standards. Thornton's 5000TOC provides an accurate TOC measurement, and responds to changes in TOC in less than a minute.

Off-line monitoring is not always sufficient

Established in 1973, Hanmi Pharmaceutical Co. Ltd. has become the second largest pharmaceutical company in South Korea, with 2009 gross sales of USD 550 million. Through its Vision 2020 program, Hanmi is focused on becoming the 20th largest pharmaceutical company in global ranking by that year. Its products include Amlodipine (hypertension), Slimmer (obesity), and Guardix (anti-adhesion tissue bonding).

Following the installation of a new WFI storage tank at one of Hanmi's main production sites, an off-line testing method indicated that TOC was above specifications. Another manufacturer's brand of analyzer had intermittently indicated TOC variations during sampling. However, the batch system measuring interval was long and the results were inconsistent; therefore, determining the cause of the TOC increase was problematic.

Real-time TOC measurement helps find leak

At this production facility, there are four conductivity systems installed in the water system. To this, Hanmi added the Thornton 5000TOC and 770MAX transmitter. The Thornton TOC sensor indicated real-time TOC variations in the water system, leading to the conclusion that TOC was directly related to system water level. Upon further investigation, a hole no larger than a pin was discovered in the upper part of a WFI storage tank's insulating water jacket. This was allowing unprocessed water to leak into the pure water loop when the water jacket was close to full. Following repair of the leak, TOC measurement was restored to required levels.

Control panel shown with Thornton 770MAX transmitter and 5000TOC sensors

With the discovery of this pinhole in the tank jacket by continuous on-line monitoring of TOC, Hanmi Pharmaceutical was able to fix the problem while avoiding a costly and time-consuming plant shut-down. The customer expressed satisfaction with the accuracy, reliability, process stability, and low maintenance of Thornton's on-line process monitoring instruments.

1 The model 5000TOC sensor is now available as model 5000TOCi with enhanced capability.

Leading Water Treatment Solution Provider
Chooses METTLER TOLEDO Thornton

Case Study

When Leo Pharma and Veolia Water Solutions & Technologies developed a cutting-edge water system and needed fast, accurate, and reliable water sensors, they turned to METTLER TOLEDO Thornton.

Leo Pharma (Vernouillet, France) is a producer of anti-thrombotics in pre-filled syringes, blister packed tablets of diuretics, and several leading antibiotics. Leo Pharma invested nearly USD 20m in a new syringe filling line to increase syringe production capacity to 18,000 syringes / hour. The new line carries out cleaning, siliconization, and sterilization of syringes in situ. This requires the use of WFI at different rinse stages on the syringe manufacturing line and clean steam for Steaming-in-Place. WFI and clean steam are supplied from a water purification plant designed and installed by Veolia Water Solutions & Technologies – using METTLER TOLEDO Thornton pure water instrumentation – which is housed in a new purpose-built "clean utilities" building.

The pre-filled syringes produced in the Vernouillet, France facility are destined for the international market including the USA, so the FDA inspects the manufacturing facility. This means that both WFI and clean steam have to be produced from purified water and that all three of these substances have to comply with the USP. Clean steam, used in the filling machine and for sterilization in situ, has to meet the same specifications as the WFI.

Advanced pure water production

The clean utilities water purification system consists of two sections: production, storage, and distribution of purified water; and production, storage, and distribution of WFI and clean steam. Veolia uses METTLER TOLEDO Thornton instruments in both sections to ensure accurate and precise measurements of the water being used, and also to make certain that the purification equipment is working at each stage.

The purified water production system is designed to produce a continuous output of 4,000L / h of USP purified water without any chemical additions. Town water is first filtered, using a 10 µm cartridge filter, to remove any particulate material and then softened in duplex softeners.

The next stage of treatment is reverse osmosis. Permeate from the reverse osmosis unit is further purified by continuous electrodeionization (CEDI) which combines ion exchange and membranes to produce a continuous output of purified water with conductivity typically less than 0.2 µS/cm and silica less than 50 µg/L. METTLER TOLEDO Thornton's cutting-edge line of

conductivity sensors ensures optimal conductivity is being monitored in this stage.

Dissolved carbon dioxide gas, which is poorly removed by both reverse osmosis and CEDI, is extracted from the reverse osmosis permeate by membrane degassing using a hydrophobic membrane which allows gas to pass through it.

