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How Smart Is Your On-Line TOC Analyzer?

by Nissan Cohen and Terry Stange, PhD

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.

Introduction

Many on-line TOC analyzers use Ultraviolet (UV) lamps to oxidize organics to CO_2. 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 implementation 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 2.2.44[4] and methods in Japan Pharmacoepia 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-

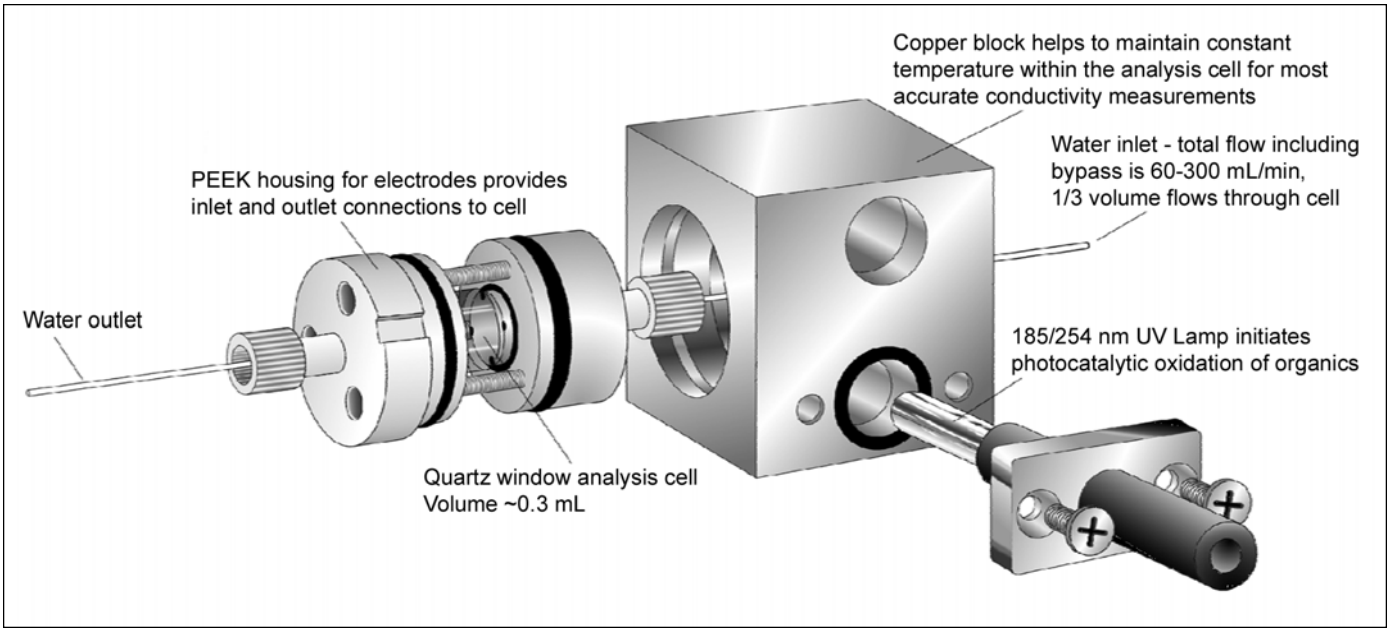

Figure 1. Oxidation cell assembly.

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

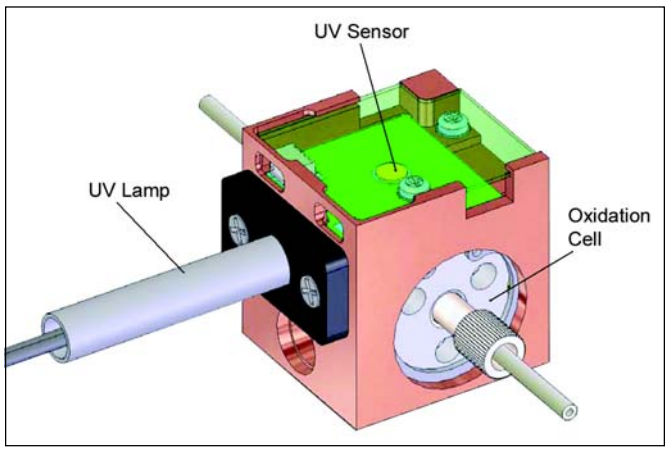

Figure 2. Oxidation cell housing modified with a UV sensor PCBA.

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 use[7] (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,

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

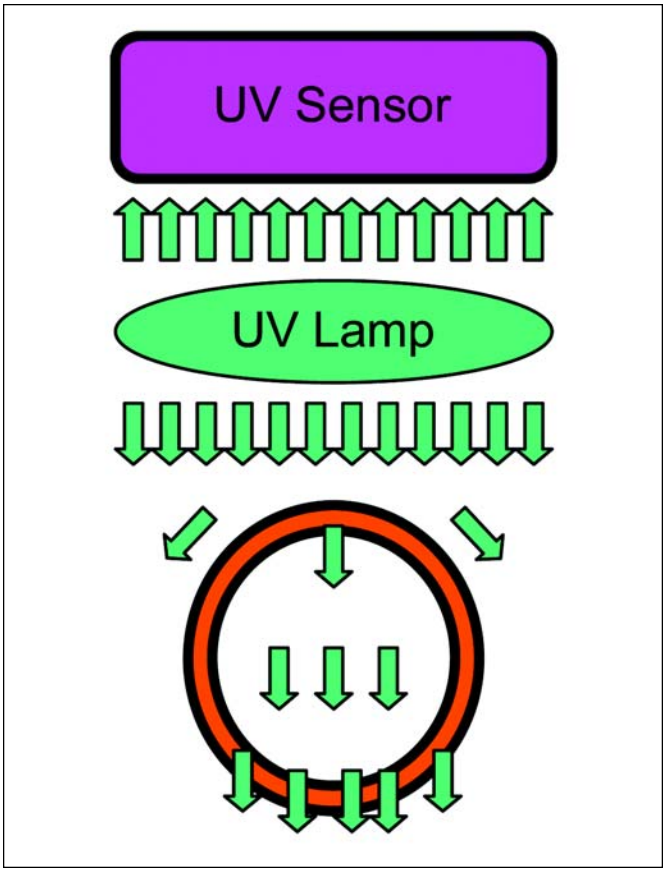

Figure 3. Illustration of oxidation cell configurations with integrated UV sensors.

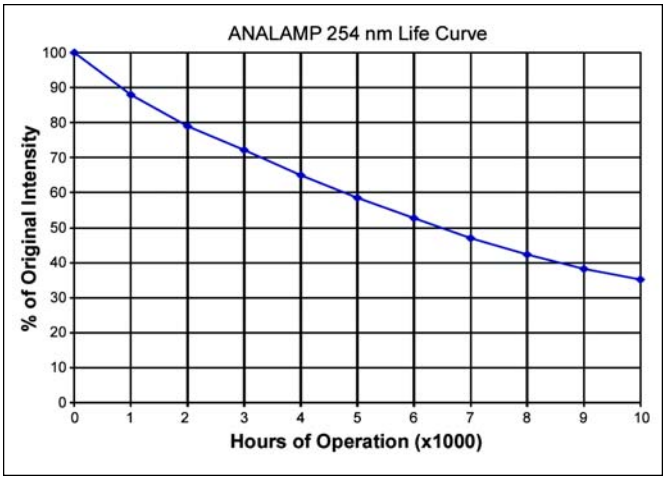

Figure 4. UV lamp ageing curve.[9]

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/cm^2) 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

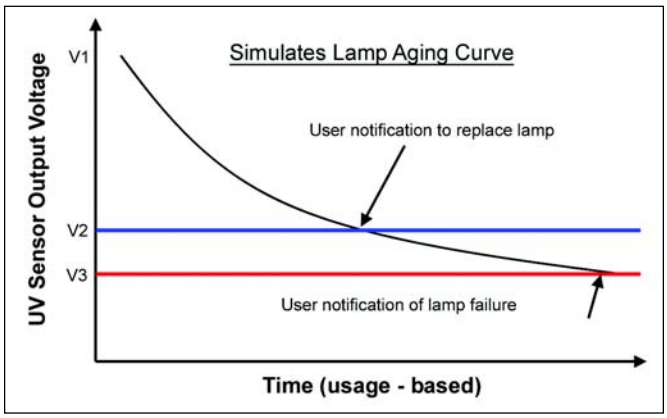

Figure 5. UV Sensor self-diagnosis application strategy for On-line TOC analyzer.

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 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.

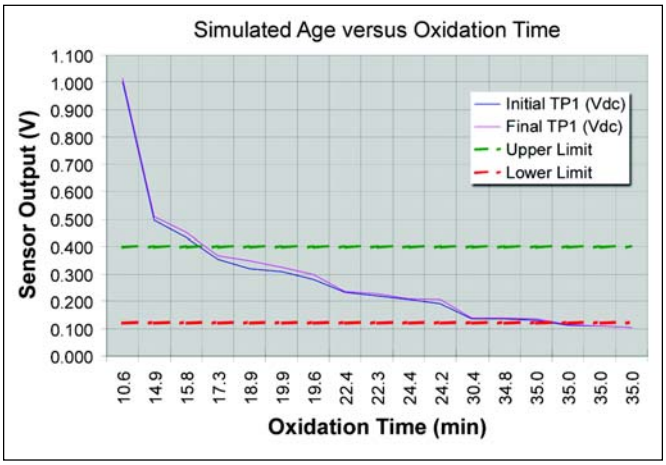

Figure 6. Actual UV sensor (lamp) output vs. Oxidation Time for 500 ppb TOC samples.

