

This article presents the development and integration of an Ultraviolet (UV) sensor for on-line TOC analyzers and demonstrates the efficacy of this critical component, its life cycle, and the usage of PAT in its determination.

How Smart Is Your On-Line TOC Analyzer?

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Introduction

Many on-line TOC analyzers use Ultraviolet (UV) lamps to oxidize organics to CO₂. UV-based TOC analyzers are the most common type for on-line use as they have exceptional stability and simplify the analysis process by not requiring the addition of oxidizing reagents. The application of on-line TOC analyzers for real-time release emphasizes the need for immediate measurement, cost effectiveness, analytical performance, reliability, elimination of sampling errors, and reduced risk factors.¹ The UV lamp is a key component of an on-line TOC analyzer and crucial for proper TOC analysis. UV lamp performance is paramount as it can affect cost of ownership, accuracy, and the speed of analysis.

The implementation of a novel scheme for on-board intelligence and self-monitoring diagnostics to on-line TOC analyzers permits real-time monitoring of the UV lamps. Integrating an internal UV sensor to monitor UV lamp intensity over time provides advanced diagnostic capability, improved instrument reliability, and reduced cost of ownership to the on-line TOC analyzer.

Utilization of Process Analytical Technology (PAT) to enhance the knowledge of a pharmaceutical production system, the use of real-time release of the pharmaceutical water to production, and the assessment and institution of risk-based management are described with reference to the FDA's 21st Century Initiative.² Although no technology is specified by PAT guideline documents, any device, component, software, or instrument used to increase process knowledge, operation, and feedback of the process in a multivariate environment is consistent with PAT goals. Growth in the PAT initiative can be enhanced by addressing issues of risk minimization through the imple-

mentation of improved reliability in applied process instrumentation. By monitoring an instrument or sensor performance in real-time, the instrument can provide immediate feedback on its operation and can be used to anticipate a potential failure – reducing operational risk. When multivariate parameters are administered in a single instrument or analyzer, diagnosis of all functioning components enhances performance, reliability, and achieves PAT goals.

This article illustrates the benefits of on-board intelligence and self-diagnosing UV sensors in TOC analyzers by presenting data regarding the increased utilization of a UV lamp, the measurement of the UV intensity, and the gradual degradation of a UV lamp during usage. Each of these measured parameters has an economic benefit to a pharmaceutical water system and directly supports the goals of PAT.

Background

The adoption of USP (643) in 1998 defined the usage and measurement of TOC in USP pharmaceutical waters. The USP 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. The use of laboratory and on-line instruments is permissible under USP (643). Some Quality Assurance (QA) personnel have been slow to endorse the usage of on-line instrumentation for real-time release, preferring traditional laboratory analysis. The unfamiliarity of some QA personnel with on-line instrumentation, its functionality, speed of response, volume of measurements, reliability, and utility has led to many situations where only laboratory measurements were deemed “official” for product release. However, the increasing number of on-line instru-

