



**PAT and TOC Analysis With an
Onboard Automated Standards Introduction System (OASIS™)**

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ABSTRACT

Traditionally, most pharmaceutical companies have relied on laboratory TOC instrumentation to meet USP, EP or JP compendia requirements for purified water and water for injection release. However, by implementing a PAT-centric real-time release program using an on-line TOC analyzer, companies have begun to realize the benefits of reduced cost, reduced waste and improved consistency of quality production. On-line TOC analyzers allow for a re-focusing of laboratory resources to more value-added critical quality control and product development activities, while still fully accomplishing regulatory compliance.

This paper describes the use of an on-board automated standards introduction system (OASIS™) that is used to run verification standards and system suitability tests in order to ensure the reliability of the TOC results. The speed and efficiency gained by use of this automated system means that the analyzer is verified quickly, bringing a risk-based approach to ensuring product quality. Furthermore, this system may be used to capture a water sample in the event of an excursion occurrence, providing the water system engineer direct evidence to discover the root cause and providing valuable information for water system remediation and protection. Risk is minimized with the assurance that the analyzer is always producing accurate and reliable results and that the water system is operating at peak performance.

REAL-TIME RELEASE FOR PHARMACEUTICAL WATER

Historically, product quality in the pharmaceutical industry was ensured through quality inspections at various stages in the procurement, production and packaging processes. Because pharmaceutical processes are defined and prescribed out of the product development process, and are carefully crafted to produce the desired pharmacological outcome, little room has existed to apply engineering principles to improve the process, and establish real-time quality control. This converts the production process to more art than science with the goal of simply reproducing the desired outcome, with rejections through quality inspection. With the advent of the Process Analytical Technology (PAT) and Quality by Design (QbD) approaches, the desire is to evolve pharmaceutical processes from an art to a science with engineering-based activity, application of enhanced science and engineering knowledge in regulatory decision-making, establishment of specifications and evolution of manufacturing processes.¹ The PAT and QbD initiatives allow for methods to develop process understanding along with applications for monitoring process critical control points during development and manufacturing (see Figure 1).

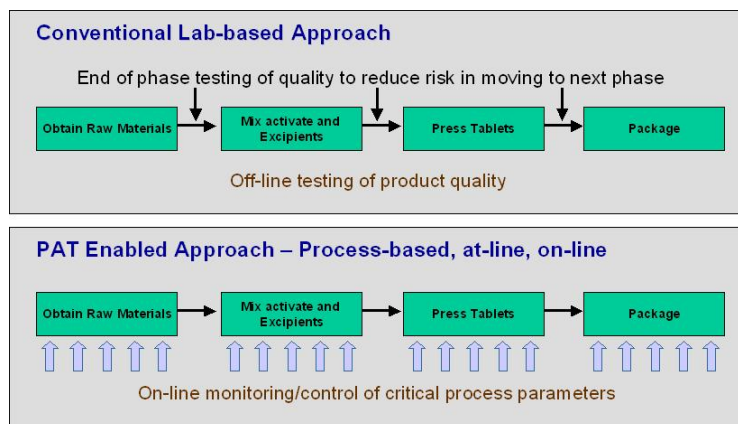


Figure 1: PAT Approach

PAT is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The PAT framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the US Food and Drug Administration (FDA).²

In accordance with the FDA, the United States Pharmacopoeia (USP 31) is the accepted guide (compendia) for producing pharmaceutical products in the United States.³ The USP specifies standards of quality, purity, packaging, and labelling for many pharmaceutical products and the ingredients used in the manufacture of these products. The guide specifies two grades of bulk ingredient water used in the preparation of compendia dosage forms, USP Purified Water (PW) and USP Water for Injection (WFI). The adoption of USP <643> in 1998 defined the usage and measurement of TOC in USP pharmaceutical waters. The USP Total Organic/Oxidizable Carbon (TOC) standards have helped in the international harmonization of TOC monitoring for all pharmaceutical waters, including the adoption of European Pharmacopoeia (EP) Method 2.2.44⁴ and methods in Japan Pharmacopoeia XV (2.59)⁵.