Membrane degassing completely eliminates the need to dose caustic soda (the usual means of carbon dioxide removal in RO membrane systems). For ultimate security, the reverse osmosis and CEDI streams are duplicated and, when there is no demand for makeup from the purified water tank, the system runs in recirculation mode to prevent stagnation and minimize bacterial growth.

Benefits of the Thornton solution

"For the purified water production skids, we have chosen the Thornton 770MAX which enables us to simplify our electrical cabinet design. The 770MAX is a compact and multi-channel transmitter designed to ensure process efficiency with minimal effort on our part," said Hervé Caron, Project Manager at Veolia Water STI.

Water for Injection

WFI is produced by distillation, as required by the EP. In order to minimize both the operating costs and the environmental impact, Veolia Water Solutions and Technologies carried out a study which showed an 8-column multiple effect still to be the most energy efficient option. The still delivers 2,800 L / h of WFI at 85 °C and atmospheric pressure, into an insulated 7,000 L vertical tank from which it is continuously circulated around a 250 m long distribution loop supplying six points of use. The complete system is designed to meet all the requirements of cGMP and the ISPE Baseline Guide, and is fabricated from 316L stainless steel electropolished to 0.6 µm Ra.

The WFI water system is sterilized by pressurized hot water at 1.5 barg in a fully automatic sequence. The sequence is automatically logged for validation purposes. The conductivities are monitored on WFI loops by multiple METTLER TOLEDO Thornton transmitters including the 770MAX. The 770MAX is coupled with the 5000TOC analyzer which measures a USP critical parameter: total organic carbon. "METTLER TOLEDO Thornton's 'Smart' sensors give us peace of mind for the commissioning phase; particularly the automatic 'plug-and-play' sensor setting recognition," emphasizes Hervé Caron.

The second point on the purified water loop is used to feed the clean steam generator, which is identical in principle to a distillation plant except that there is only one column and the steam is not condensed. The generator produces 660 kg / h of clean steam at a pressure of 2 bar which is used for in situ sterilization of vent filters, purified water and WFI tanks, feeding the autoclave, and for the Steaming-in-Place of process equipment. Each WFI generator is fitted with METTLER TOLEDO Thornton transmitters for design consistency.

Automatic control of the clean utilities plant is by six independent programmable logic controllers linked via a PROFIBUS DP network. The operator interface complies with 21 CFR Part 11. The design, construction and start-up phases of the clean utilities plant were managed under Good Automated Manufacturing Practice, allowing the project to be executed in an orderly, standardized form recognized by the pharmaceutical industry.

The Value of Measuring TOC
in CIP and Cleaning Validation Applications

In pharmaceutical manufacturing, process vessels, fermentation tanks, process piping, medicine packaging machines, and other equipment that comes in contact with the product must have a user-defined and validated cleaning method. Thorough cleaning is required to avoid cross contamination between product batches as well as preventing microbial buildup on vessel walls and equipment. Examples of cleaning are WFI rinse or Steam-in-Place (SIP). Clean-in-Place (CIP) frequently employed for process vessels, typically uses an acid followed by a caustic rinse. A final rinse(s) with WFI ensures that all chemicals used to clean the vessel have been removed and that the vessel can be put back on-line for production. In all cases where a WFI or PW rinse is part of the cleaning process, the vessel or equipment can be considered "clean" when the TOC and conductivity of the water flushing out to drain is the same as that of incoming water. [Note - Any retention of residue or biofilm on the vessel walls is not included in this analysis.]

The current trend for the control of cleaning applications is to flush the final WFI or PW rinse for a predetermined amount of time, monitoring conductivity until a specified water quality is reached. Once the water quality has improved sufficiently, grab samples of the final rinse product are taken for lab or batch analysis of TOC concentration or other analysis such as High Performance Liquid Chromatography (HPLC). This time-consuming procedure not only causes significant downtime of equipment, it also may introduce sample contamination. Continuous on-line monitoring of TOC and conductivity in real time during the final rinse phase of the cleaning cycle, rather than grab or batch sample analysis, is an enhanced strategy for monitoring the cleaning process of the final rinse cycle.