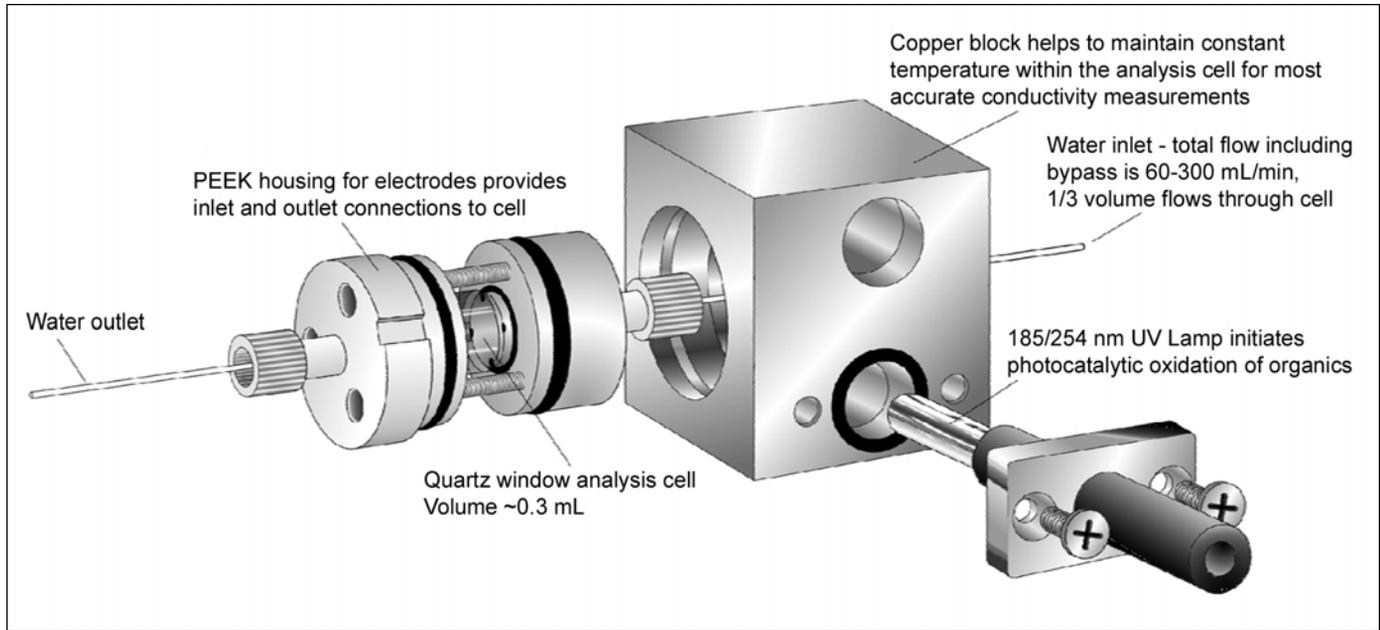


Figure 1. Oxidation cell assembly.

ments and the release of the FDA's 21st Century Initiative are changing QA personnel's perception of on-line instrumentation, its value in parametric measurement for process monitoring, and its operational characteristics. Improved reliability and automated calibration of on-line TOC analyzers reduces user interaction, allowing lab personnel to focus on more intricate analyses. On-line TOC instruments are generally designed to be less maintenance intensive, less expensive to operate, and require less personnel intervention for calibration, standards administration, and formulations. On the other hand, laboratory TOC instruments using methods of combustion and NDIR detection can have annual totalized costs exceeding \$100,000 when calculated for maintenance, laboratory labor, glassware, chemicals, test preparations, labor for point-of-use samples, process sampling, and calibration. Thus, the use of on-line TOC analyzers for water product monitoring, at some pharmaceutical facilities, has been incorporated for more than 10 years.

Most on-line TOC analyzers use a UV lamp to produce ·OH radicals to oxidize organics in the sample water. UV lamps

are a consumable item and lamp output degrades over time. There are several issues related to lamp life and/or the ability of UV light to penetrate the water sample, which should concern people moving to on-line release.

- UV lamps will solarize the quartz sleeve encasements over time causing transmissibility issues.
- The UV lamp intensity will degrade over time. Typically, UV lamps are recommended for replacement after six months of use⁷ (Figure 5).
- Rouge and contamination as external factors in the water system can have an adverse affect on transmissibility of UV light to the sample.

In any of the above individual or combined effects, a lessened amount of UV energy penetrating the sample will lead to lower ·OH production. Low ·OH concentration will lengthen the oxidation time and can cause an inaccurate TOC measurement. Excessive oxidation time is particularly problematic for fixed-time TOC analyzers without dynamic oxidation endpoint detection capability.

To have a robust, reliable, and accurate TOC instrument,

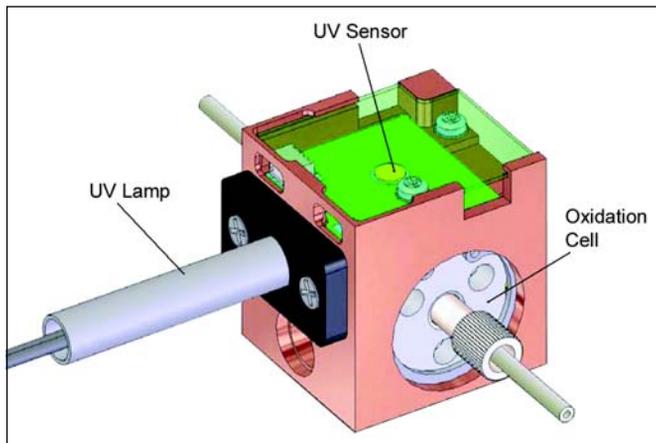


Figure 2. Oxidation cell housing modified with a UV sensor PCBA.