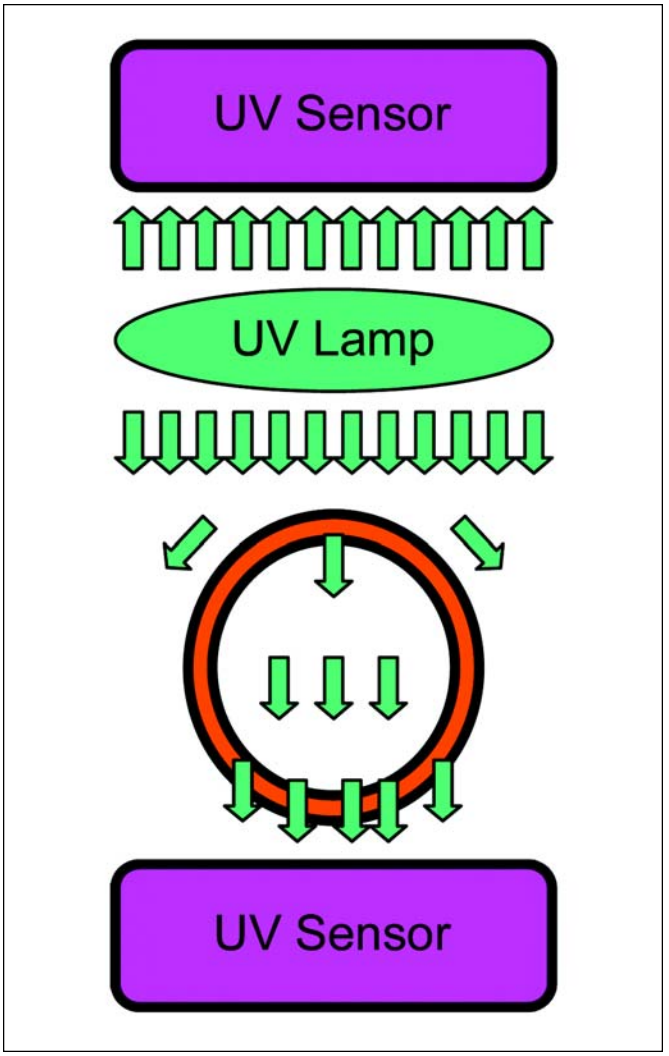

Figure 7. UV sensor implementation for rouge detection.

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, PFTE, 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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Improving Water System Performance: A Continuous TOC Measurement Technology to Enhance Real-Time Process Control

by Giovanni De Dona and Robert Theriault

This article discusses real time TOC tracking in the water purification process and the importance of rapid, continuous, and reliable TOC monitoring for real time critical water release.

Introduction

Water is the most widely used excipient in pharmaceutical and biotech manufacturing processes. It is used as an ingredient, reagent, solute, delivery device, cleaning material, and in some cases, the water is the end product such as sterile water for injection. In pharmaceutical production, the accurate measurement of water quality is critical to the water purification process. This industry mandates the monitoring of Total Organic Carbon (TOC) as specified in the monographs of the United States Pharmacopoeia (USP) for Purified Water (PW) and Water for Injection (WFI), and in the European Pharmacopoeia (EP) monographs for these same waters as well as Highly Purified Water (HPW). In these monographs, the specific TOC testing requirements for these waters are referenced in USP ⟨643⟩ and in the EP 2.2.44 general test chapters.

Organics are introduced into natural water systems by leachates in soil typically from the decomposition of vegetation, animal waste, and soil runoff. Humic acids are a common product of plant decomposition and a main contributor to elevated levels of organics in potable water during the fall season. These compounds are a complex mixture of high molecular weight substances containing carbon, hydrogen, and oxygen predominantly. Organic compounds in water are a concern at all levels of water purity from potable water to pure waters used in the manufacture of pharmaceuticals. The source water used for the production of Purified Water and WFI is drinking water as indicated in the major pharmacopeia. Potable water quality can vary seasonally according to climatic changes and municipal treatment strategies, and this results in varying TOC concentrations. In pharmaceutical manufacturing, organics are a contaminant to be controlled as they are a food source for bacteria in the water purification system. An increase in TOC concentration can be the result of an increase in potable water TOC or a decrease in water purification efficiency. The decrease in water purification efficiency can be due to the degradation of water distribution system components such as ion exchange resins in the form of fines, pump lubricating oils, polymer material dissolution, polishing resins, stagnant water zones, and membrane erosion among other contributing factors. A change in the TOC load in the water system can be the result of changed TOC in the source water, change in the water system components, or change in the purification efficiency of the water system. This change can influence microbiological control.

In pharmaceutical water quality monitoring that is performed on-line, the predominant method to measure TOC is based on differen-

$$C_XH_YO_Z \xrightarrow{UV\,185nm/254nm/\bullet OH\ radical} CO_2 + H_2O \rightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

non-ionic — ionic-conductive (carbonated water)

Figure 1. UV oxidation process of organic compounds.

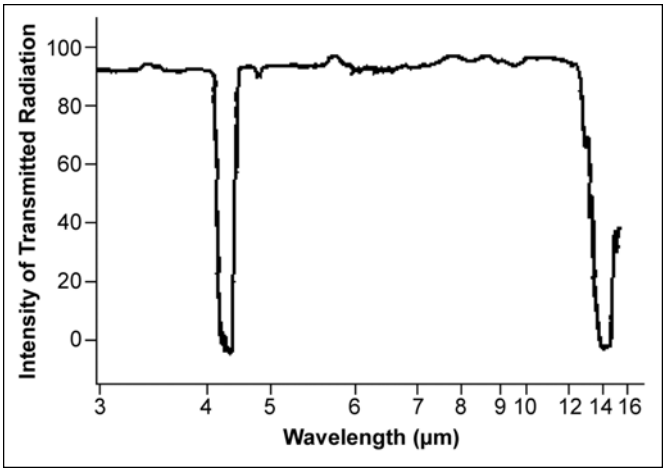

Figure 2. Infrared absorption bands for Carbon Dioxide.

tial conductivity measurements. Electrical conductivity measurements respond to the presence of ionic species in ultrapure waters which have an intrinsically low, but measurable, conductivity. Most organics do not exist in ionic form and are not detectable by conductivity, but exposure of water to UV light at wavelengths shorter than 200 nm leads to the formation of free hydroxyl radicals, ·OH. The hydroxyl radicals are highly reactive and subsequently proceed to break bonds of the organic molecules and oxidize the organic species present, producing carbon dioxide and water. The carbon dioxide forms carbonic acid, H_2CO_3, which partially dissociates to form H^+ and HCO_3^- which are detected as a change in conductivity - *Figure 1*. Based on the physical and chemical properties of CO_2 and H_2CO_3 in water,[1] this change in conductivity is related to the TOC concentration. The UV light is usually produced using Hg lamps that are similar in some regard to the TOC reduction lamps found in water systems today. These lamps produce 185 nm radiation to make the reaction proceed. There is also extensive 254 nm radiation present (5 to 20 times more intense than 185 nm) to facilitate the photolytic reaction.

The other detection technology used in the measurement of TOC in Purified Water is based on an infrared measurement of the carbon dioxide produced from various types of oxidation. The CO_2 generated from the oxidation reaction is sparged from the solution and transported to a measurement chamber. A C=O bond stretch vibration produces a prominent absorption band that is measured at a wavelength of 2330-2350 cm^{-1} (4.255-4.290 µm) in Figure 2.[2]

Irrespective of the technology, all TOC instruments that are used for "critical water release to production" must meet the USP ⟨643⟩ standard for TOC measurements and instrumentation.

USP Requirements and PAT Initiatives

Current monographs for PW and WFI mandate meeting USP ⟨643⟩. USP ⟨643⟩ contains both instrument acceptance criteria, and specific upper limits for the TOC concentration. Both the EP and Japanese Pharmacopoeia (JP) have specifications for the TOC measurements and instrumentation.

One of the requirements for USP ⟨643⟩ is that PW and WFI must not contain TOC levels exceeding 0.5 mg C/L (500 ppb carbon). Most pharmaceutical water purification systems will produce TOC levels that are typically a factor of 10 lower than this limit.

Also, USP ⟨643⟩ places acceptance criteria on TOC instrumentation. This criteria requires that the measurement system must meet the following:

1. It must distinguish between inorganic and organic carbon.

2. The limit of detection is 50 ppb carbon or less.

3. It must meet the System Suitability Test (SST).

The SST concept is used by the pharmacopoeia to challenge the suitability of a technology. In this case, the test is based on the ability to convert and detect two dissimilar organic compounds equivalently. Specifically, the standard compound is sucrose, a simple organic molecule consisting only of single bonds. The challenge chemical is p benzoquinone, which is an aromatic pi-bonded molecule and it has stronger bonds to break, requiring more energy to cleave each bond - *Figure 3*.

Both chemicals are prepared to a concentration of 500 ppb of carbon using Reagent Water (typically Purified Water quality or better, but not necessary) that must contain less than 100 ppb TOC. The TOC measurement system measures each solution, and the instrument readings for each solution are recorded. The TOC value of the Reagent Water is also measured since this water also contributes TOC to the standard and challenge chemicals. The instrument response for these three solutions is recorded for the Reagent Water (R_w), the sucrose (R_s), and the p-benzoquinone (R_{ss}). The ratio of the instrument response for the 500 ppb p-benzoquinone solution to the sucrose, corrected for the Reagent Water, is expressed as the response factor below.

$$Response\ factor = 100 \times \frac{(R_{ss} - R_w)}{(R_s - R_w)}$$

The response efficiency must be within 85 to 115 % in order for the TOC system to be suitable.

TOC sensors are used to analyze the purity of water. To ensure water quality and water purification system performance, constant monitoring is critical to allow actions to be taken in a timely manner, especially in the case of excursions. It is this approach that is embodied in the FDA's Process

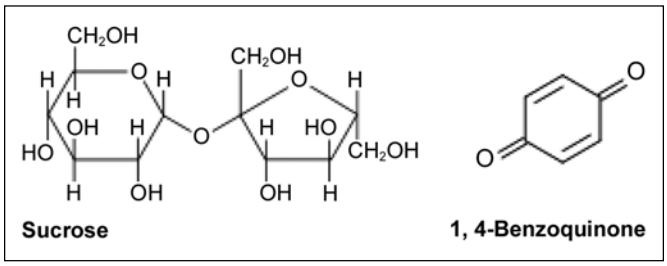

Figure 3. Sucrose and 1, 4-benzoquinone chemical structure.