By continuously monitoring the TOC and conductivity quality of the final rinse water, better control of the process can be maintained, saving both time and water. The Thornton family of TOC and conductivity sensors provides continuous, on-line, real-time monitoring, ensuring that the CIP or cleaning cycle is determined by water quality and not a pre-set time or number of rinse cycles, which may result in prolonged wasted cycles or improper and incomplete cleaning, and therefore non-compliance.

5000TOCe and SST/CAL module

Meeting TOC and conductivity instrumentation requirements for cleaning processes

Appropriate cleaning methods and validation processes are defined by individual pharmaceutical users for their specific equipment and in accordance with internal Good Manufacturing Practice. However, because the WFI or PW waters used in CIP and cleaning applications come in contact with process equipment and process vessels, these waters must meet USP standards for TOC and conductivity measurements.

These TOC standards include a limit of detection of 0.05 mg carbon/L (50 ppb), the ability to calibrate the sensor, and that the sensor meets a System Suitability Test (SST). This SST challenges the TOC sensor with two standard solutions [500 ppb sucrose and 500 ppb p-benzoquinone] and requires that the response efficiency of these standards, adjusted for the TOC of the water used to make these solutions, be between 85% and 115%.

770MAX transmitter and 5000TOCe TOC sensor

The ability to quickly and easily perform the calibration and SST in-house is an important feature of any TOC sensor used in CIP and cleaning processes, as it can further reduce costly equipment downtime as well as allow closer control of internal validation practices. In instances where low or no flow to the TOC sensor exists due to gravity drainage of the process vessel or other restrictions, the accessory Thornton Pump Module can be used in conjunction with the Thornton 4000 and 5000TOC sensor families, providing constant delivery of the water sample to the sensor for accurate monitoring.

Ensuring the Absence of Ionic Impurities with Conductivity/Resistivity Measurements

The measurement of water's electrical conductivity, or resistivity, can provide an assessment of total ionic concentration (the presence of impurities) and hence its suitability for use in pharmaceuticals manufacture.

The most common method of measuring low-level ionic impurities in ultrapure water systems is on-line instrumentation. This technique is industry-tested in the identification of trace ionic contaminants, where the addition of 1 ppb of NaCl increases the conductivity of water from 0.055 to 0.057 µS/cm at 25 °C. This difference is readily measurable with today's instrumentation. The measurement of water's electrical conductivity is described in microsiemens/cm (µS/cm) and is measured by a conductivity meter and sensor. Resistivity is described in megaohm-cm (MΩ-cm), and is the inverse of conductivity.

Conductivity sensors are also employed in TOC measurements where they are used to quantify the change of non-ionic organic compounds to conductive species following exposure to deep ultraviolet light.

Conductivity testing is required for USP Purified Water, Water for Injection, Water for Hemodialysis, and Pure Steam Condensate.

Effective July 1, 2004, the European Pharmacopoeia (EP) revised its conductivity requirements for the EP monographs for WFI and Highly Purified Water. These waters have the same conductivity limit test required for USP Purified Water, WFI, Water for Hemodialysis and Pure Steam. This test requirement is harmonized with USP <645> Water Conductivity test.

UniCond 2-electrode conductivity sensor with ISM

Calibration Solutions
for Pharmaceutical Waters

METTLER TOLEDO Thornton has developed simple analytical calibrators for use with the respective UniCond® sensors and M300 Analog transmitter firmware to easily demonstrate that the conductivity and temperature measurement circuitry complies with the electronics accuracy specification of USP ‹645› Water Conductivity as well as global pharmacopeia requirements.

Pharma Waters Calibrators
Conductivity Calibrators are used to adjust the electronic measurement circuit located in either a transmitter or a sensor to comply with the electronics accuracy specifications. Calibration is used to check, adjust, or standardize a measuring instrument, usually by comparing it with an accepted standard. Periodic conductivity calibration is required to meet global pharmacopeia regulations.

Conductivity Calibrator

Pharma Waters Verifiers
Pharma Waters Verifiers are uniquely designed tools which validate the accurate measurement display at the transmitter and provide verification of communications between the end of the cable and the transmitter.

Pharma Waters Verifier

Pharma Waters Verifiers confirm the accuracy of the electronics at specific points within USP ‹645› guidelines.