Lamp Utilization Increase	Lamp Life (months)	3 Year Savings (per unit)	5 Year Savings (per unit)	7 Year Savings (per unit)
17%	7	\$574	\$957	\$1,340
33%	8	\$1,005	\$1,675	\$2,345
50%	9	\$1,340	\$2,233	\$3,127
67%	10	\$1,608	\$2,680	\$3,752
83%	11	\$1,827	\$3,045	\$4,264
100%	12	\$2,010	\$3,350	\$4,690

Table A. Per unit cost savings from extended lamp utilization (System Suitability Testing verification).

Lamp Utilization Increase	Lamp Life (months)	3 Year Savings (per unit)	5 Year Savings (per unit)	7 Year Savings (per unit)
17%	7	\$1,654	\$2,757	\$3,860
33%	8	\$1,950	\$3,250	\$4,550
50%	9	\$2,180	\$3,633	\$5,087
67%	10	\$2,364	\$3,940	\$5,516
83%	11	\$2,515	\$4,191	\$5,867
100%	12	\$2,640	\$4,400	\$6,160

Table B. Per unit cost savings from extended lamp utilization (UV Sensor verification).

the device should have a simple design with minimum complexity and discernible diagnostics of all critical parameters, especially key components such as the UV lamp.

PAT Methodology and Adoption

PAT methodology encompasses process knowledge and its feedback, continuous process improvement, measurement and monitoring of parameters in a multivariant environment.⁵ Some TOC analyzers provide more than just the TOC readings and may include water temperature, conductivity, and flow. These information points may be primary or secondary measurements used in the operation of the water system. The greater frequency of data and parameter measurement, a greater confidence in the operation of the water system will ensue, as many unknowns are removed from speculation. With the initiation of on-line instrumentation, the operation of pharmaceutical water systems has greatly improved due to constant monitoring of critical and non-critical parameters. Today, more than 80% of all pharmaceutical water systems have TOC levels below 50 ppb. Increased usage of reverse osmosis and continuous deionization systems has reduced TOC, conductivity, and microbial counts, while increasing water quality. The basic tenet of PAT is that more data, more feedback, better process knowledge, and better process manufacturing yields a high quality product manufactured consistently within specifications and controls with no scrap or excursions. The adoption of PAT and risk-based management has increased production throughput with higher quality product.⁶ Defining the critical path and critical components of an instrument or process is a basis for PAT and risk-based management.

It is now rare to suspect the water system as the main contamination culprit in a failed production lot, as the implementation of on-line instrumentation with higher frequency measurements and readings obviates the need for laboratory confirmation. The reluctance to use on-line instrumentation for product release is changing. Large pharmaceutical companies are slowly changing from laboratory verification to on-line verification for product release. The overriding factor in the reluctance of large pharmaceutical companies to implement on-line release is the traditional reliance on the laboratory for analytical analysis. Even though on-line and laboratory TOC analyzers were authorized in the original USP (643)

mandate, the current SOPs designating laboratory procedures, previous investment in equipment, and the training of personnel are common arguments used to validate laboratory testing versus on-line. Although these arguments serve the laboratory personnel well, it may be a disservice to manufacturing personnel who need immediate data and information on their process, quality, and manufacturing systems. Installing on-line instrumentation frees laboratory personnel to perform more complicated analyses that cannot be automated for on-line usage.

UV Lamp Utilization – Reducing Cost of Ownership

Like any electrical component with a finite lifetime, UV lamp warranties are established based on time-based failure distributions. Warranty periods are set somewhere below the point at which typical lamp failures begin to occur, thus covering premature or product defect based failures, and making sure there is sufficient margin between the warranty period and the onset of a typical lifetime based failure. However, from the failure distribution curve, lamps would be expected to last much longer than the specified warranty period with some lamps lasting significantly longer. Anecdotally, reports of UV lamp longevity have reached close to two years by some users of on-line TOC analyzers. Each water system is different. The ability to monitor UV lamp output in real-time and report impending lamp failures to a TOC

