Clean-In-Place Processes and Total Organic Carbon Analyzers

Introduction

Clean-in-place (CIP) and Clean-Out-of-Place (COP) are two automated cleaning methods commonly employed in the pharmaceutical industry to ensure that process equipment is thoroughly cleaned and ready for the next batch. While COP involves removing the equipment from its operational area for cleaning, CIP allows for cleaning without the need for major disassembly. Despite the differences in approach, both methods share the common goal of achieving optimal cleanliness.

CIP systems offer several advantages, including increased efficiency, reduced labor requirements, and enhanced safety by minimizing chemical exposure risks. These systems can be conveniently mobile on wheels, allowing them to be easily moved next to the equipment to be cleaned. Alternatively, they can be custom designed to suit specific applications.

To control the final step of the CIP process and ensure an efficient process, the Water For Injection used in the final rinse should be monitored for cleanliness to ensure quality of the cleaning process. This is where Total Organic Carbon (TOC) analyzers play a key role.

Validation of CIP process and why TOC Analyzers can help.

Total Organic Carbon Analyzers play a crucial role in determining the purity of water, particularly in pharmaceutical and biopharmaceutical processes where Purified Water (PW) and Water for Injection (WFI) purity are of utmost importance.

There are various technologies available, but the fundamental principle of a TOC Analyzer revolves around carbon dioxide (CO_2) measurements:

- The CO_2 level in a sample is measured to determine the Total Inorganic Carbon (TIC).
- The sample is then exposed to intense ultraviolet (UV) radiation to oxidize the organic matter, resulting in the generation of CO_2.
- The CO_2 level is measured again after oxidation to determine the Total Organic Carbon or Total Carbon content.

A CIP program for a fermentor/bioreactor may involve the following steps:

- Pre-rinse: Two cycles of pre-rinsing with low-temperature or ambient-temperature water to remove most of the product residues. The pre-rinse cycles are drained directly.
- Alkaline cleaning: A detergent containing potassium or sodium hydroxide is used for the alkaline wash cycle. The alkaline solution is circulated through the vessel to effectively clean the surfaces. Elevated temperature is typically applied to enhance the detergent's efficacy.
- Post-alkaline cleaning rinse: Water (purified or injection grade) is used to remove the alkaline solution and detergent residues. This rinse is usually a single pass to drain.
- Acid cleaning: A second wash cycle is performed using a formulated detergent based on phosphoric acid. This step helps eliminate caustic cleaning residues and can also remove oxidation from the stainless-steel surface of the bioreactor vessel. Elevated temperature is applied.

- Post-acid cleaning rinse: A high-temperature water rinse (purified or injection grade) is conducted to remove the acid solution and acidic residues. This rinse is typically a single pass to drain.
- Final rinse: Injection grade water is used for the final rinse and is drained from the vessel to eliminate any drug product residues and cleaning agents from the vessel.

The cleanliness is assessed during the final rinse step. For an efficient process, TOC Analyzers should be used to monitor the conductivity and TOC level of the WFI drained from the vessel. Conductivity helps detect residual cleaning agents, while TOC detects potential organic carbon residues from the drug. Once the WFI meets the desired target values, the final rinse cycle is completed.

By assessing the purity of rinse water used in CIP processes, TOC analyzers effectively evaluate the efficiency of cleaning procedures, especially when combined with conductivity measurements. This combination enables the detection of both organic and inorganic contaminants, including the drug product itself and any cleaning agents employed during the CIP process.

Depending on the specific technology used, these analyzers can operate without the need for reagents, maintain calibration stability for up to one year, and require only a single annual preventive maintenance session to ensure optimal performance.

Laboratory TOC Analyzer vs. Online TOC Analyzer for CIP

CIP processes can be validated and verified through laboratory grab sample analysis. The WFI used for the final rinse is sampled in a clean TOC vial designed to prevent ionic leaching and atmospheric CO_2 dissolution.

This method has some drawbacks:

- It is prone to contamination during the sampling process, leading to overestimated values of TOC.
- It requires multiple grab samples, which can be time-consuming and expensive in terms of laboratory instrument reagents.
- The time taken to collect grab samples and perform tests can cause delays in getting confirmation of cleanliness, reducing throughput and economies of scale.

To improve process efficiency, especially when working with time-constrained processes, the TOC analyzer can be placed at-line. This setup significantly improves response time. However, it still involves sampling, which remains susceptible to contamination and overestimated TOC values. It also necessitates the analysis of multiple grab samples, leading to increased costs and limiting throughput and economies of scale.