Thornton Calibrators and Verifiers:

- Easy to use unit provides confirmation of the conductivity and temperature accuracy requirements of the measurement electronics to meet USP ‹645› Water Conductivity
- Simple menu driven transmitter interface walks the user through the verification process
- Accurate to ± 0.1µS/cm; ± 2°C
- Includes NIST traceable resistors for global acceptance
- Compliant to USP, EP, JP, ChP, IP, other international pharmacopeias
- **Available for use with the Thornton M800 and M300ISM for UniCond sensors and M300 analog transmitters for analog sensors. Applications**
- Required for compendial pharmaceutical water applications to demonstrate compliance with instrument requirements of USP ‹645› and global water conductivity regulations
- Recommended for all low conductivity pharmaceutical water applications <5 µS/cm.

Clean-in-Place Systems Manufacturer
Relies on METTLER TOLEDO

Case Study

In-line conductivity measurement technology plays an essential role in the efficient operation of Clean-in-Place (CIP) systems, ensuring the highest possible levels of cleanliness as well as optimal control over the cleaning solutions. A leading manufacturer of CIP systems has selected Thornton conductivity instrumentation for their performance and reliability.

Suncombe Ltd is one of the UK's leading mobile Clean-in-Place systems manufacturers and hygienic process engineers.

Established in 1961, they have a wealth of knowledge in designing and manufacturing cleaning and hygienic process technology for the biopharma, food, and other hygiene critical industries. Suncombe's products are supplied to UK, European, and international companies who demand high quality, reliable CIP systems.

CIP application

The CIP cleaning procedure is a multistep process. Wash solutions are prepared in storage tanks and used in specific 'recipes' to carry out the cleaning of vessels, pipework, etc. A final rinse with pure water takes place at the end of the cycle. Control of various process stages such as start of dosing of alkaline or acid, or rinsing with water is carried out effectively using in-line conductivity measurement. The system detects the conductivity of the solutions and provides outputs to the local process control system to manage the CIP program.

New mobile CIP system

When Suncombe launched its latest range of portable CIP systems, it required the highest standard of instrumentation. Dave Adams, director at Suncombe said, "Our CIP systems are designed to incorporate top quality equipment to ensure that they provide reliable results in every use. We selected METTLER TOLEDO Thornton to provide conductivity instrumentation on our MobileCIP™ systems, as we use their products extensively with excellent results. We view METTLER TOLEDO as an excellent strategic partner for our systems as they provide excellent service and support."

Conductivity equipment expectations

The conductivity instrumentation in mobile CIP systems for pharmaceutical customers requires a number of conditions including:

- Tri-Clamp® sensor connections
- Conductivity ranges from 0.01 uS/cm to 500 mS/cm
- Material certificates for wetted parts, including USP <88> Class VI
- Panel mount transmitters providing analog outputs for both temperature and conductivity
- Sanitary designed sensors

METTLER TOLEDO solution

METTLER TOLEDO Thornton provided a conductivity system using the M300 dual-channel conductivity transmitter. This allows two conductivity sensors to be connected to the same transmitter. The M300 comes in two convenient sizes, ¼ DIN specifically for panel mount applications and ½ DIN for field, post or wall mount applications.

The system uses a Thornton 2-electrode conductivity sensor for final rinse control as well as a Thornton 4-electrode conductivity sensor for cleaning agent control. Both of the sensors are hygienically designed and have Tri-Clamp process connections as well as 3.1 B and Class VI material certificates to satisfy the requirements of the pharmaceutical industry.

Reliable, Cost-effective Sanitization
the Power of Ozone

Sanitization of pharmaceutical water systems has historically relied upon either chemical or thermal processes. But today, ozone production systems are being installed in an increasing number of water systems as an alternative sanitization method. Ozone (O_3), an unstable triatomic form of oxygen, is 2,500 times stronger as a disinfectant than chlorine. In addition, ozone reacts with organics to break them down ultimately to CO_2, thus removing color and odor, and eliminating a food source that could encourage biofilm growth. Ozone, when dosed at the proper concentration and monitored before and after the ozone destruction system, meets the pharmacopeia regulation for "no added substances" to the water.

Ozone molecule

The increased use of ozone as a sanitization method over the past decade can be attributed to a number of reasons including effectiveness in microbial and biofilm control, and avoidance of harmful halogenated by-products, and cost efficiencies due to the low cost of ozone preparation and the zero cost of ozone removal (compared to traditional chemicals).