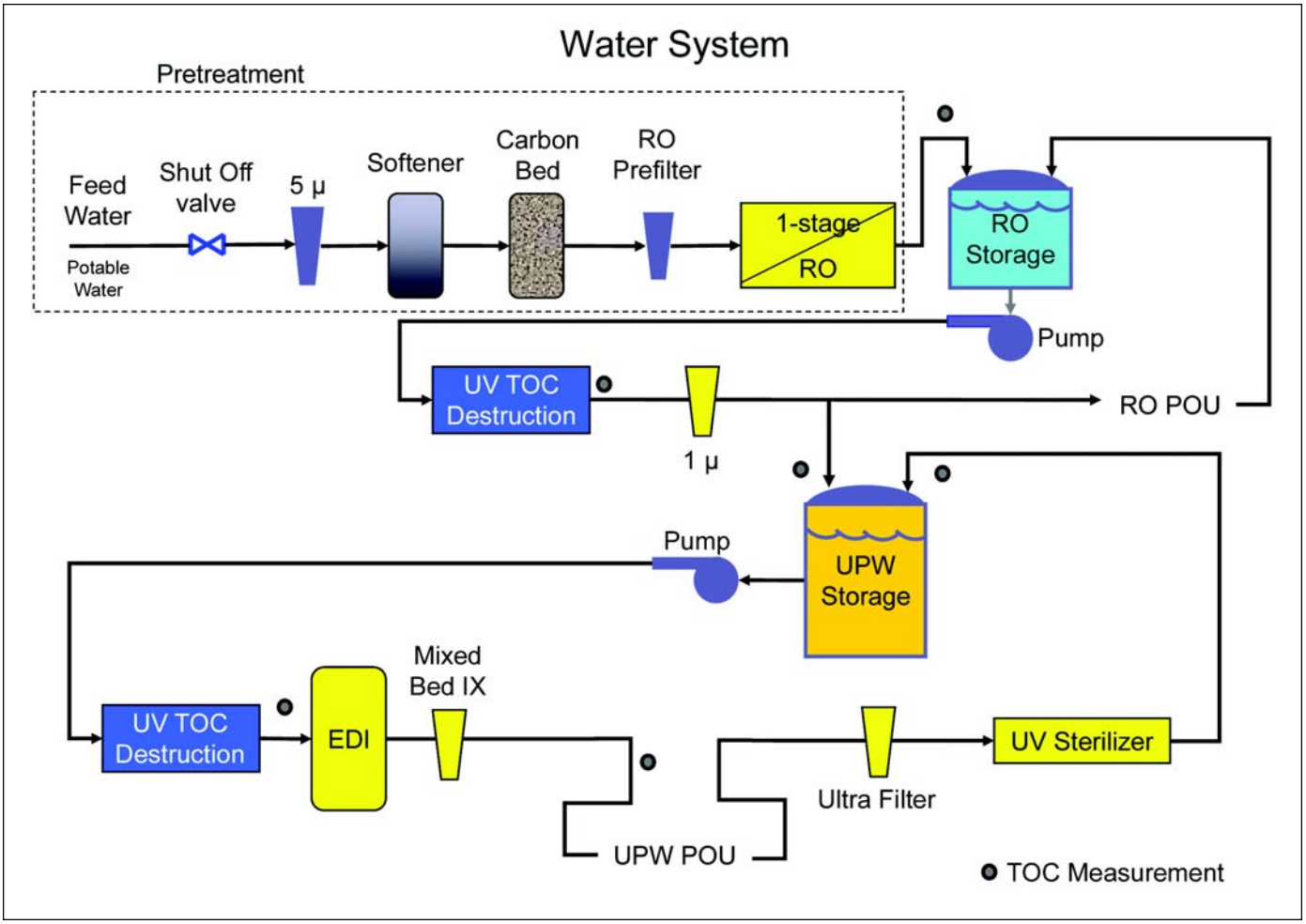

Figure 4. TOC sampling points within a water system.

Analytical Technology (PAT) initiative.[3,4] The initiative states the following, "PAT is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process material and processes with the goal of ensuring final product quality." This provides criteria that can be applied for any sensor used in the control of a production process. The main objective is the assurance of product quality through process monitoring and process understanding. As indicated in the initiative, this can be achieved through prompt measurements that are related to control and understanding of the process, and ultimately to product quality. In fact, the PAT initiative promotes the use of real time measurements with the objective of ensuring good product quality. This allows Real Time Release (RTR) of product and leads to a more efficient operation.

Water Systems and Measurements

A water system is a dynamic process consisting of various components and equipment whose collective purpose is to provide clean water meeting a certain specification. When a sensor is used to monitor levels of a component mixture such as TOC, the measurement is not only a regulatory tool, but it is also a diagnostic monitoring device. It allows the failed or weakened component within the water system to be easily identified and full water capacity to be restored in a timely manner, ideally prior to failure. Measurement of the TOC levels of the water in the return loop from the Points of Use (POU) to the UPW storage tank (Figure 4), allows the user to confirm they are meeting USP water standards for critical water release to production. Other measurement points of interest as indicated in Figure 4 include:

- after Reverse Osmosis to monitor membrane efficiency
- before the UPW storage to ensure low organic levels have been maintained after storage of RO water in tanks
- after TOC destruction to monitor the efficiency of the UV TOC reduction process
- after Deionization (DI) beds to monitor resin life and efficiency, but before the Points of Use distribution lines to ensure final water quality

When four TOC measurement systems were placed at the UPW Points of Use to monitor the water system shown in Figure 4, repeatability data was collected as shown in Figure

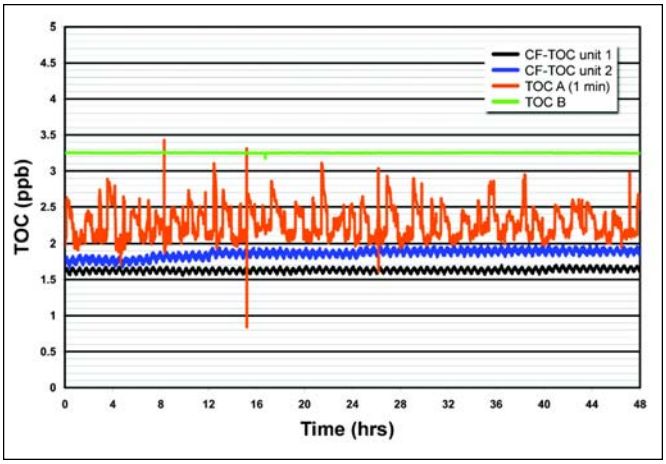

Figure 5. Repeatability of different TOC technologies.

5. Two of the TOC sensors were Continuous Flow TOC (CF-TOC) sensors and the other two measurement systems (labeled TOC A and TOC B) are existing product technologies. All technologies utilize conductivity measurements of pre- and post-oxidized water samples to determine TOC. The TOC sensors were all calibrated and passed SST prior to performing any testing and data collection.

A comparison of more than 48 hours of repeatability for the four TOC measurement systems revealed several results that warranted closer inspection - *Figure 5*. The CF-TOC sensors both show some baseline activity. On closer inspection, it reveals that the CF-TOC sensors are showing a consistent pattern. Conversely, TOC A appears to have a random baseline response and TOC B shows an offset flat line compared to the other TOC sensor responses.

Other data was collected for the CF-TOC sensor and re-scaled to a one hour interval; it also showed repeatable behavior in the water system - *Figure 6*. This new data revealed that the continuous flow TOC sensor showed a repeatable increase followed by a decrease in the TOC value over approximately a 40 minute period (Figure 6) and this cycle recurs without end. The water system diagram (Figure 4) shows how potable water is pretreated by a combination of filtration, softener, carbon bed, reverse osmosis, and UV radiation, before final treatment by further filtration, UV treatment, EDI, and mixed-bed ion exchange.

In Figure 6, the TOC is measured at ~10 second intervals, and a recurring increase and decrease in the TOC level is observed to be cyclical. Upon close inspection of the operation of the water system, it appears that an increase correlates with the delivery of water from the RO storage tank to the UPW storage tank. This increase continues until the UPW tank fills and the pre-treated water is no longer being delivered. While the tank is filled, the recirculation through the UV treatment and polishing distribution system causes the TOC to decrease. There is consumption of the water by multiple users as well as some reject water from the EDI. As a result of the consumption, the tank drains and eventually the control system calls for more water from the RO storage tank, and the cycle repeats.

An increase in the scale to three hours shows that the cycles are regular and correlate to the usage of water in the UPW system and the filling step from the pre-treatment system - *Figure 7*. The cycle typically ranges from 4.2 to 5.6ppb TOC. This illustrates how continuous and real-time TOC sensors can provide finite detail of the water purification system characteristics.

When the water system is fully operational, a continuous TOC sensor does not only reveal an excursion, but can provide sufficient resolution detail such as cycles within the water system - *Figures 5 to 7*. These cycles can show UPW water recirculating from the tank to the POU and back again, as well as water transfer from the RO tank. When the UPW tank

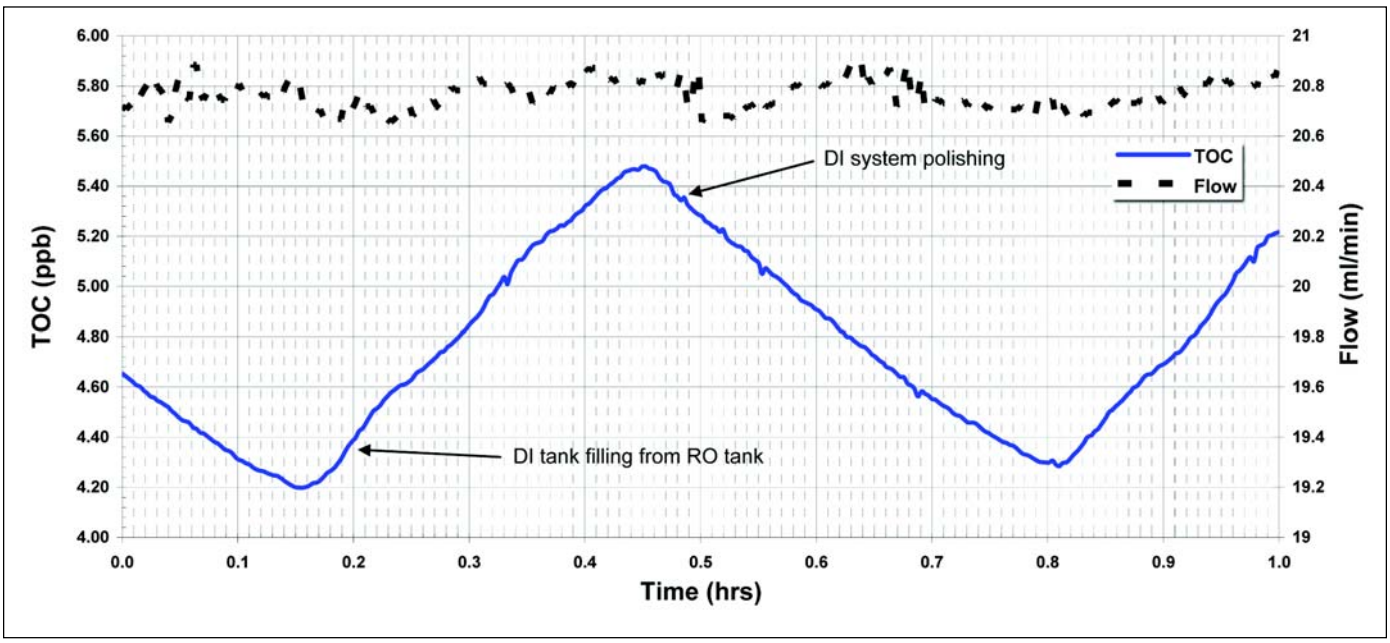

Figure 6. One hour data sampling from Continuous Flow TOC sensor.