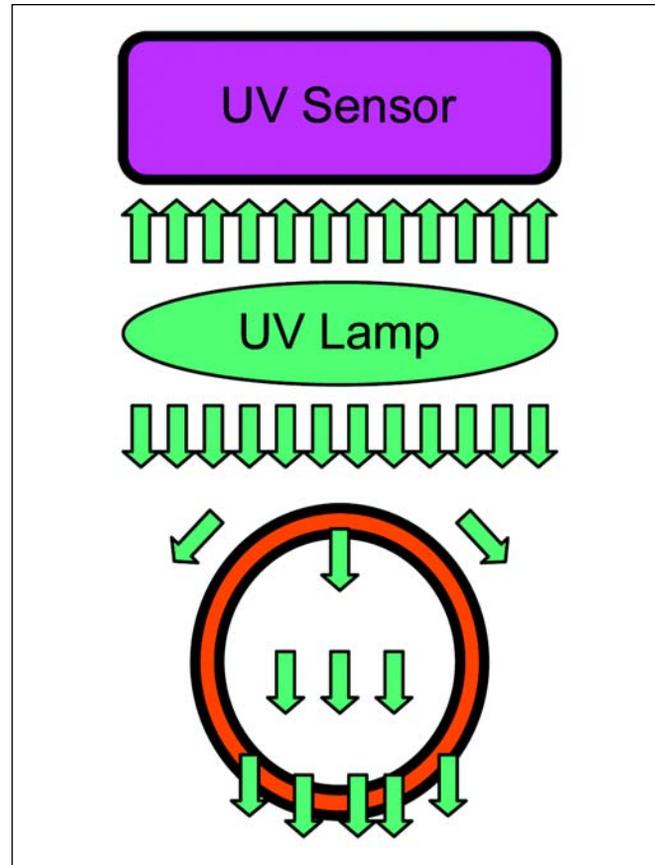


Figure 3. Illustration of oxidation cell configurations with integrated UV sensors.

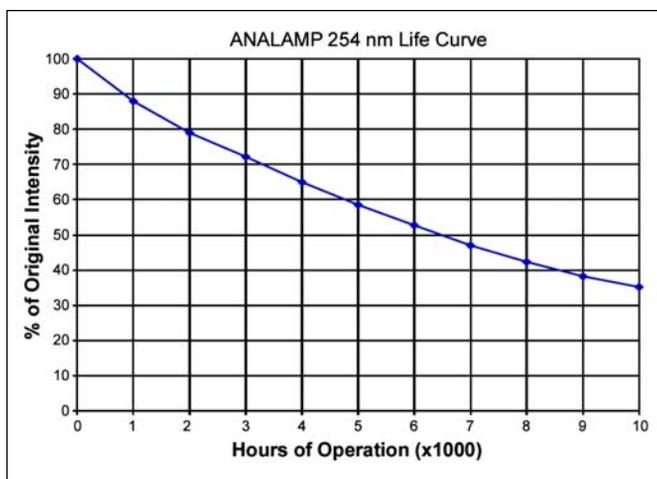


Figure 4. UV lamp ageing curve.⁹

analyzer would maximize the utilization of the lamps and reduce the cost of downtime and replacement. UV lamp life in TOC analyzers is typically warranted for six months (~4200 power-on-hours).⁷

Increasing lamp utilization in an on-line TOC analyzer can have a significant benefit in terms of reduced cost of ownership per analyzer as shown in Table 1. To arrive at the cost savings shown, the following assumptions are used based on real-world information:

- Assume the lamp is normally replaced every six months per manufacturer's recommendation
- Two labor hours to replace the lamp and run a System Suitability test to verify lamp performance
- Cost of replacement lamp = \$400
- Cost of System Suitability kit = \$150
- Labor rate = \$60 per hour

If a pharmaceutical facility has installed five analyzers, then savings can be five fold, and so on. The more analyzers used and the longer the lamp utilization, the greater the overall cost savings.

Now consider relying on an integrated UV sensor to report the output of a new lamp to verify the lamp is working properly, and eliminate the cost associated with running a System Suitability test to confirm lamp performance. The reduced cost of ownership in this case is shown in Table B, only one hour of labor is needed to replace the lamp. Clearly, the implementation of a lamp output sensor can lead to cost savings when employed in an on-line TOC analyzer.