In addition, pharmaceutical manufacturers are concerned about the rising expenditure for regularly sanitizing a large pharmaceutical water system with heat or steam, and the consequent impact on their operating budget. As energy costs increase, the use of ozone becomes more attractive, contributing to a trend that is expected to continue.

Application and Control of Ozone Sanitization for Pharmaceutical Waters

Ozone is a strongly oxidizing gas that is injected into water or electrolytically generated in water. Dissolved ozone converts back to oxygen in a matter of minutes, depending on the temperature (chart below) and pH of the water, so it must be generated on demand. Ozone leaves virtually no harmful breakdown products, unlike chlorine and its related compounds which can produce trihalomethanes and other carcinogenic compounds.

Liquid sanitizing chemicals or biocides such as hypochlorite and related compounds are liquid/liquid mixtures. Recent studies have demonstrated that biofilm can be more hydrophobic than PTFE, preventing liquid biocides from penetrating a bio-layer. Ozone, as a powerful oxidizing dissolved gas, penetrates and destroys biofilm to a much greater extent.

Dissolved ozone decay rate at pH 7:

Temp °C	**Half life**
15	~30 min
20	~20 min
25	~15 min
30	~12 min

Ozone generation

Traditional ozone generators pass dry air or oxygen between high voltage electrodes where the corona discharge converts some of the oxygen to ozone. This is the same phenomenon that occurs during a lightning storm. The gas mixture is then contacted with the water, either through a tank diffusion system or in a pipe with a venturi ejector. Intimate contact is made to maximize dissolution of the ozone. Excess air is vented outside the system.

Another ozone generation method is to electrolyze water using a specialized catalyst to yield ozone as well as oxygen and hydrogen. The hydrogen is vented outside the system and the ozone is generated and released directly into a side stream of the process water.

Ozone for disinfection in pharmaceutical water production

The sanitization of pharmaceutical water systems typically relies on heat/steam, traditional chemicals, or ozone. Heated water systems must ensure that temperature is maintained adequately throughout the circulating water loop. Heating large volumes of water and maintaining it throughout the system represents a large energy load. The heat lost by piping, even if insulated, puts an additional burden on plant air conditioning systems. As a result, hot water systems are known for their high energy consumption and utility costs.

Traditional chemical treatments, while effective from a microbial perspective, bear the burden of not only the chemical costs, but the costs of chemical removal and

the added downtime and risks to ensure that the chemicals have been rinsed out of the water system.

Ozone is recognized by the industry as an excellent alternative for disinfecting pharmaceutical, biotech, and personal care products water systems. It complies with international pharmacopeias stating there can be "no added substances" since it will decay into oxygen under UV light. It is necessary to monitor for ozone after the UV ozone-destruction lamps to ensure the ozone has been fully removed before the water is distributed to points of use in production or lab areas.

Monitoring ozone

In a continuously ozonated system, on-line measurement and control of ozone are typically required. To achieve reliable sanitization of these water systems, ozone monitoring is required at three critical points (see Figure 1).