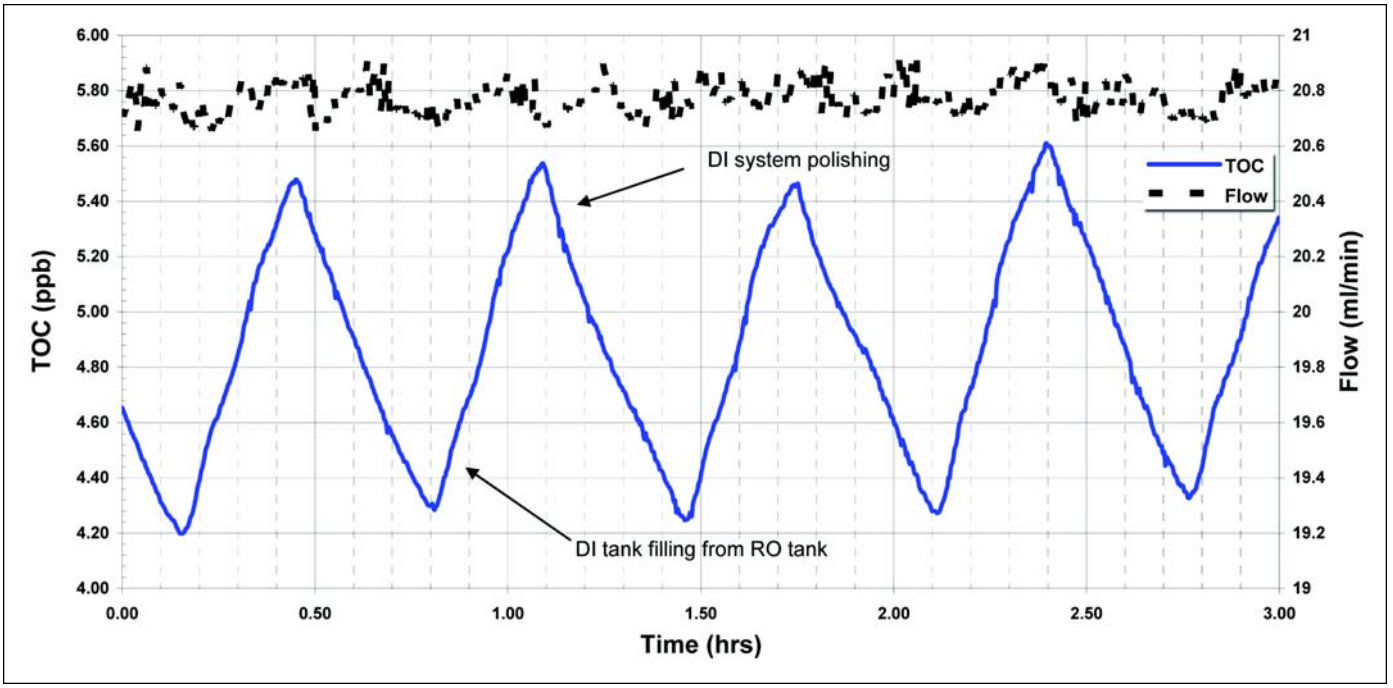

Figure 7. Three hour data sampling from Continuous Flow TOC sensor.

is full and this water is recirculating, the TOC levels continually decrease as the water is continually purified by the combination of the UV lamps and the mixed bed ion-exchange polisher. As the water is consumed by the combination of usage and EDI rejection, the UPW tank level eventually lowers and the control system calls for RO water. As more water is distributed from the RO tank to the UPW tank, the TOC levels continually increase. The result is a TOC concentration that reflects the cyclical makeup and usage processes of the water system. Conventional TOC measurement technologies which record a measurement every 10 to 30 minutes cannot see this detailed behavior.

Real-Time Sensors

Until the mid-1990s, testing for organics in bulk pharmaceutical waters had been based on wet chemical testing using potassium permanganate and sulfuric acid. This test is known as the "Oxidizable Substance Test" (OST), and it is still in use today for several USP packaged waters such as Sterile Water for Injection. This test is based on the color retention of potassium permanganate. The premise of this test was that this powerful oxidizing agent (Mn^{7+} in the form of permanganate) would lose its pink-purple color and become a clear solution if sufficient organics or other oxidizable substances were present in excessive quantity in the water. This test was deficient in several regards. OST was not quantitative, it required some subjective determination, and was not sensitive to low level TOC. Furthermore, OST required discrete samples to be collected and tested which added to the time and cost of analysis. Manual handling of samples also added the potential for contamination. This was an opportunity to provide real-time, quantitative analysis for process control in addition to RTR. In 1996, the USP replaced the Oxidizable Substance Test with USP ⟨643⟩ with a requirement for the control of organics in Purified Water and WFI, providing an opportunity for a TOC measurement that is ideally suited for on-line quality control. Instrumentation meeting this specification was now able to perform multiple analyses per day. As the technology improved, on-line sensors were introduced capable of measuring lower TOC levels in less than 20 minutes, and this analysis does not require any sample handling. Present day instruments are capable of real time continuous measurements allowing Real Time Release (RTR) of Purified Water.

Continuous Measurements

For this discussion, a continuous measurement is described as one that monitors a physical or chemical property of a process, and the measurement is followed by another measurement within seconds. This continuous measurement technology is based on constant flow of sample through the sensor and the ability to measure the process change in a brief time. This technology allows low sample volume per analysis increasing the volume of water available for release to production, consequently reducing the cost of producing Purified

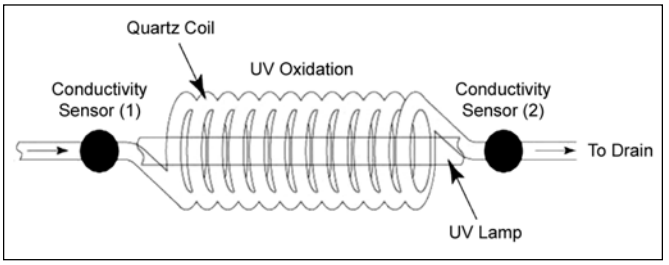

Figure 8. Continuous Flow Technology based TOC sensors.

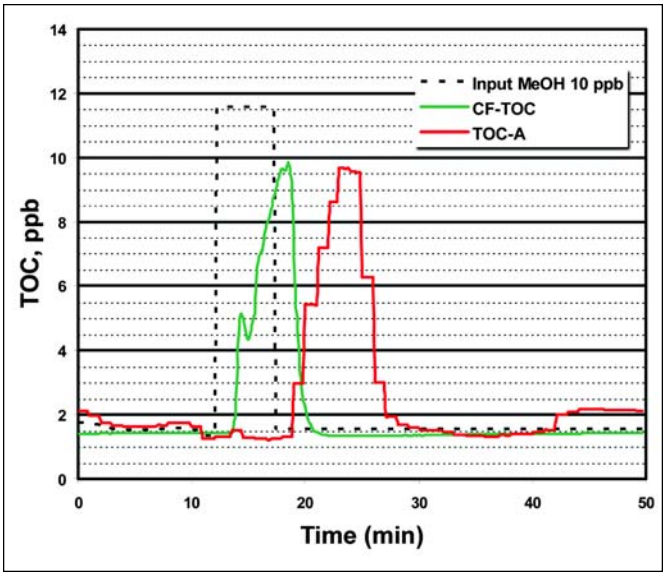

Figure 9. MeOH response curves. CF-TOC vs. TOC A.

Water. An excursion can be rapidly identified with this type of TOC sensor. Identifying an excursion rapidly allows an immediate response, preventing non-compliant water from being used in the production process or contamination from the return loop to the UPW water storage tank. If contaminated water reaches the UPW storage tank, it is then possible that non-compliant water may reach the use points. The additional costs of lost production time, additional testing, and product impact assessments depend on the usage of the water and the products that are impacted, but accurate and fast measurement of the TOC in the UPW system can result in significant cost savings by eliminating non-value-added steps.

A TOC sensor using continuous flow technology is based on constantly flowing water. In the example in Figure 8, initial background conductivity is measured at conductivity sensor 1. As the water travels through the quartz coil, it is exposed to UV light where hydroxyl radicals are generated and break down any organic molecules present to carbon dioxide which forms carbonic acid, H_2CO_3 . The acid partially dissociates to form H^+ and HCO_3^-, and the second sensor measures the resultant conductivity. The difference is detected as a change in conductivity and is related to TOC. The time between successive TOC measurements is five seconds, and the resulting TOC measurement is delayed <60 seconds from the time the water enters the TOC sensor.

If a contaminant is introduced into the water system, it may be necessary to respond to the contamination and possibly divert the water from returning to the UPW tank to prevent contamination. A real-time measurement is one that provides a rapid response to an excursion and allows immediate action to be taken. Continuous flow TOC sensors provide fast real-time measurements and allow excursions to minimally effect the production of pharmaceutical waters.