Modifying a TOC Analyzer with a UV Sensor

UV sensors are based on the use of photodiodes to convert light to an electrical signal. The key to implementing UV sensors for monitoring lamp output in TOC analyzers is to use photodiode materials that are sensitive to UV light, while at the same time, are not degraded by long-term exposure to UV radiation. Degradation of the UV sensor would lead to photodiode drift and instability. The photodiode must be

sensitive to the specific wavelength of light emitted by the UV lamp (e.g. 254 nm). Photodiodes have been used in many applications for monitoring UV output, but until recently have never been commercialized in UV-based on-line TOC analyzers.⁸ When implementing UV sensors in a TOC analyzer, the following specifications are important for both analyzer performance and end-user confidence:

- UV sensor must work over specified TOC analyzer environmental range.
- No additional calibration requirements by end-user.
- UV sensor should not require factory re-calibration for more than five years.
- Proper notification of lamp degradation that would result in excessive oxidation time.
- Proper notification of lamp failure that could cause inaccurate TOC readings.
- Easy ability to verify lamp status through instrument diagnostic menus.
- NIST-traceable sensor output that guarantees accurate UV lamp intensity measurement.

Figure 1 shows a schematic of the cell assembly from a common on-line TOC analyzer used in pharmaceutical water systems. The key components of the oxidation cell include the UV lamp and quartz oxidation cell used to enclose the on-line water sample.

Figure 2 illustrates the cell assembly in Figure 1 after modifying the housing with a UV sensor Printed Circuit Board Assembly (PCBA) with integrated photodiode. Drilling a small hole into the copper housing of the cell assembly creates a light pipe leading from the UV lamp to the photodiode sensor.

UV light falling on the photodiode creates a small electrical current, which is further amplified and converted to a voltage output supplied to the TOC analyzer's main controller board. An illustration of the cell – sensor arrangement is shown in Figure 3.

UV sensors are calibrated to full-scale irradiance (in mW/cm²) against a NIST-traceable master sensor. A calibrated sensor PCBA is placed in the master sensor slot transferring the intensity value of a NIST-traceable light source to the

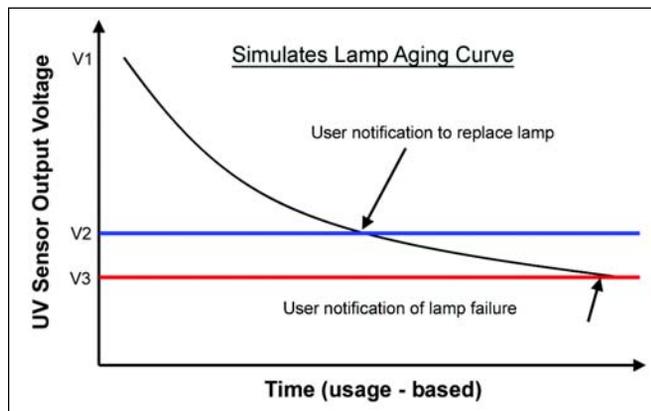


Figure 5. UV Sensor self-diagnosis application strategy for On-line TOC analyzer.

uncalibrated sensor PCBA. The newly calibrated UV sensor board is then installed into the oxidation cell housing. Internal validation of the performance of the UV Detect™ system is achieved through a manufacturing test plan that addresses trigger points, temperature testing for thermal drift, humidity testing, electrical compliance, and firmware and software verification. Customer validation is addressed through the installation and operational qualification procedures to validate the calibration and accuracy of the UV Detect™ sensor.

UV Lamp Monitoring

Effective implementation of self-diagnosis relies on the integration of sensor hardware with instrument firmware to provide useful information to the end user. To effectively monitor UV lamp output, it is important to first understand the typical lamp life curve as depicted in Figure 4. As a UV lamp ages, the intensity of 254nm light output diminishes. At some point, the lamp will degrade to a level where it will not emit enough UV light to oxidize the organics in the water sample. An effective strategy for employing self-diagnosis would allow the instrument user to be notified of an impending lamp failure giving the user time to order and install a replacement lamp before it ultimately fails. In addition, the user should be notified when the lamp has actually failed and TOC measurements are no longer accurate. Figure 5 shows how the UV sensor self-diagnosis and reporting strategy is implemented in the UV Detect TOC analyzer.⁸