Most pharmaceutical companies around the world use laboratory-based TOC analyzers to meet USP, EP and JP compendia standards for release of water to manufacturing. This approach is consistent with historical quality-by-inspection approaches to manufacturing. But, many companies desire to reduce cost, reduce waste, and improve consistency of quality production, while achieving regulatory compliance by implementing a PAT-centric real-time release program using on-line analysis. On-line analyzers (Figure 2) also allow for a re-focusing of lab resources to more value-added critical quality control and product development activities, while still fully accomplishing regulatory compliance.⁶



Figure 2: On-line TOC Analyzer

ONBOARD AUTOMATED STANDARDS INTRODUCTION SYSTEM (OASIS™)

USP <643> and the other international Pharmacopoeia established acceptance criteria for any on-line or laboratory TOC instrument for pharmaceutical-grade water. These criteria are based on detection limits, the instrument's ability to distinguish between organic and inorganic carbon, and a suitability test designed to challenge existing measurement technology. The system suitability test compares the "recovery" of the analyzer for an easy-to-oxidize (sucrose) standard and a hard-to-oxidize (1,4-benzoquinone) standard. The relationship of the independent recoveries must be periodically demonstrated and fall within specified limits.³ In addition to the required system suitability test, an on-line instrument will require periodic calibration and

verification. Each of these procedures involves analysis of certified reference standards and comparison of the analytical results to the certified value of the standard. These solutions must be carefully administered and analyzed to ensure the on-going performance of the analyzer. Historically, introduction of these standards required an operator to spend significant time at the instrument administering multiple standards of varying concentration along with manual entry of the data associated with each standard. The analyzer would analyze multiple repetitions of each concentration to ensure statistically significant results. This process was time consuming and could be prone to operator error and/or technique error. Valuable operator time had to be invested that could be better applied to other activities.

Proven technology exists today that allows for the automation of standards introduction and data management.⁷ Through the innovative use of Radio Frequency Identification (RFID), standards can be loaded into the TOC analyzer and automatically processed in sequence to produce the necessary results. Figure 3 shows an example of an automated standards introduction system in an on-line TOC analyzer.



Figure 3: Automated Standards Introduction System

RFID is a well known technology that is currently used in the pharmaceutical industry as a preventative measure against counterfeiting.⁸ The technology makes use of an RFID tag (comprised of a microchip, antenna and substrate on which they reside) and a reader/writer. The RFID tag is programmed with all the data related to a specific standard, including the contents of the bottle, certified concentration, lot number and expiration date (Figure 4).

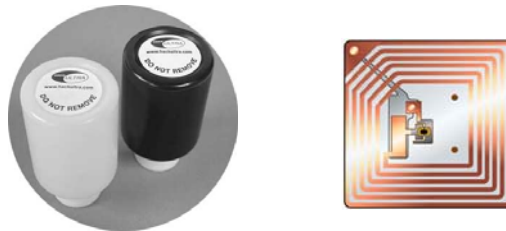


Figure 4: Standards bottles with RFID tags and example tag

When the RFID tag aligns with the reader/writer the data is automatically and seamlessly transferred to the analyzer, eliminating the need for any user interaction. The user interaction that is required is simplified through the use of a touch-screen man-machine interface (MMI) (Figure 5).

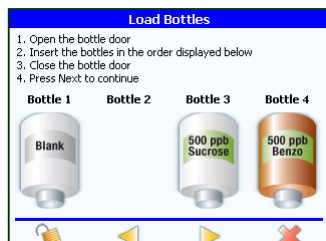


Figure 5: Touch Screen Interface – bottle mode

These two combined technologies dramatically reduce the time and errors associated with manual data entry. It also ensures that the proper standards are installed in the appropriate bottle location. As each standard is analyzed, the quantity of standard left in the bottle is tracked and a used bottle is tagged to avoid reuse and potential cross contamination. With a fully automated test, the time and cost associated with the required compendia standards tests are dramatically reduced, freeing operators to perform other value-added tasks while the tests are run (Table 1).

TOC Analyzer	Standards Introduction	Test Type	Test Time
Brand A	Automated - RFID	Verification (One Standard)	31 minutes
Brand B	Cartridge	Verification (One Standard)	165 minutes
Brand C	Manual	Verification (One Standard)	80 minutes
Brand A	Automated - RFID	Multipoint Calibration	62 - 75 minutes
Brand B	Cartridge	Multipoint Calibration	270 minutes
Brand C	Manual	Multipoint Calibration	180 – 270 minutes
Brand A	Automated - RFID	System Suitability	49 - 52 minutes
Brand B	Cartridge	System Suitability	180 -240 minutes
Brand C	Manual	System Suitability	120 -180 minutes

Table 1: Typical standard test times

PAT ENABLING

The implementation of PAT in a pharmaceutical process can produce numerous benefits, including:

- Better process understanding, gained through prediction and control of relevant and critical process/product attributes.

- Alternative mechanisms to demonstrate validation with a high assurance of quality on every batch manufactured.
- Continuous learning through data collection and analysis.
- Application of risk-based approaches to quality.
- Real-time monitoring of quality throughout the manufacturing of products
- Implementation of change control systems that are easier to manage and implement.⁹

Automated standards introduction systems directly associated with TOC analyzers provide an alternative mechanism that demonstrates a high degree of confidence in the performance of the instrument, and therefore the quality of pharmaceuticals produced using water released by the instrument. The speed and efficiency gained by use of these automated systems means that an analyzer can be verified quickly, bringing a risk-based approach to ensuring product quality. Risk is minimized with the assurance the analyzer is producing accurate and reliable results.