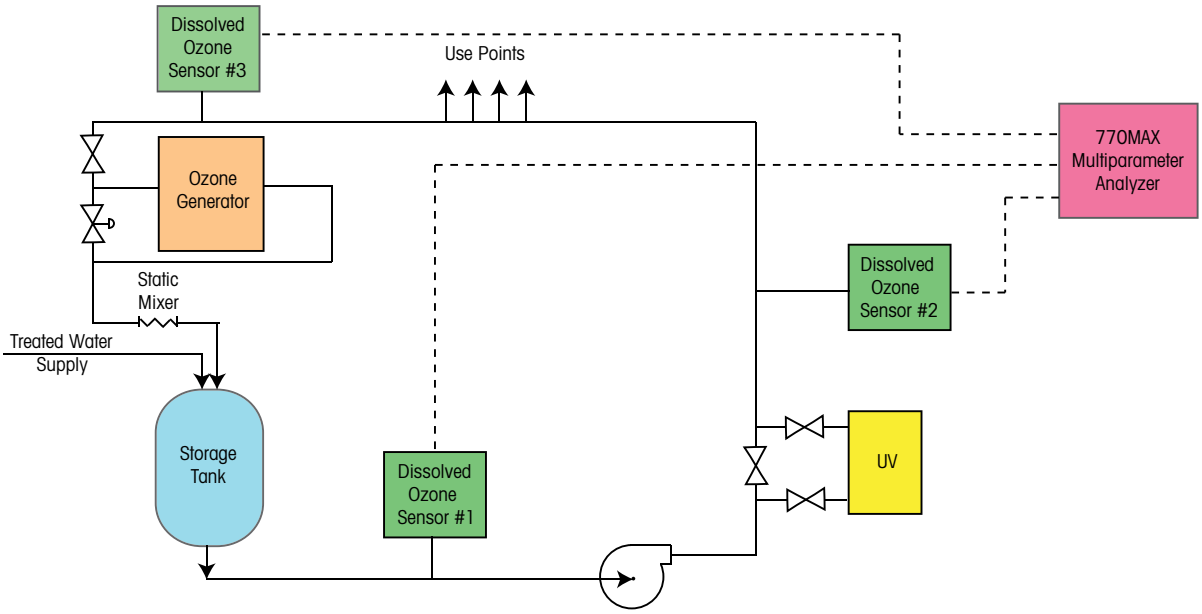


Fig1: Ozone monitoring points

The first ozone measurement point (sensor #1) is after the storage tank to ensure the proper concentration of ozone is maintained for effective disinfection. It also provides the signal for controlling the ozonation rate required from the ozone generator. The second measurement point (sensor #2) is after the ozone destruct system (254 nm UV light) to ensure the decomposition of the ozone before the water is distributed to production points of use. The third measurement point (sensor #3) is utilized when sanitizing the entire distribution loop. It is located at the end of the circulation loop to make certain that the required level of ozone is reached and maintained throughout the distribution system during the sanitization cycle. During this cycle the water is not used for production. The ozone concentration maintained in the storage tank and the time and concentrations used for the sanitizing cycle are established for the individual system and its standard operating procedures (SOPs). The concentration could be as low as 0.03 ppm for normal continuous operation to as high as 0.35 ppm for the sanitization cycle.

For a pure water system using ozone disinfection, the ozone instrumentation plays a critical role for proper control of disinfection and periodic sanitization to help achieve regulatory compliance.

Instrumentation for measurement and control of ozone

Dissolved ozone instrumentation is available with a range of capabilities and costs. For measurements with excellent performance, high reliability, and ease of maintenance at reasonable cost, METTLER TOLEDO Thornton offers dissolved ozone measurement with a choice of three multi-parameter instrument platforms.

Individual measurements

For basic pharmaceutical water applications, the METTLER TOLEDO Thornton M300 analyzer/transmitter provides one- or two-channels of measurement of dissolved ozone and/or conductivity plus temperature in any combination. This is a cost-effective choice where few measurement points are required.

Multi-parameter measurements

To meet the requirement of many measurement points, the METTLER TOLEDO Thornton M800 or 770MAX analyzer/transmitters can accept up to four analytical sensors in any combination of ozone, conductivity, and TOC. The latter two are required by most international pharmacopeias. For pharmaceutical water systems requiring three points of ozone plus conductivity with temperature measurements, these four-channel transmitters with up to eight analog outputs provide the ideal platform. In other systems, the four analytical channels of the M800 or 770MAX can also provide measurements of dissolved oxygen, pH or ORP in any combination, plus two additional channels for flow measurement.

The M800 platform utilizes digital sensors with Intelligent Sensor Management (ISM). ISM sensors include the complete measuring circuit and digital signal conversion within the sensor plus memory that retains all sensor data, calibration, and diagnostics information, all within the sensor. ISM provides predictive maintenance tools with such capabilities as the continuously updated Dynamic Lifetime Indicator (DLI) and Time To Maintenance (TTM) that can help avoid unneeded maintenance time and expense with ozone and other sensors. ISM sensors can also be calibrated remotely and then installed on-line with no extra effort.

Conclusion

Dissolved ozone is an effective sanitizer for pharmaceutical, biotech and personal care products water systems. In order to ensure that concentrations or absence of ozone meet requirements during the sanitization cycle as well as during normal operation, ozone instrumentation plays a critical role for proper measurement and control. METTLER TOLEDO Thornton offers reliable solutions for ozone measurement with a range of especially convenient instrument platforms to match individual system requirements.

