

USP Acceptable TOC Levels for Pharmaceutical Water: How to achieve them?

M. Y. Z. Abouleish, PhD, R. H. Clifford, PhD

Meeting the regulations and validation rules is an important task for the pharmaceutical industry. In order to be compliant with the regulations and meet the required quality and safety standards, the Pharmaceutical industry must develop economical and competitive production and cleaning methods, which in turn will help the industry develop appropriate operational methods¹.

Compliance with the regulations must be maintained within the pharmaceutical industry throughout the different processes. The processes can be grouped under three general categories: Preparation (includes processing and innovation), Production, and Waste Discharge (Figure 1).

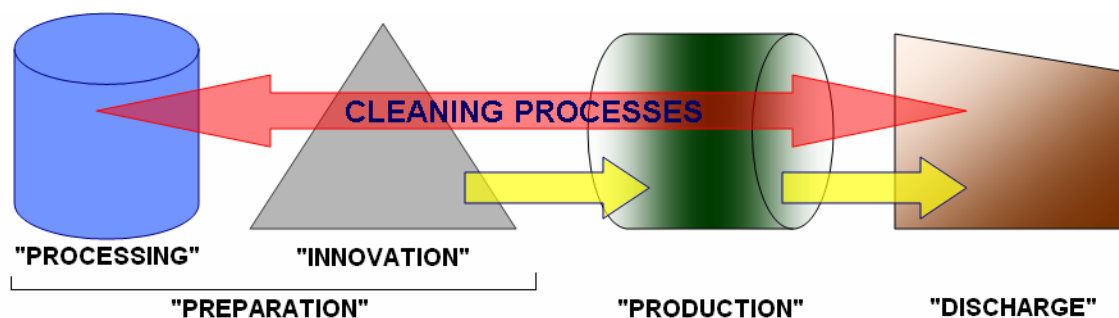


Figure 1

Throughout such processes, requirements include using pharmaceutical quality water, monitoring the pharmaceutical water used, and achieving the required cleaning level to avoid any cross contamination. During the process of monitoring the pharmaceutical water and maintaining the required quality and safety to meet the regulations, the FDA does not recommend any one specific analytical technique to be used for the analysis. The FDA states that any “Specific” or “Non-Specific” analytical technique can be used, as long as the technique provides results that prove its ability to detect any contaminants that would affect the quality of the water used¹.

Several Specific and Non-Specific analytical techniques exist that may help the industry monitor the pharmaceutical water used and also help achieve the required cleaning validation. A “Specific” technique is defined as an analytical technique that identifies the concentration of a specific chemical within the analyzed sample. A “Non-Specific” technique relates to analytical techniques that identifies the presence of all the chemicals present in the analyzed sample, i.e., a cumulative representation of the effect of all the chemicals present within the sample. During the cleaning processes, pharmaceutical water and different cleaning agents are used. Based on the cleaning agents used during the cleaning process, the drug residue under concern, and the excipients, different analytical methods can be used to identify them. In addition, depending on whether a specific chemical within the residue is required to be monitored, or a cumulative study of all of the chemicals within the residue are required to be monitored, either a Specific or Non-Specific analytical method will be used. Table 1 presents some of the available techniques that can be used.



ANALYTICAL METHOD	SPECIFIC METHOD	ADVANTAGES	DISADVANTAGES
TOC	NO	Broad spectrum analysis with low level detection, and requires minimal sample preparation. Quantitative analytical method	Non-Specific Method
HPLC	YES	Highly specific with moderate to high sensitivity, quantitative method	Requires long analysis time and is very expensive tool
TLC	YES	Highly specific with moderate to high sensitivity, and fairly expensive	Visual endpoint not quantitative and require long time sample preparation
CONDUCTIVITY (Not TOC Method)	NO	Rapid and inexpensive analysis	Non-specific with limited sensitivity
SPECTROPHOTOMETRIC	YES/NO	Moderate to high specificity, high sensitivity, and used as screening method	Not quantitative

Table 1: Specific and Non-Specific Analytical Methods

Total Organic Carbon (TOC) analysis is a “Non-Specific” analytical method. TOC is not only used in the cleaning validation process, but also for the monitoring of the pharmaceutical water used within the cleaning process and for the preparation of the drugs. TOC can measure the active compounds, excipients, cleaning agents, and water system organics within the sample. As a result, TOC is a “Non-Specific” tool that provides an accurate result that represents all of the chemicals under study within the sample, in a few minutes (Table 2). According to the FDA, TOC analysis is an acceptable method for evaluating cleaning effectiveness, as indicated in several studies that have been published since the publication of *Inspection Guide on Cleaning Validation* in 1993².