To address these challenges, the use of on-line analyzers located on the CIP skid can eliminate the need for grab-sample analysis. These analyzers provide instantaneous data, enabling real-time release and enhancing equipment uptime.

PAT700 TOC Analyzer for Clean-In-Place

The simplicity of implementation of the PAT700 TOC Analyzer from Beckman Coulter Life Sciences makes it an excellent choice for online monitoring of CIP processes. A schematic of a CIP process with the PAT700 TOC Analyzer for analyzing the WFI used in the final rinse is shown in Figure 1.

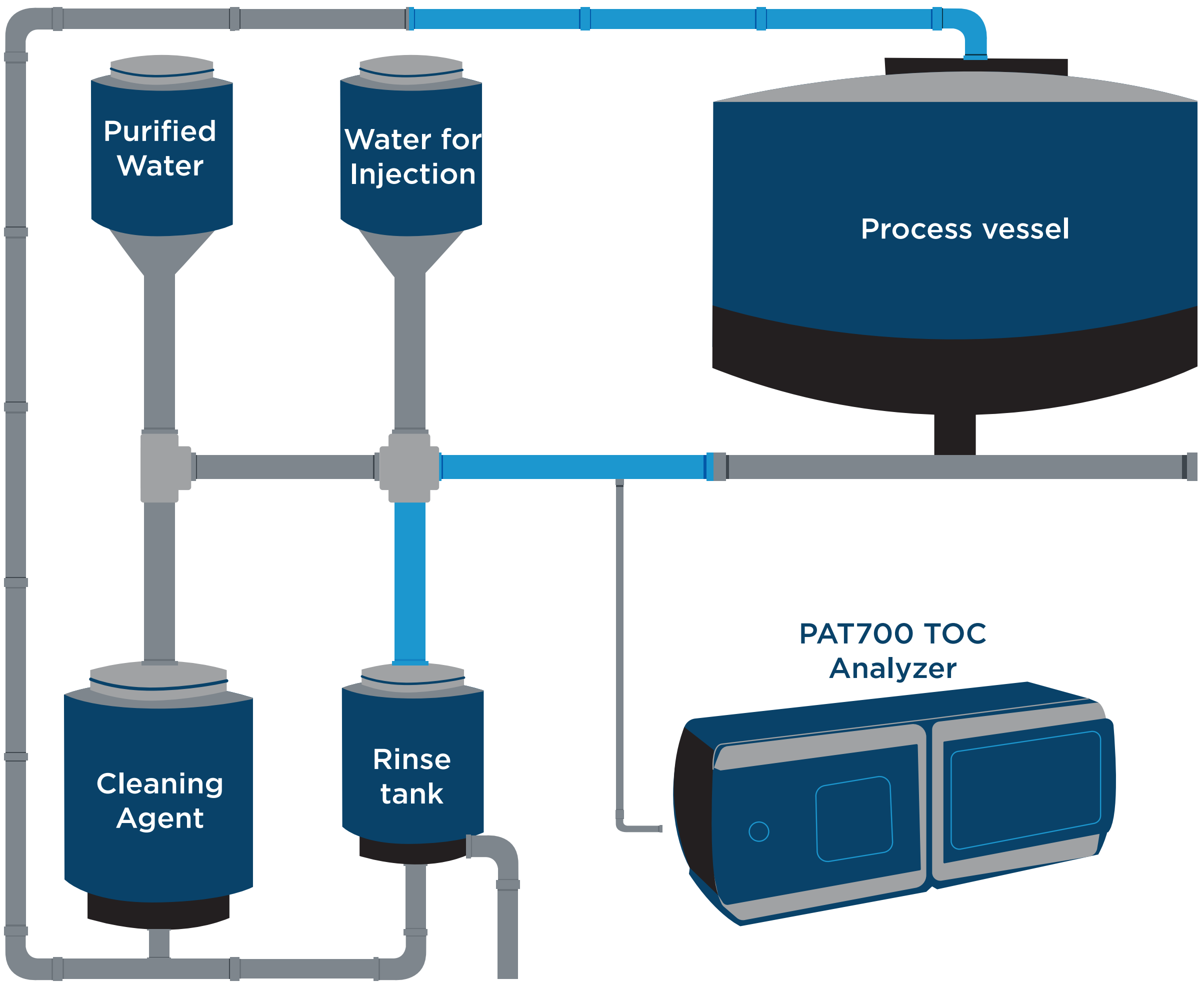

Figure 1. Schematic of CIP Skid equipped with TOC online analyzer for real-time analysis of WFI during final rinse.

The PAT700 TOC Analyzer utilizes direct conductometric (DC) analysis. It employs a single conductivity meter to measure the increased conductivity of a water sample after all organic material has been oxidized to CO_2 using UV light.

