Application Note

THORNTON
Leading Pure Water Analytics

The Use of TOC Measuring in CIP and Cleaning Validation Applications

Background

Pharmaceutical manufacturing is one of the most strongly regulated industries in order to protect patient safety. This is particularly true in regards to the manufacture, use and testing of Water for Injection (WFI), Pure Water (PW) and Highly Purified Water (HPW). The United States Pharmacopeia (USP) and European Pharmacopeia (EP) and all other pharmacopeias set strict guidelines for water quality (chemical and microbiological impurities) and testequipment as used in pharmaceutical and biotech manufacturing.

TOC (Total Organic Carbon) and conductivity are closely monitored as a means of ensuring proper chemical qualities for these waters have been maintained throughout the manufacturing process. The use of WFI, HPW, and PW in cleaning and validation of process equipment and process vessels is common practice, and these waters, as well as the instrumentation used to test them, are required to meet the USP Chapter <643> or EP 2.2.44 guidelines for TOC. The TOC limit for Pure Water is 500 ppb at 25°C. (Note: the Japanese Pharmacopeia has specified a TOC limit of 400 ppb when measured offline and 300 ppb when measured online for process control). See Table 1.

Table 1a - Pharmacopeia requirements for Purified Water

Attribute*	**USP 34**	**EP 6.6**	**JP 16**
Production Method	Suitable Process	Suitable Process	Distillation, ion-exchange, UF, or combination
Source Water	US, EU, Japan, WHO drinking water	Human consumption	JP water specification
Total Aerobic (cfu/mL)†	100	100	100
Conductivity (µS/cm at 25°C)‡	1.3 (3 stage)	5.1 (1 stage)	2.1 offline
TOC (mg/L)	0.5	0.5 (optional)	0.5
Nitrates (ppm)		0.2	Not detectable
Heavy Metals (ppm)		0.1 ††	Not detectable
Oxidizable Substances (/100 mL)		<0.1 mL** 0.02 KMnO**	< 0.10 mL 0.02 KMnO**

Note * : All tests are maximum, unless otherwise stated.
Note † : Microbiological testing is considered to be harmonized, with the exception noted that the EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter
Note ‡ : Limits are temperature dependent
Note ** : Alternative to TOC
Note †† : Not required effective Jan 1, 2009 if WFI conductivity requirements are met

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Table 1b - Pharmacopeia requirements for Water For Injection (WFI)

Attribute*	USP 34	EP 6.6	JP 16
Production Method	Distillation or suitable process	Distillation	Distillation, RO with UF, from Purified Water
Source Water	US, EU, Japan, WHO drinking water	Human consumption	JP water specification
Total Aerobic (cfu/100 mL)†	-	10	
Conductivity (µS/cm at 25°C)‡	1.3 (3 stage)	1.3 (3 stage)	2.1 offline
TOC (mg/L)	0.5	0.5	0.5 (0.3 for control)
Bacterial Endotoxins (EU/mL)	0.25	0.25	0.25

Note * : All tests are maximum, unless otherwise stated.
Note † : Microbiological testing is considered to be harmonized, with the exception noted that the EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter
Note ‡ : Limits are temperature dependent

Use of TOC and conductivity in cleaning validation applications

In pharmaceutical manufacturing, process vessels, fermentation tanks, process piping and medicine packaging machines and other equipment that come in contact with the product must have a user defined and validated cleaning method. Thorough cleaning is required to prevent cross contamination between product batches as well as from microbial buildup on vessel walls and equipment. Examples of cleaning processes include a rinse with WFI, HPW or PW, chemical cleaning Clean In Place (CIP) followed by a WFI rinse or Steam in Place (SIP) cleaning. CIP, typically used for process vessels, uses an acid rinse/spray followed by caustic treatment, and finally multiple WFI rinses.

This final use of WFI ensures that all chemicals used to clean the vessel have been removed and that the vessel can be put back online for production. In all cases where a WFI or PW rinse is used, the vessel or equipment can be considered "clean" when the TOC and conductivity of the incoming water is the same as that flushing out to drain.

The current trend for the control and monitoring of TOC and conductivity in typical CIP and other 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 is improved sufficiently, grab samples of the final rinse product are taken for time-consuming lab or batch analysis of TOC concentration or other analysis such as HPLC. This not only causes significant downtime of equipment, but also may introduce sample contamination. Continuous online 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 online 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 thus non-compliance.

THORNTON 5000TOCe sensor and 770MAX transmitter

Meeting TOC and conductivity validation 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 Practices (GMP). However, because the WFI or PW waters used in CIP and cleaning applications come in contact with process equipment and process vessels, these waters are required to 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 System Suitability Test 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%.

The ability to quickly and easily perform the calibration and System Suitability Test in-house is an important feature of any TOC sensor used in CIP and cleaning processes, as it can further reduce costly equipment down-time as well as allowing 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 TOC sensor to provide constant delivery of the water sample to the sensor to ensure accurate monitoring.

Conclusion

TOC and conductivity have been process monitoring points within the pharmaceutical industry for many years. The ability to use the continuous online real-time measurement technology of the Thornton TOC sensor for cleaning validation and CIP applications can greatly improve the efficiency of the process as well as reduce equipment downtime, resulting in higher product yields.

In addition to continuous online monitoring of TOC and conductivity to improve CIP and cleaning processes, validation and calibration according to USP or EP requirements are essential in maintaining regulatory compliance in pharmaceutical manufacturing. The Thornton 5000TOCe sensor in conjunction with 770MAX transmitter meets the strict requirements of USP <643> and EP 2.2.44 for TOC measurement. This reduces downtime associated with excursions, maximizes efficiency, and reduces cost associated with product loss, staffing and equipment. System Suitability Testing as well as sensor and transmitter calibration, key components of both mandates, can be conveniently performed in house. A number of products such as Thornton pre-packaged System Suitability standards, calibration kits and validation packages can reduce equipment maintenance labor and downtime and help to ensure FDA compliance and Good Manufacturing Practices.

Thornton calibration/SST module with 5000TOCe sensor

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