The initial UV sensor output voltage (V1) is set to full-scale for a new lamp (i.e., 100% intensity). As the lamp ages, the sensor output drops to a level (V2) where the lamp intensity is still enough to oxidize a 500 ppb TOC sample, but oxidation time is significantly extended vs. a new lamp. At this point, the user is prompted to replace the lamp. If the original lamp remains in the analyzer, it will eventually decay to a point (V3) where the lamp intensity is barely enough to complete oxidation of a 500 ppb TOC sample within the maximum time allowed by the analyzer. In this case, the lamp is considered failed and should not be used for further TOC analysis. The instrument reports the lamp failure to the end user and prevents further TOC analysis until the lamp is

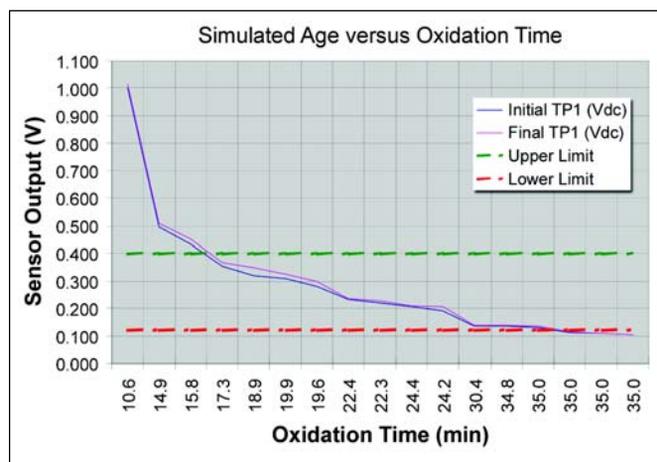


Figure 6. Actual UV sensor (lamp) output vs. Oxidation Time for 500 ppb TOC samples.

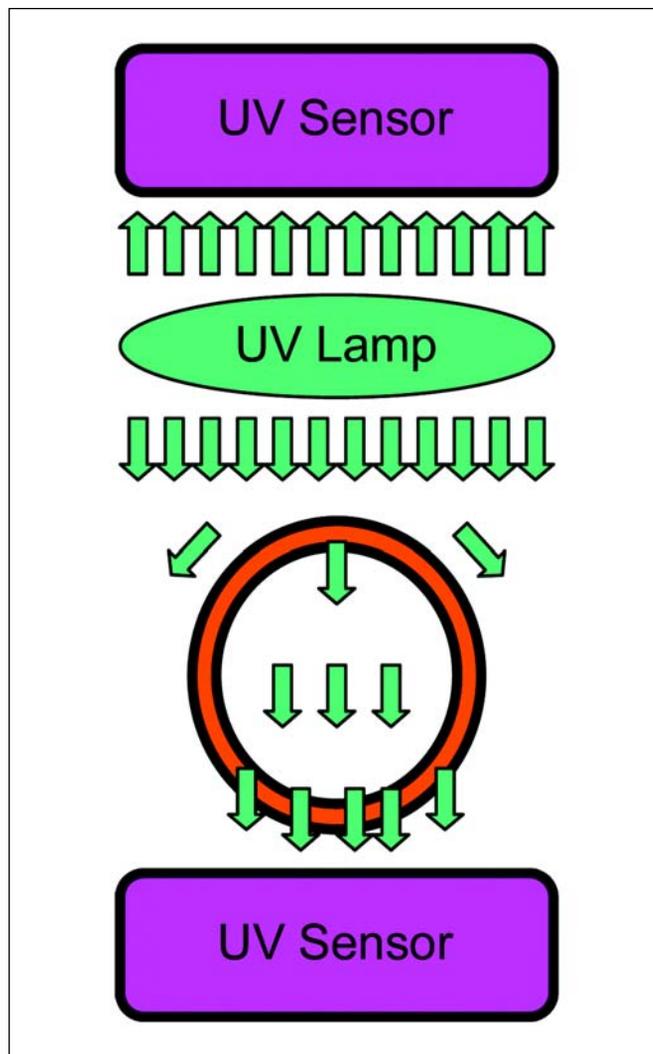


Figure 7. UV sensor implementation for rouge detection.

replaced. It is important to note that the voltage threshold values are based on sensor output only and not lamp Power-On-Hours (POH). In this case, the sensor output represents the real life remaining on the lamp. Continuously monitoring UV lamp output and reporting status to the TOC analyzer provides real-time risk assessment of the UV lamp within the guidelines of FDA’s 21st Century Initiative for risk-based management.