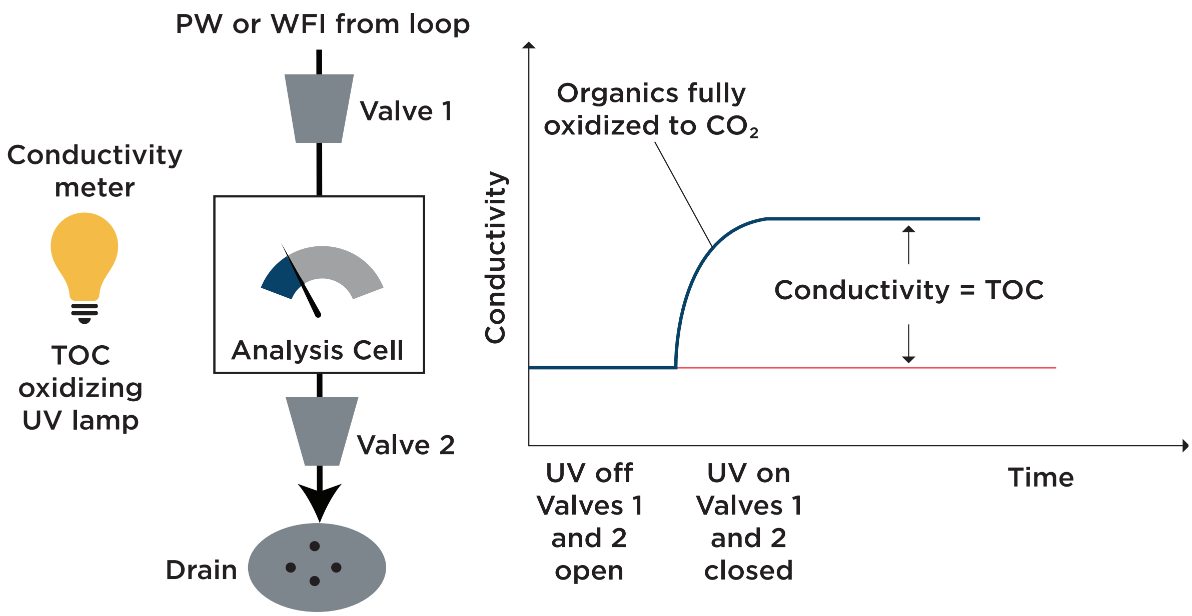

Figure 2. Direct Conductometric TOC Analyzer - Principle.

During the final rinse step, the WFI from the drain is trapped in the analysis cell by valves. The oxidizing UV lamp is activated to oxidize the organic matter and signal is measured using dynamic endpoint detection to ensure full oxidation of organic materials. The difference in conductivity caused by the CO_2 produced during the oxidation process is directly proportional to the amount of TOC in the sample (Figure 2).

DC TOC analyzers are based on the assumption that the only conductive species generated during UV oxidation is CO_2. This assumption is rarely violated in advanced PW and WFI distribution systems, as well as in CIP applications. However, if additional conductive species are present after oxidation (e.g., cations or anions), the analyzer measures the contribution to conductivity from all these species and converts it to TOC. In such cases, the analyzer may report higher TOC values than actually present in the sample. This overestimation of TOC values can be advantageous for extending the final rinse cycle, as the presence of cations or anions may be due to residues of cleaning agents or other organic compounds.