ANALYTICAL METHOD	DETECTION CAPABILITY		
	Drug Residue	Excipient	Cleaning Agent
HPLC	YES	YES	
TLC	YES	YES	
TOC	YES	YES	YES
Spectrophotometric	YES/NO	YES/NO	
Conductivity (Not TOC Method)			YES

*Table 2:
Comparing TOC
to other Specific
and Non-
specific
Techniques*

Several Pharmaceutical waters exist, such as Purified Water (PW) and Water for Injection (WFI). PW is used for the cleaning process as well as in the preparation of drugs that do not enter into the blood stream³. As a result, PW must be maintained under certain chemical purity levels, but need not be biologically ultra-pure. The TOC acceptable level for PW should be less than or equal to 500 ppb. WFI, on the other hand is used in the production of intravenous drugs, i.e., drugs that enter the blood stream, and in the cleaning validation process of specific systems³. WFI must be maintained under the same chemical and biological purity levels of the PW. In addition, WFI must undergo other tests such as bacteria count and endotoxin content to achieve a more stringent biological purity level. WFI's TOC level must be maintained at 500 ppb or less.



TOC analysis for either the cleaning validation processes or monitoring of pharmaceutical water can be measured using different organic carbon analyzers (Figure 2).

Figure 2: Shimadzu TOC analyzer

TOC can be measured for both liquid and solid samples using the organic carbon analyzer, i.e., whether it is a residue that was swabbed directly from the vat or if it was a solution in which the residue collected on a swab was desorbed in it. The organic carbon analyzer identifies the carbon level within the samples that is contributed from all of the chemicals present in the sample. The organic carbon analyzer identifies the carbon levels present in the sample by oxidizing the carbon to carbon dioxide, and consecutively detecting the carbon dioxide produced⁵. Results for TOC can be either reported as TOC or NPOC (non-purgeable organic carbon)^{5,6}. TOC within a sample consists of purgeable organic carbon (POC), volatile carbon, and NPOC (hard to volatilize carbon). According to the USP, “the amount of POC in pharmaceutical water is negligible and can be discounted”⁶; therefore, TOC can be reported as NPOC and vice versa.

Several oxidation and detection methods exist on the market that can be used in conjunction with each other to accomplish the carbon analysis (Table 3).

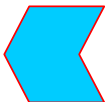
DETECTION METHOD	OXIDATION METHOD		DETECTION METHOD	
NDIR		TOC INSTRUMENTS	CONDUCTOMETRIC	
Non-Dispersive Infrared			Membrane	Direct
		COMBUSTION		
X		Catalytic / High Temperature		
		WET CHEMICAL		
X		Persulfate		
X		UV/Persulfate	X	X
X		Heated Persulfate		
X		Heated UV/Persulfate		
X		Heated UV		
X		UV	X	X
		TITANIUM		
X		Photocatalytic Oxidation		X

Table 3: TOC instruments with different oxidation and detection methods (X denotes possible and available combinations)

Use of any of the combined oxidation/detection methods, depends on the preference of the user, required detection levels, oxidation and detection method, matrix of the sample, characteristics of the sample, and/or sample type (solid or liquid).

References:

1. Weitzel, S. Critical Process Cleaning and Cleaning Validation, CFPA 2006
2. FDA. <http://www.fda.org/cder/guidance/cGMPs/equipment.htm>
3. USP 29, <1231> USP/NF The Official Compendia of Standards. U.S. Pharmacopeia. Webcom Limited: Toronto, Canada.
4. Shimadzu Scientific Instruments, Inc. www.shimadzu.com
5. TOC-V CPH/CPN & TOC-Control V Software User Manual. Shimadzu Corporation: Process & Environmental Instrumentation Division. Japan, Kyoto, 2001.
6. USP 29 <643>. USP/NF The Official Compendia of Standards. U.S. Pharmacopeia. Webcom Limited: Toronto, Canada.