When standards bottles are loaded in the OASIS™, the operator can have the option of running the standards immediately or programming the analyzer to run the standards up to three days later. This approach reduces water system downtime and eliminates periods of uncertainty during the normal daily operation while standards are being analyzed. By scheduling the standards during off-shift hours, verification of the analyzer can be performed overnight and in essence “brackets” the front end of production for the next day. When the operator prepares for daily production, the quality of the production run is ensured with results from the overnight standards test that are immediately available for validation verification.

The philosophy of PAT is that more process understanding, data, real-time monitoring and better process control will lead to higher quality product manufactured consistently within specification with no excursions. Since an on-line TOC analyzer resides on the water system it provides a unique opportunity to help monitor for potential water system problems, commonly referred to as excursions.

EXCURSION MONITORING

Despite on-line monitoring of a water system for TOC levels, occasional problems can arise or contaminants can enter the water system that are detrimental to proper water system operation. While current water system technology produces very consistent and reliable results, excursions can occur. Excursions in water systems are defined as a deviation or digression from normal water system operating conditions. When an excursion occurs the quality of the water produced from the system may be in question. In the event of an excursion it can be extremely beneficial to obtain a sample of water from the system that can be made available for independent analysis. Analysis of the water sample can provide valuable information as to why the excursion occurred and help facilitate rapid remediation of the issue.

Some TOC analyzers today use technology specifically designed to separate compounds from the analysis that are not normally expected in the process water. For example, reverse osmosis (RO) membranes are susceptible to damage from chorines and chloramine by-products from the disinfection process. “This is particularly true for systems using thin film composite polyamide RO membranes that are incapable of tolerating trace concentrations of residual disinfectant – the most popular membranes use in pharmaceutical water purification systems.”¹⁰ A chlorine break-through in a water system, or the presence of trichloromethane, represents a significant failure of a water system. If a TOC analyzer is designed to separate these compounds from the analysis it will conceal the problem and suppress valuable diagnostic information. TOC analyzers designed to respond to contamination in the water sample, including the presence of

such compounds, can respond and capture a sample of water if equipped with excursion monitoring capability. This will enable the water system engineer to identify the root cause and remediate accordingly.

A TOC analyzer equipped with an OASIS™ may be configured for excursion monitoring. Excursion monitoring is the capability to extract and save a sample of water from the water system immediately following a pre-programmed water condition, such as high TOC levels, water conductivity exceeding USP limits, or water chemistries deemed abnormal by the analyzer. Problems with the water system can be identified well before compendia limits are exceeded with the ability to program a specific TOC level that must be exceeded for excursion capture. When an excursion has been identified, the analyzer will immediately capture a sample of water directly from the water system and place it in an empty bottle, equipped with an RFID tag that has been loaded into the analyzer. Upon sample capture, all the data associated with the excursion is recorded on the RFID tag using the writing capability of the RFID reader/writer. This approach ensures that the data associated with the captured excursion water is protected and cannot be altered. A lab equipped with the appropriate RFID reading capability, would be able to read the tag and associate the data with the water sample, such as the serial number of the analyzer, date, time, last TOC, conductivity and temperature values. Through a thorough analysis of the water sample a better understanding of what may have caused the excursion can be identified. Because the excursion capture is initiated by the TOC analyzer results, the sample is as indicative of the water condition as possible.

The PAT initiative calls for the application of risk-based approaches to quality. By applying excursion monitoring capability, the risk associated with producing off-spec water is dramatically reduced. The TOC analyzer becomes a water system diagnostic tool, rather than just a regulatory sensor to monitor TOC limits.

CONCLUSION

The introduction of innovative technology can create uncertainty and regulatory concerns. PAT has been designed to facilitate the implementation of innovative technology, manufacturing and quality control approaches. Through the application of innovative technology in the area of TOC analysis, such as RFID and simplified MMI, operator intervention is significantly reduced and time can be spent on other high value activities. The dramatic reduction in time required to run standards tests minimizes the risk of producing off-spec water. Furthermore, the PAT initiative asks for a risk-based approach to quality. Through diagnostic tools, such as excursion monitoring, a TOC analyzer becomes more than just a TOC sensor for regulatory purposes - an on-line diagnostic tool to help minimize the risk of producing off-spec product. New innovative technology is allowing for true value to be added wherever traditional regulatory compliance is required.

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AUTHOR

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