Figure 6 shows actual UV sensor output data vs. oxidation time for a 500ppb TOC sample. Reducing the current applied to the lamp simulates lamp aging and diminishes UV sensor output. After dropping the lamp output, a 500 ppb TOC sample was injected into the analyzer and the oxidation time was recorded.

In addition to active warning indications, the UV lamp status can be queried through the TOC analyzer diagnostic menu. This is particularly useful under conditions where TOC readings are suspect due to a deviation from normal operating values, an unexpected increase in analysis time, or the standard deviation jumps significantly from measurement to measurement. These are all symptoms of impending lamp failure, but they also can be caused by actual water

system conditions. Verifying correct lamp performance allows the user to focus on the water system rather than questioning the accuracy of the TOC analyzer.

UV Sensors for Rouge Monitoring – A Novel Application

Figure 7 depicts another novel implementation of UV sensors in an on-line TOC analyzer. By integrating a second UV sensor in the oxidation cell housing, the transmissibility of UV light through the oxidation cell can be monitored. Measuring transmissibility allows the analyzer to detect cell contamination, such as rouging, which could lead to poor analyzer performance (e.g., under-reporting TOC). Rouge is a common problem in many pharmaceutical water systems. While low temperature water tends to inhibit rouge formation, high temperature water systems often have fast and large rouge build-ups, which can migrate to non-metallic surfaces such as quartz, PTFE, and PFA tubing in TOC analyzers.^{10,11}

Table C compares TOC oxidation data from a new cell and a heavily rouged cell within a TOC analyzer. Thick rouge layers on the quartz walls of the oxidation cell can significantly increase the oxidation time, even to the point of causing an inordinately long oxidation. The rouge layer prevents UV light from entering the oxidation cell and oxidizing the organics in the water sample. UV transmissibility sensors placed in the oxidation cells used to generate the data in Table C show the problems caused by rouge. Thick rouge layers reduce the transmissibility of UV light to nearly 0%, which causes prolonged oxidation and oxidation time-out errors for higher TOC levels (e.g., during TOC excursions). Analysis of lower levels of sucrose (50 ppb) appear to be unaffected by the rouge. Apparently, there is still enough UV light entering the oxidation cell to complete oxidation or the photocatalytic effect of the titanium electrodes is enough to complete the oxidation quickly. However, at 500 ppb sucrose levels, the rouged cell takes more than four times longer to oxidize the sample. A self-diagnosis and reporting implementation strategy similar to Figure 7 can be employed for rouge monitoring to notify users of excessive cell contamination, requiring either cleaning or maintenance.

Standard Injection (ppb Sucrose)	Non-Rouged Cell Oxidation Time (sec)	Rouged Cell Oxidation Time (sec)
50	325	321
500	421	1854
1000	1158	< 2100
Cell Condition	Sensor (mA)	% Relative Transmissibility
New	4.81	100%
Used	4.77	95%
Rouge	4.01	0%

Table C. Effect of rouging on TOC oxidation time.

Summary

Adopting a self diagnosis and reporting strategy for any key component in on-line instrumentation used for process monitoring achieves PAT goals by providing feedback mechanisms to increase reliability, prediction of component failure, and health of the device. This strategy effectively helps to lower operational risk in concert with the goals of the PAT initiative. Employing UV sensors into on-line TOC analyzers can lead to cost savings in addition to improvements in reliability. UV sensors can be used for increasing lamp utilization and predicting lamp failures to prevent unscheduled downtime. Eliminating the need for expensive System Suitability testing after replacing UV lamps will lead to lower cost of ownership and improved instrument up-time. UV sensors can also be used for monitoring rouge build-up in oxidation cells, which can lead to slow analysis, instrument errors, or in the worst case, inaccurate TOC measurement. Slow analyzer response can delay the ability to detect TOC excursions, which can lead to manufacture of poor quality product that may need to be discarded. Using NIST-traceable UV sensors provides a science-based approach to on-line TOC measurement and gives users more confidence in their TOC analyzer.

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