Excursions and Real-Time Recovery

In addition to measurement and control, TOC sensors are used to monitor deviations, sometimes rapid or intermittent, from a baseline measurement. These excursions are caused by the introduction or release of contaminants into the purification process. It may be a brief disruption with duration of seconds or minutes caused by a valve opening and closing for example, followed by a return to baseline reading. Alternatively, it may be a longer disruption which results in a long term baseline drift or change such as an RO membrane defect. It also can be normal cyclical behavior due to water consumption (as described above) or sanitization cycles. For these types of excursions, rapid continuous and real-time measurement technology is an invaluable tool for TOC measurements. These attributes are expected and provided in conductivity, pH, DO, pressure, temperature, flow, and other measurement systems so it is reasonable to strive to achieve a similar speed performance with a TOC measurement technology.

When the disruption is brief or intermittent, a fast and continuous measurement update rate will allow the excursion to be detected, whereas a slow sample rate measurement is likely not to detect the intermittent failure. If there is a significant baseline shift, a slow sampling frequency measurement system is similar in terms of its detectability to a continuous measurement system. Both fast and slow technologies will see the shift. However, in the example, the response time is the more critical attribute. The sooner the excursion can be detected, the sooner the control system can identify a potential for product impact. In the case of a measurement technology where there is a combination of speed (response time) and continuous measurement, a close and rapid (real-time) inspection of the process is possible. The resolution provided by data that are only seconds apart allows real time tracking of the water system process. This combination of speed and continuous measurements provides an opportunity for non-compliant water to be re-directed to drain or recirculated, rather than inadvertently used for product contact directly or indi-

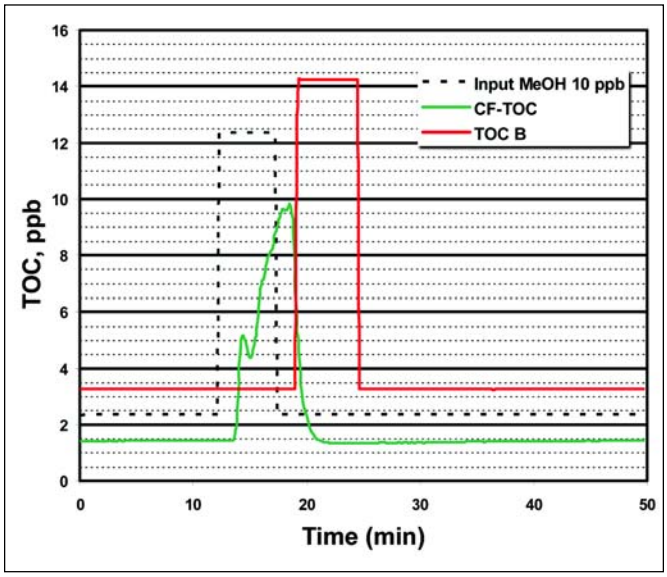

Figure 10. MeOH response curves. CF-TOC vs. TOC B.

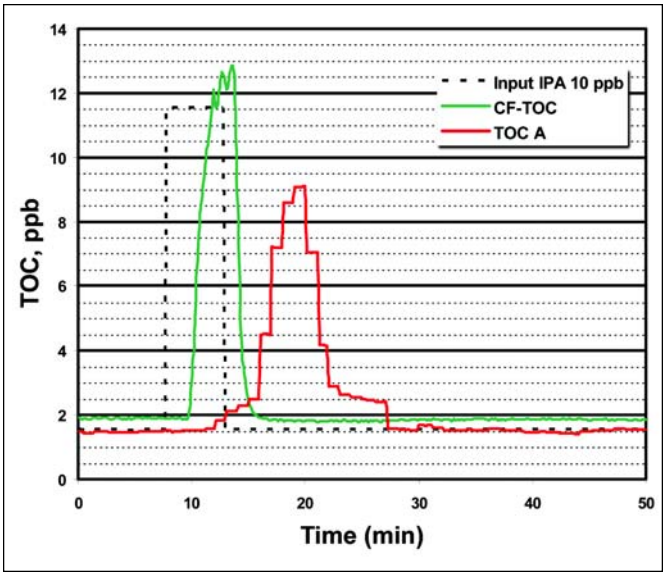

Figure 11. IPA response curves. CF-TOC vs. TOC A.

rectly, such as a cleaning/rinsing process. Today's TOC instrumentation and sensors are routinely equipped with various analog and digital outputs that interface with any control system.

In a series of real time recovery tests, three conductivity based TOC systems (CF-TOC, TOC A and TOC B) were compared by performing testing on select typical organic chemicals. All chemicals were prepared at concentrations of 10 ppb Carbon. Water was flushed through each analyzer for 30 minutes. An organic solution was pumped into each of the units for five minutes and the TOC data observed for up to one hour to track the response. The delay from a common manifold was calculated to be 21 +/- 5 seconds for all sensors tested. The Continuous flow TOC technology and two other technologies were evaluated under these test conditions.

A concentration of 10ppb TOC Methanol was introduced into each TOC sensor by standard addition. This was achieved by the injection of a stock solution of methanol at a set rate based on the flow of the water through an injection station. The solution was homogenized by passing through a mixing chamber which delayed the flow by one minute prior to entry into the TOC sensors. The dotted pulse in Figures 9 and 10 represent 10ppb TOC of methanol over a five minute interval. When methanol is injected into the three instruments simultaneously, the CF-TOC sensor responds within two minutes of the injection time, while TOC A and B show a response, but seven minutes after the beginning of the excursion for the methanol. In both cases (Figures 9 and 10), the five minute excursion is over before TOC A and TOC B detect it.

Under similar test conditions, another test was performed with 10ppb TOC IPA. The CF-TOC sensor responds within two minutes of the injection time to IPA with a proportional response - *Figure 11*. By comparison, TOC A responds similarly, but five minutes after the beginning of the excursion. In a similar test (Figure 12), TOC B responds proportionally to the TOC disturbance, but eight minutes after the IPA is injected. Again, in both cases (Figures 11 and 12), the five minute excursion is over before TOC A and TOC B detect it. The CF-TOC technology responds to the excursion within two minutes after its appearance, and it also detects the disappearance of the excursion in real time.

When discrete batch measurements in the laboratory were more common, sampling one liter of water which took about five seconds to produce (out of a 10 hr day, this represents sampling of <0.014% of the time) means that the water is not being monitored >99.98 % of the time. Since water production is a continuous purification and consumption process, a real water system can be enhanced by a "real-time" detection and analysis. When an excursion occurs, it is essential to relate the accuracy of a TOC sensor to its ability to respond and identify the upset condition in a timely manner. Directly stated, if the duty cycle of the measurement system is low, the ability to detect an event is low. If the duty cycle is high, the ability to detect is high. Unless an event is being monitored, it will not be detected.

If the excursion duration is regarded as an integration window over which we determine the response factor from a TOC sensor, a sensor with continuous measurement technology would respond immediately and be more accurate because the response is within the time that the excursion was occurring. Conversely, if a sensor's main response is after the upset condition due to a slow response time, then its integrated error is greater, and it exhibits a greater response error. A real time recovery error would incorporate both speed of response and the percentage recovery or sensor response. Then the definition of the real time error would be, Equation 1:

$$\text{Real Time Recovery Error } \% = 100 \times \frac{\text{Abs}[R(t) - I(t)]}{I(t)}$$

Where I(t) is the input disturbance at time t, R(t) would be the sensor measurement in response to I(t) at time t, and Abs is

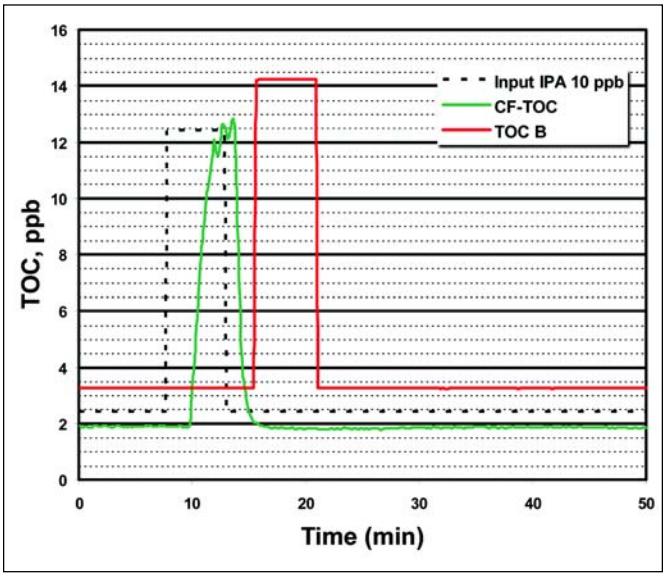

Figure 12. IPA response curves. CF-TOC vs. TOC B.

the absolute value. A perfect response would be when R(t) = I(t) at all times because the response is instantaneous and equivalent to the disturbance. The total recovery error for a perfect sensor would then be the sum of all the real time recovery errors and would be equivalent to zero, i.e., Equation 2:

$$\text{Total Recovery Error for a perfect sensor} = \sum_{t=0}^{T} \text{Real Time Recovery Error}(t) = \text{zero}$$

In actuality, equations 1 and 2 are relative errors as they are calculated as deviations from a baseline response which can vary from one type of sensor to the other.

If the total recovery error for all the tested sensors was calculated for IPA using data collected from response curves in Figures 11 and 12, the plot in Figure 13 would be the result. Figure 13 shows how with time, the longer the delay in the response from the TOC sensor after an excursion, the greater the accumulated error. The total error for the CF-TOC is then lower because of the response within two minutes of the beginning of the disturbance.

Figure 14 shows the final value of the total recovery error at the end of the experiment. As shown in the bar graphs, the total recovery error is dependant on the organic compound and the sensor being used. The bar graphs represent the total recovery error for a TOC sensor grouped by organic compound. The lower the bar graph value, the closer that sensor responded to a perfect response for the organic compound injected. The varying errors show that no one sensor responded perfectly for all tested organic compounds. Where NR is shown, this indicates that there was No Response or a less than 1ppb shift from the baseline was observed during the measurement.