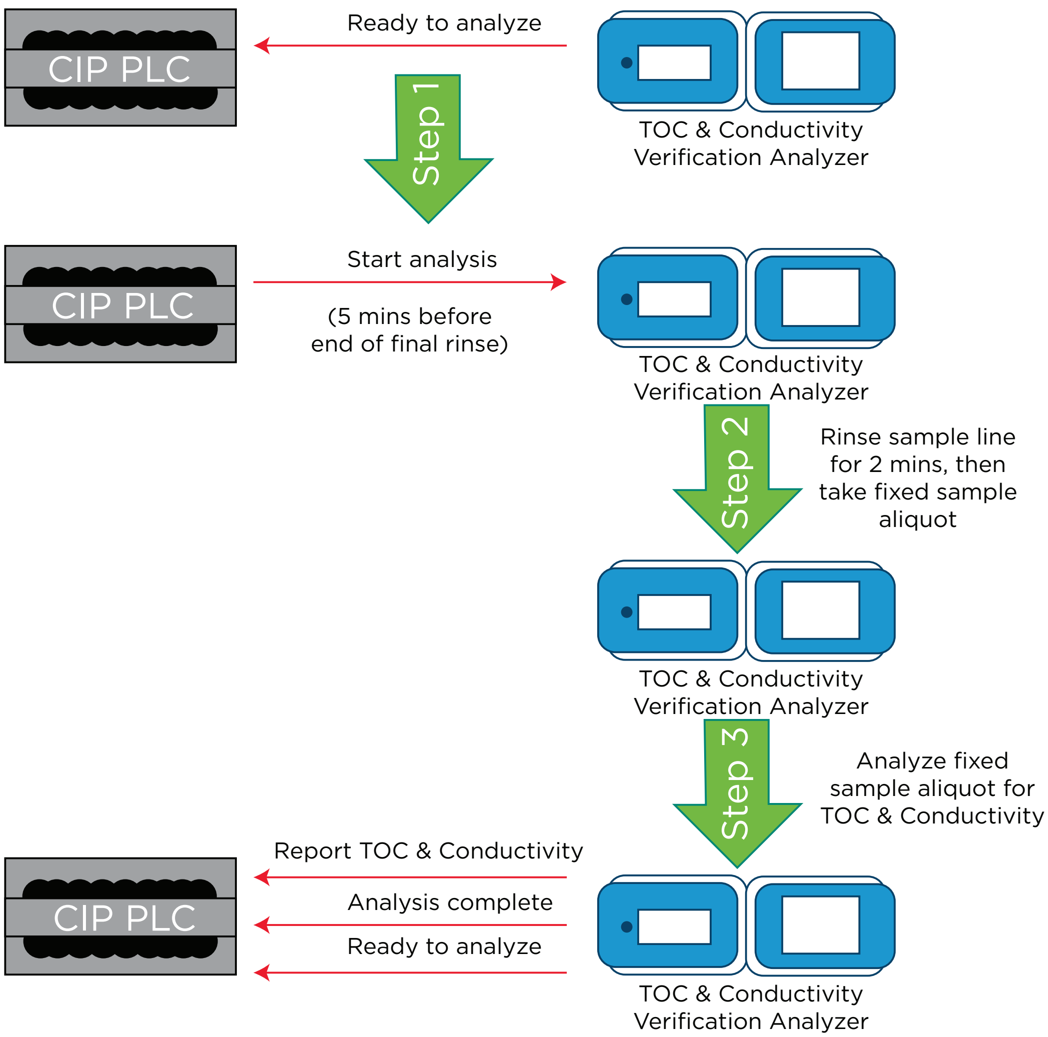

Figure 3. Typical signal exchange between PAT700 TOC analyzer and PLC

The PAT700 TOC analyzer can be integrated with a PLC/SCADA system that will interact with the analyzer as shown in Figure 3. The system can send a signal for control or abort sample, feature especially useful for CIP processes.

Other TOC analyzer technologies that utilize membranes and/or multiple conductivity cells may be less suitable for CIP applications. For instance, in a CIP skid that is used multiple times each day or experiences prolonged periods of inactivity, membrane-based TOC analyzers (indirect conductivity) may encounter issues with drying out and require frequent membrane replacement. These systems can also be affected by residue from the cleaning process, leading to fouling of the membranes, which impacts their permeability and calibration. Membrane-based TOC analyzers may necessitate regular calibration checks using TOC calibration reference standards before each use, resulting in increased cost of ownership due to frequent recalibrations and membrane replacements.

Similarly, TOC analyzers using multiple conductivity cells may be less accurate due to the combined uncertainty of multiple cells that affects the final result, and they require more frequent recalibration routines each time the sample starts, which prolongs the time before the analyzer can provide a reading. As CIP processes are not continuous-flow applications and typically involve small sample aliquots, TOC analyzers designed for continuous flow may not be ideal since they require a flow period of several minutes to stabilize and report TOC results.

Conclusion

Clean-In-Place processes offer several benefits in terms of reducing the risk of process equipment contamination, maintaining a cleanroom environment, and improving efficiency compared to Clean-Out-of-Place processes.

By implementing an online TOC analyzer to monitor the WFI used for the final rinse, the need for grab samples is eliminated, leading to significant improvements in equipment uptime. The combination of TOC and conductivity measurements can be employed to ensure that the process vessel's final rinse water is free from both inorganic and organic matter, meeting the quality level of WFI.

The PAT700 TOC analyzer is an ideal choice for this application as it can report both TOC and conductivity measurements. It utilizes direct conductivity analysis and requires only a small sample aliquot, making it highly suitable for this purpose. Additionally, the PAT700 TOC analyzer offers key advantages over membrane-based TOC analyzers and TOC analyzers utilizing multiple conductivity cells.

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