M300 transmitter

M800 transmitter

Dissolved ozone sensor

Critical Ozone Measurement
in Purified Water Systems

Case Study

Ozone is a powerful disinfectant but also a strong oxidizing agent that can damage pharmaceutical products. In purified water systems, ozone determination is vital for purity assurance purposes. Christ Pharma & Life Science in Shanghai, China chooses Thornton ozone sensors for their accuracy and durability.

Christ Pharma & Life Science GmbH, and Christ Pharma & Life Science (Shanghai) Ltd. (formerly part of the BWT Group), with operational centers in Europe and Asia, offer a comprehensive spectrum of technologies for producing all grades of water required in R&D and production environments in the pharmaceutical and life sciences industries. In Shanghai, Christ Pharma & Life Science has a manufacturing facility where their LOOPO purified water storage and distribution system is produced. LOOPO maintains the quality of Purified Water, Highly Purified Water and Water for Injection right up to the point of use. The system has passed both China's GMP test and the relevant European drug production tests.

Analytical performance is key

In the LOOPO system, pharmaceutical purified water is disinfected using ozone generated from the water itself, thus lowering the risk of external contamination resulting from ozone produced from ambient air. As ozone is a strong oxidizing agent that could be damaging to final products, the water is irradiated with UV light before the first point of use to ensure all ozone is destroyed. Precise ozone measurement in the LOOPO system is therefore very important, and the system operators must be alerted to abnormal ozone values so that corrective measures can be taken. When points of use are closed for a complete disinfection of the unit, the UV lamp is turned off and water with a high ozone content is circulated through the whole system. The disinfection level is directly reflected by ozone measurement. Ozone is determined at three positions in the LOOPO distribution system: before the UV lamp, after the UV lamp, and in the loop return past the last point of use.

Important function of Thornton instruments

For ozone detection, Christ employs METTLER TOLEDO Thornton's dissolved ozone sensor and compatible transmitter. Thornton high-quality analysis instrumentation plays a key role in Christ's purified water systems, enabling their customers to achieve excellent quality in their pharmaceutical products. According to Gu Lingna, Senior Project Manager at Christ Pharma & Life Science (Shanghai) Ltd, "The performance of the ozone sensor system has a direct bearing on the reliability of the disinfection process, so it is of great importance. The Thornton instrumentation operates stably and works consistently well."

Ozone probe offers durability and low-maintenance

The main body of the probe is made of corrosion-resistant stainless steel. A reinforced silicone membrane offers high-level performance as well as the durability required in the application environment. Gu Lingna reports that, "In actual use the ozone membrane can have a lifetime of up to two years with regular maintenance." The electrolyte in the probe must be changed periodically, but this maintenance is very simple and can be accomplished in a few minutes. After changing electrolyte or membrane, it is necessary to polarize the probe in an ozonated sample for an extended period. Where necessary, a single probe can test the ozone content of more than one sample. For

each sample, before the actual ozone reading is taken, sufficient rinsing time is required to achieve a stable ozone value.

Flexible measurement and monitoring of up to four channels

Along with the ozone sensor, METTLER TOLEDO Thornton offers a range of compatible analyzers. The Thornton M300 transmitter provides dual-channel measurements with the ability to monitor a combination of ozone and conductivity sensors. The 770MAX model can accept up to four channels of ozone, TOC and conductivity sensors in any combination. Due to the transmitters' convenient and flexible configuration, and clear and simple interface, Christ Pharma & Life Science GmbH and Christ Pharma & Life Science (Shanghai) Ltd. have employed both on their various systems to display ozone content.

Dependable performance

Since 1995, Christ has used an ozone generator on over 300 of its pharmaceutical purified water systems. Parts of these systems typically incorporate Thornton ozone sensors. "Experience has demonstrated that this probe is of consistently high quality and durability", says Gu Lingna.

LOOPO is a registered trademark of Christ Pharma & Life Science GmbH.

M300 transmitter

Dissolved ozone sensor

In-line Analytics Website

Dedicated to the Pharmaceutical Industry

The METTLER TOLEDO Process Analytics website for the pharmaceutical industry is packed with information on how our in-line measurement solutions improve process reliability, increase production yield and reduce operating costs.

Visit our Pharmaceutical Competence Center to:
- Discover our extensive portfolio of sensors and transmitters.
- Download white papers and application notes, watch videos and webinars.
- Find out how intelligent measurement solutions can prevent batch losses and simplify sensor documentation.

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