Each instrument has a variable real time recovery error depending on the organic compound injected. Each of these compounds represents one of thousands that may be present in a water purification system that make up the TOC measurement.

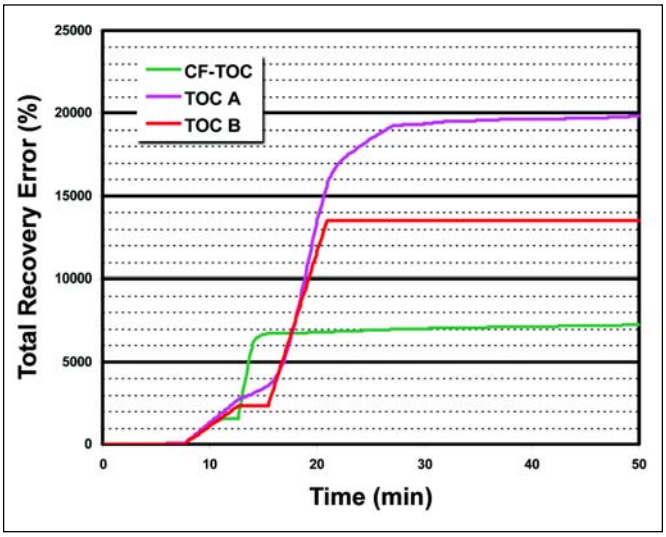

Figure 13. Total error accumulated over time.

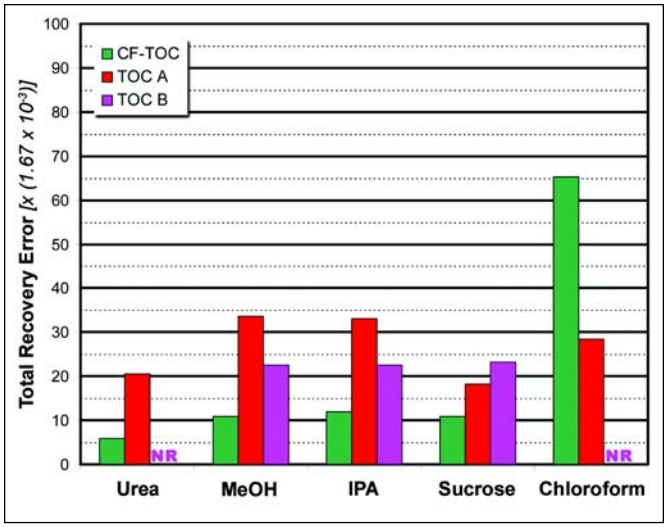

Figure 14. Summary of Total Recovery Error- NR is no response.

In real water systems, both speed of response to an excursion as well as recovery of response back to normal conditions are important in real-time monitoring. A TOC sensor needs to respond rapidly to an excursion and then equally as fast recover when the excursion has passed.

An introduction of 100ppb TOC as acetic acid reveals a rapid response from the CF-TOC sensor with a TOC of 90ppb Carbon - *Figure 15*. Alternatively, the TOC A analyzer shows a varying TOC value approximately 165ppb Carbon. An autozero reset was initiated by the TOC A unit taking it offline for 35 minutes. TOC B did not respond.

The varying responses by the different sensors to each of the organic species show that each technology is susceptible to interferences. However, when TOC is measured in a real water system, the organic species discussed represent small fractions of a mixture that is measured as the Total Organic Carbon measurement.

Maintenance, SST, and Calibration

One of the main attributes of real time TOC sensors is the need for maximizing operational time and in return minimizing downtime associated with functions such as maintenance, SST, and calibration. Depending on the initialization or start up time required for the TOC technology, calibrations and SST tests can be performed in less than two hours if both tests are performed sequentially. Most of the time a requirement to perform these tests involves ensuring the sensor has been sufficiently rinsed to eliminate any cross contamination. The SST test and calibration are typically performed using a kit which can be incorporated as a dedicated component on a TOC sensor or separated kit which is connected when needed. Its function is to deliver SST and calibration solutions into the TOC sensor. If multiple TOC sensors are utilized in a process, the kit can be moved from one sensor to another in minutes. SST tests and calibrations are typically performed on a six month cycle maximum for a system that is in operation on a 24 hour basis; however, a greater testing

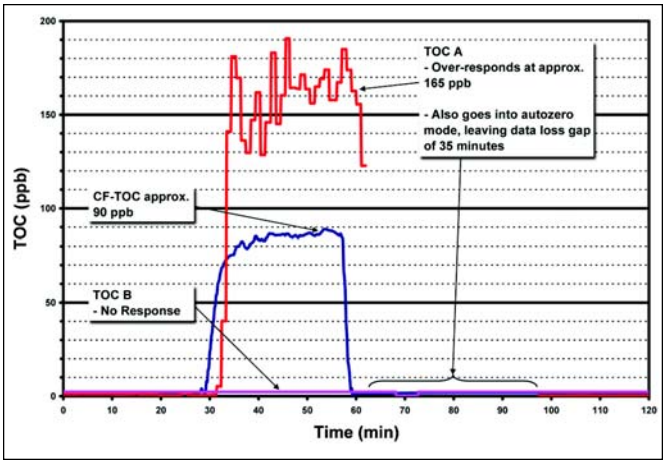

Figure 15. Acetic acid response curves.

frequency can be adopted. The six month frequency for the SST and calibration can coincide with the maintenance program which is the replacement of the UV lamp. Another maintenance requirement is changing the inlet filter element which takes less than five minutes to perform. The filter element replacement frequency is dependant on the quality of water being supplied to the TOC sensor.

Operation of CF TOC sensors require no gases or reagents, and there are no associated disposal costs due to chemicals. The simplicity of CF TOC sensors means that there are no moving parts, which result in less wear on system components.

Transmitter-Sensor Design

On-line process TOC sensors are designed as a transmitter-sensor combination. The transmitter is an instrument that measures the two conductivity and temperature measurements from the TOC sensor, processes the measurements into a TOC measurement, and then produces an output. The output can be viewed on the transmitter display, or it can be transmitted via analog or various digital means to an external chart recorder, PLC, or other recording device. The advantage of a separate transmitter-sensor is the ability for a multiparameter transmitter to add other process measurement tools in addition to the TOC sensor. Measurement sensors such as conductivity, pH, ORP, oxygen, flow, and pressure/tank level also can be connected to the transmitter in addition to multiple TOC sensors. This approach is advantageous to the end user from both a cost and training perspective. The use of patch cables up to 300 feet allows the sensor to be located next to the transmitter or far from the transmitter if the sensor needs to be installed in a difficult location. In the case where the water system control panel is a distance from the sample port, the transmitter-meter concept has a distinct advantage that allows the user to install the sensor at the sample port and install the transmitter at the control panel.

The transmitter-sensor concept with multiparameter functions has evolved since its introduction in 1989. If a transmitter is designed to accept sensors based on different measurement principles, it would need to identify the type of sensor. Manually entering the sensor calibration and setup information every time a sensor is connected to the transmitter can be both cumbersome and lead to an array of human errors with incorrectly entered data. A plug and play concept utilizes smart sensor technology that stores the relevant identity information on a non volatile memory chip that the transmitter reads when the sensor is connected into the transmitter. This allows the sensor to be taken to another transmitter, and the identity as well as the calibration data of the sensor is accessible through the new transmitter.

When determining low level TOC, the CF sensor transmitter also will display the conductivity (compensated or uncompensated), resistivity (compensated or uncompensated), and temperature. These are critical additional parameters when monitoring water system quality. The TOC, conductivity/resistivity, and temperature readings are not only quality monitoring parameters, but also useful diagnostic tools when attempting to determine the source of an excursion.

Conclusion

The response of the continuous flow sensor to various organics shows that, like the other TOC technologies, it is susceptible to interferences. Despite differences in response to individual organic species, these represent small fractional contributions to the Total Organic Carbon content. A change in a component organic species may be insignificant when compared to numerous other organics that may be present in treated water in an UPW system making up the TOC response. A TOC sensor is a tool used to determine changes in the overall organics, and it has no specificity. However, the TOC sensor must respond rapidly, be functional, and stay on-line. This allows the pharmaceutical water to be produced and released with confidence without costly repercussions.

A Real Time Release continuous flow TOC sensor provides rapid response to an excursion with an opportunity in real time to respond to and divert contaminated water. This reduces downtime associated with excursions, maximizes efficiency, and reduces cost associated with product loss, manpower, and equipment. In brief, it allows closer control of the entire water purification process through the understanding of the UPW system characteristics. It ensures the end users are receiving reliable good quality water for the various uses in production.

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Process Gases and Distribution Systems in Pharmaceutical Production

This article discusses the use of process gases in the pharmaceutical industry.

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Pure gases and well-defined gas mixtures are used in the pharmaceutical industry for a very broad range of purposes. These can be classified according to the chemical or physical application involved - *Table A*. The most commonly used gas in pharmaceutical production is nitrogen, but argon, oxygen, carbon dioxide, and compressed air are also common. Gas can be considered a raw material, component, or processing aid (excipient), depending on how it is used and whether the process is API production or the production of final pharmaceuticals. Since gases are used for different purposes, a variety of gas purities and specifications exist on the market. Guidelines and regulations offer little guidance. This creates a big challenge for today's drug producers to find and choose the appropriate gas quality. In general, three main definitions of gases are commonly used: industrial, traceable, and medicinal gases.

Medicinal gases are finished drug products, and manufacturers of medicinal gases must follow the requirements of current Good Manufacturing Practice (cGMP) regulations. Medicinal gases are specifically reviewed in the EU Guide to GMP, Annex 6 Manufacture of Medicinal Gases,[1] the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products, Annex 6 Manufacture of Medicinal Gases,[2] and in the FDA's draft guidance cGMP for Medical Gases.[3] According to the EU classification, "any gas or mixture of gases intended to be administered to patients for therapeutic, diagnostic, or prophylactic purposes using pharmacological action" is classified as a medicinal product.[1,2]

Table A. The use of gas applications in the pharmaceutical industry.

- Reactants in chemical reactions such as oxidation and hydrogenation
- Fermentation and cell-cultivation
- Inerting media, e.g., to prevent oxidation
- Fluidized bed dryers or coaters
- Drying of equipment
- Particle transport and jet milling
- Sparging of liquids
- Stirring of liquids
- Low-temperature cooling, e.g. low-temperature reactions, freezing or lyophilization
- Super-critical extraction
- Cryo condensation
- Propellants for inhalers
- Cleaning with dry ice
- Cryo grinding
- pH regulation

Industrial and traceable gases are terms and categories used by gas suppliers. For that reason, no common and well-defined definition exists. The differences between the three categories are illustrated in Table B. A traceable process gas is a gas characterized by its traceability. The product should be purchased according to an agreed specification and should always be delivered with a Certificate of Conformity (CoC) or a Certificate of Analysis (CoA), depending on how critical the gas is, i.e., where in the process the gas is used. While a typical CoC states the supplied product meets minimal purity specifications, it generally does not offer analytical results. A typical CoA states the minimal product specification, along with the results of a specific analysis of the batch. The product may be analyzed for impurities according to pharmacopoeias or pharmaceutical industry production demands with qualified instruments and validated methods. However, since the gas is not a medicinal product, it does not need to be produced according to cGMP.

There is a wide range of gas distribution system installations in the pharmaceutical industry:

- industrial installations (maintenance and welding)
- specialty gas installations (laboratories)
- process gas installations (GMP production)

	Industrial Gas	Traceable Gas	Medicinal Gas
Use	Utility, cutting and welding	Raw material, process aid, excipient, high-purity gases	Healthcare applications
Specification	Standard from supplier	Agreed specification, e.g. according to Pharmacopoeia	Pharmacopoeia
Type of Certificate	On demand	Certificate of conformity or Certificate of analysis	Certificate of conformity
Applicable Quality System	ISO or equivalent (non-cGMP)	ISO or equivalent (non-cGMP)	cGMP

Table B. Differences between industrial, traceable and medicinal gases.

The main differences between these systems are quality of the gas, system tightness, and level of documentation. Specialty gas systems in laboratories have higher tightness requirements, whereas the critical parameter for process gas systems is documentation. This article focuses on the use of process gases in the pharmaceutical industry. These gas systems may be regarded as a critical utility as well as non-critical utility depending on the influence on the final product.

Risk-Based Approach to the Specification of Gases

In order to determine the requirements for the gas, a drug producer needs to find the requirements of the drug product, the manufacturing process, and applicable cGMP regulations. What production requirements will be fulfilled, controlled or influenced by using the gas? Identify these requirements and set values according to the product specification. Divide the manufacturing process into logical process steps, and identify the stage in the process at which the gas will be used in order to fulfill production requirements.

Product or process impact assessment:

- How might the gas related requirement fail?
- Can the gas affect any other drug product requirements?
- Can the gas affect the process step in any other way?

For each point that might make the requirement fail, ask: "If this failure occurs, what effect may it have?" and then determine the severity of the effect of the failure if it were to occur.

Define requirements and/or measures that, if fulfilled, would mitigate or eliminate the failure or its effect. The mitigation activity is a method to design out potential failures early in the process. The number and level of mitigations for a given failure or its effects are determined by its severity. The list of mitigations will form the basis for the user requirement of the intended gas and/or gas system.

Regulatory Requirements, Guidelines, and Standards

The FDA's system-based inspections have a risk-management approach and focus on operating systems. The system-based inspections are an initiative of the FDA intended to ensure the more efficient use of resources, and to provide more focused inspections. The inspections are based on knowledge gained from previous inspections, and on scientific and technological developments.[4]

The facilities and equipment system includes utilities that are not intended to be incorporated into the product, such as HVAC, compressed gases, and steam and water systems. The system inspection covers aspects,[4] including:

- equipment installation and operational qualification where appropriate
- adequacy of equipment design, size, and location
- controls to prevent contamination, particularly with any pesticides or other toxic materials, or other drug or non-drug chemicals
- equipment identification practices (where appropriate)

The materials system includes measures and activities that control finished products, components (including water or gases that are incorporated into the products), containers, and closures. Areas to be covered during an inspection of the materials system include the following gas-related areas:[4]

- identification and inventory
- at least one specific identity test conducted on each lot
- testing or qualification of the supplier's test results
- water and process gas supply, design, maintenance, qualification, and operation

The FDA has recently focused attention on process gases, and acknowledges that they are used both in non-critical and critical processes, in which the API or finished pharmaceutical products are exposed to the gas.

End users and their qualification and quality assurance personnel must demonstrate that the facility complies with 21 CFR 211.65(a) which states:

> *"Equipment shall be constructed so that surfaces that contact components, in-process materials or drug products, shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."*[5]

All utilities that could impact on product quality (e.g., steam, gases, compressed air, and heating, ventilation and air conditioning plants) should be qualified and appropriately monitored. Action must be taken when limits are exceeded. Drawings for these utility systems must be available. A gas system qualification may include Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Gas samples are taken

during the OQ and/or the PQ stage, and analyzed according to agreed specifications, which in most cases will be the specifications in the pharmacopoeia monographs.[6]

The Aide-Memoire – Inspection of Utilities of the PIC/S provides guidance for GMP inspectors for use in training and in preparation for inspections. It is not mandatory; however, the industry should consider the PIC/S recommendations and aide-memoire to be appropriate. The Aide-Memoire is designed as checklists for HVAC, water, steam, and gases.[7]

Improved standards and guidelines, such as the ASME Bioprocessing Equipment Standard (BPE-2002) and the ISPE Baseline® Pharmaceutical Engineering Guides, have driven the quest for quality in pharmaceutical piping systems. The material generally used in high purity biopharmaceutical applications is stainless steel. Requirements also have been specified for the quality of the components chosen, welding, cleaning, etc.

A process gas system having direct contact with the product or preserving product status is defined as a "Direct Impact System," and the point of use filter is a "Critical Device."[8] The manufacturer of sterile products should use the following design considerations for a process gas system:[9]

- Process gas quality must meet the product specification.
- Construction materials should be compatible with any external sanitizing agents or internal sterilants (such as steam).
- 5 µm or better pre-filtration and 0.2 µm filtration at point of use in the case of a sterile or aseptic application
- The distribution system design should include sampling points.

ISO 8573 "Compressed Air" is intended to establish purity classes and harmonize air contamination measurements. The standard deals with contaminants in the form of water, oil (both as vapor and as aerosols), solids, microbiological organisms, and gaseous contaminants. At present, seven of the nine planned parts have been published. Since the standard is designed for any industrial application, it may not be sufficient for all pharmaceutical purposes, and in many ways does not correspond to or is not compatible with the text in the Pharmacopoeias.[10]

Documentation is vital for gas distribution systems if they are to comply with regulations.

Impacts from the Gas System on the Quality of Gases

Impurities other than water are almost negligible since the magnitude of their presence is the same in the ambient air as inside the process gas distribution system. However, if the system passes through rooms with perceptibly higher concentrations of impurities in the air, i.e., with a partial pressure higher than that inside the system, one should consider even small leaks in the system as a potential source of contamination due to diffusion. Another risk is the injector effect, where a gas passing a leak at high speed can cause vacuum, introducing ambient air into the system. Therefore, it is recommended to perform leak tests on gas supply systems on a regular basis. First, gas leaks can be very expensive in the long term. Second, a leak can be the source of contamination of the gas. Leak tests should always be performed as part of the commissioning activities on the system after maintenance and any alterations.

Contamination of the gas with another gaseous substance also could originate from a mix-up in the filling of gas systems. However, this should be prevented by the supplier's quality assurance system, including dedicated trucks and filling equipment for the gases.

The accumulation of gaseous pollutants in cryogenic vessels is considered a risk. Cryogenic vessels are rarely emptied completely and condensed gases that do not enter the gas phase at the low temperature of the gas in the cryo vessel may accumulate. According to EU GMP, Annex 6, 5.2.11,[1] deliveries of gas may be added to bulk storage tanks containing the same gas from previous deliveries. The results of a sample must show that the quality of the delivered gas is acceptable. A sample could be taken from:

- the delivered gas before the delivery is added
- the bulk tank after adding and mixing

Water

Water in process gases is critical because it is the basis for the growth of microorganisms. Therefore, water content should always be part of the specification for the gas. In monographs from the European Pharmacopoeia, the allowed value is 67 parts per million volume (ppmv) for nitrogen, oxygen, and carbon dioxide.[11] The value corresponds to the water saturation pressure at minus 50° Fahrenheit (-45,6°C) and atmospheric pressure of the gas. In such a dry environment, the microbial growth rate will be very close to zero. The advantage of employing ppmv instead of dewpoint is that it is independent of the actual pressure of the gas.

However, water can enter the distribution system itself from the surrounding environment.

Though gases are usually distributed at pressures six to eight times the ambient air pressure, the water vapor pressure in the ambient air is higher than the water vapor pressure inside a system containing a dry gas. This may allow the moisture to diffuse inward through the weaker components of the system. Therefore, it is recommended to restrict the use of hoses and other non-metallic components. Particularly if consumption is limited or if the system remains pressurized with no consumption, the threat should be considered real and could be one of the main challenges when validating the system.

Particles

In older systems made of galvanized steel or copper, oxidation of the pipe walls also may lead to contamination. The initial particles, formed by oxidation, may act as an abrasive that grinds off more particles from the pipe wall. Opening the distribution system also will expose the system to particles from the outside environment. When altering the system, the

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contamination risk can be minimized by using strict specifications on how to conduct activities, such as cutting pipework and handling pipes and components before the actual installation, e.g., storage of pipes on the building site.

To ensure that contamination with particles does not influence the quality of the gas at point of use, it is necessary to flush the system after maintenance and repairs. A final test of the particle content of the gas before using the system is recommended. Contamination of the gas with particles also can be caused by faulty equipment such as compressors or filters. A maintenance and surveillance program for the components can only minimize this risk to the system. This may include pressure difference monitoring over filters and regular inspection of compressors and driers.

Hydrocarbons

Hydrocarbon impurities can originate from malfunctioning compressors, from pipe work or components that have not been properly cleaned before installation. Risks can be minimized with proper specification and guidelines for documenting the cleanliness of the materials used. Malfunctioning equipment can only be avoided by maintenance and surveillance. In compressed air systems, the inlet should be located in a place where the ambient air is not subjected to exhaust from motor vehicles or other gaseous pollutants. It is recommended to include hydrocarbon measurement as part of regular testing.

Bioburden

Bioburden of gases also must be considered, especially in sterile manufacturing facilities. Microbial growth requires the presence of water (condensed or as vapor and/or nutrition, such as hydrocarbons). The specification for process gases should eliminate these contaminants.

To rule out the presence of microorganisms, point of use sterile filters should be used and regularly maintained.

Designing Process Gas Distribution Systems

A general rule for designing a process gas distribution system is *Keep It Simple*. Avoid the introduction of elbows or dead-legs and try to have as many straight lengths of piping as possible.

Due to the long lifespan of a gas system, it is highly likely that there will be changes, such as additions and removals of points of use, to the system during its lifetime. If possible, it is a good idea to include easily replaceable pipe elements to simplify additions of T-joints for new points of use when building the original system. To distinguish between gas systems and water systems, gases such as nitrogen and air are dry and non-corrosive, whereas dead-legs in water systems can trap stagnant water promoting microbial growth.

The capacity of the system also should be considered in order to accommodate additional expansion requirements. Although common practice is not to design distribution systems to be drainable, it will be a good investment even if the system needs to be cleaned with a fluid only once in its lifetime.

Redundancy of the supply and distribution system should be considered in the design phase. Questions to consider are: What might the value of a steady supply be? What are the costs of the gas supply failing during a critical process?

Dedicated (separated) systems for critical and non-critical applications also should be considered.

The initial costs for installation will be higher, but the running costs of maintaining the system in a validated status for critical applications will be lower. With one system to serve all users, any alterations even for non-critical purposes must be conducted within the system of change control, and will require revalidation of the system.

Construction Material

The material for gas systems should be specified as low-carbon stainless steel (EN1.4404, 1.4432 or 1.4435 corresponding to ASTM 316L).

Specifications for the inner average surface roughness, Ra, also should be stated. The finer the inner surface, the less hygroscopic the piping will be. For compressed air, Ra < 0.8 µm is widely accepted in the industry for components and pipes. For process gas systems, Ra < 0.4 µm is commonly used, and components with Ra < 0.8 µm also may be accepted for process gas systems. Stricter specifications may apply to high-purity applications and applications for reactive or corrosive gases.

The need for material certificates for pipes and components should be addressed either during the commissioning or qualification activities.

PVC and rubber must be avoided in any distribution system since they are highly permeable.

If hoses must be used, PTFE (Teflon) is the best choice. However, the British National Physics Laboratory (NPL) does not recommend the use of PTFE for dewpoint temperatures below -20°C (-4°F).[12]

Welding

Pipes may be connected by welding or by press fittings. Using press fittings can be more cost-effective; however, they should only be applied in cases where the risk assessment allows it (dry and non-corrosive gases). Unlike WFI systems where the requirements for the inner surfaces are always of paramount importance (due to the risk of microbial growth), this may not be needed for all gas distributing systems.

Welders should be certified according to local standards. Welding procedures should be verified according to applicable ISO standards such as ISO 15614-1:2004.[13]

Components

Materials of construction in components that are in contact with the product should be specified as non-reactive. It is not always possible (or reasonable) to specify components built of stainless steel. An assessment of the risk of using other materials should be made and the system design should take into account the risk that other materials might pose to the gas quality. The component itself should not pose a risk of contamination of the gas. Once again an assessment of the risk should be made. For instance, it can be assessed whether the use of oil-lubricated compressors poses a risk of contamination as the air is filtered through activated carbon before passing into the distribution system. The risks should be weighed against the costs if the filter should fail.

Piping

The surface finish inside the pipes in a distribution system for process gases is an important parameter for the hygroscopic properties. Although it is not as critical as piping for Water For Injection (WFI), where insufficient finish may result in microbial growth, one should pay adequate attention to this when specifying the user requirements for a process gas distribution system.

When specifying piping for the gas system, the material should be chosen according to the applicable standards. Furthermore, it is important to remember the following:

- Specify oil-free stainless steel pipes.
- Specify the quality of the inner surface: i.e. Ra < 0.8 µm.
- Specify seamless tubing if possible.

Filters

Because most process gas systems serve both critical and non-critical applications, it should be addressed during the risk assessment where points of use filters are needed. Point of use filters are advisable at all critical points to have a final barrier before the application and thereby, confidence that the gas fulfills the requirements for particles and microorganisms. If filters (sterile filters) are used, there must be established procedures for how often they are changed and integrity-tested.

Other features to be considered are traps or inline filters to catch solid particles such as dust or dirt that may enter the system through an adverse incident arising from faulty inlet filters on compressed air systems or from the improper mounting or connection of gas cylinders to the system. These foreign bodies will be caught in the point of use filters, but their presence in the last barrier before a delicate process will certainly not boost confidence in the system.

A very delicate use of gases is in fermentors, especially if mammal cells are involved in the fermentation process. It may be necessary to heat up the gas in an incinerator in order to inactivate any bacterial germs or bacteriophages (viruses) that are too small to be caught in the filters.

As for all the above, the specification for filters should be that all parts in contact with the product should be non-reactive. Furthermore, materials such as plastics and/or other synthetics must be guaranteed not to give off any sort of gaseous pollutants. Filter houses made of stainless steel with filter cartridges should comply with the requirements of the FDA 21 CFR 177.[14]

Hoses and Gaskets

Hoses and gaskets can pose a threat to gas quality due to potential diffusion of contaminants such as humidity. Some gases may break down or dry out plastic material making it porous. And some plastic material itself can contribute chemical pollutants. Therefore, it is essential to ensure the compatibility of the material of construction with the gas in question. Materials for hoses and gaskets should be chosen in cooperation with the supplier and comply with FDA 21 CFR Part 177.[14] Where possible, the number of hoses used should be kept to an absolute minimum.

Monitoring

When preparing a risk assessment for an application where gases are used, the critical parameters (e.g., water, hydrocarbons, and pressure) should be identified and appropriate monitoring and sampling solutions found. Whenever possible, critical parameters should be monitored continuously and alarm levels decided upon. This is also one of the principles in Process Analytical Technology (PAT). Gas systems pressure and dewpoint, which together express water content, are often critical parameters. A continuous flow of valid data provides much more information on system performance than the information contained in random samples. If a sample can be considered a snapshot of a condition in the system, the continuous data stream can be considered a moving picture.

Commissioning and Qualification of Gas Distribution Systems

This section should be read as a list of possible issues to be considered, such as gas quality, capacity, alarm test, and leak test. Local conditions may call for a more comprehensive approach. The qualification of a gas system follows the common practice of qualifying/validating equipment. Choosing ISO 9001 certified suppliers could be an advantage as these companies have documented systems for commissioning activities and are easier to audit.

When planning a process gas distribution system, an impact assessment is an effective tool for defining commissioning and qualification activities. The impact assessment focuses on critical issues, components, and systems and defines the qualification activities. Since the ISPE Baseline Guide for Commissioning and Qualification can easily be applied to gas systems,[8] we recommend the following items to be considered specifically for process gas systems. Table C states different stakeholders in commissioning and qualification activities.

Activity	Stakeholder Group
Commissioning	Engineering, Manufacturing, Contracting, Supply
Qualification	Engineering, Manufacturing, Quality Assurance (QA), Validation, Contracting, Supply

Table C. Stakeholders in commissioning and qualification activities.

User Requirement Specification and Design Qualification

In the User Requirement Specification (URS), the basic properties of the system are addressed. This includes capacity, based on a study of possible simultaneous consumption of the specified gas requirements to be distributed. The URS may stipulate that use of oil, such as for cutting the pipes during construction, is not allowed since oil is difficult to remove.

Selection of materials and components may be a part of the URS or it may be transferred to a requirement specification based on an analysis performed in the requirement classification. The first element of the qualification of new gas systems will be design qualification. The compliance of the design of the process gas system with cGMP should be demonstrated and documented.

Installation Qualification

The IQ area of coverage can include verification of specified materials of the components, including gaskets and washers, instruments and their calibration, the presence of updated and approved P/I diagrams, and can include a system leak test. It also includes evaluation of workmanship according to methods and acceptance criteria defined prior to testing. The presence of approved SOPs, such as for maintenance and daily operations, including changing and testing filters, may be included as a part of IQ validation as well.

Operational and Performance Qualification

Some schools of validation prefer addressing the challenges during PQ, but our experience is that it adds value to perform the challenges during OQ. Alarm tests and functional tests of critical components are a natural part of the OQ. This may include capacity tests, i.e., if a sufficient amount of gas is delivered in a specified period. In the case of compressed air, if the dryers have sufficient capacity if one or more are in regeneration mode at any given time.

The PQ focuses on demonstrating the ability to continuously produce and distribute gas that meets the specification. Samples should be taken or monitoring points for continuous monitoring should be determined both centrally, such as immediately after the dryers or main tank, and at the points of use. If there is a difference in the content of water vapor between the sample points, it might be due to leaks or inward diffusion through poorly sealed joints. A possible challenge could arise from the system being left pressurized with no consumption for a period of time, trapping the gas in the distribution system. Does this affect the content of water vapor as a function of time? If so, diffusion is likely to be the cause.

As is common practice in other utility systems, the initial qualification (IQ, OQ, and PQ) of a gas system should be followed by a period of intensified sampling and monitoring, usually throughout a full year. This provides data on how the system performs during the changing conditions that vary with the seasons. The demand can vary from idle to full capacity during a campaign, and climatic conditions such as temperature and humidity will cover the whole scale.

Operation

Maintenance

Repair and maintenance operations should not affect the quality of the gas. The maintenance of systems for gas and compressed air is in many ways not complicated to perform as such systems are seldom technically very complex. However, it is imperative that the personnel performing the maintenance are properly instructed, both regarding personal safety and contamination risk to the product. It is highly recommended to prepare SOPs describing the maintenance procedures. Defining roles and responsibilities is particularly important.

Maintenance of a gas system should include:

- inspection of compressor equipment for compressed air systems
- prescribed service for all mechanical equipment, such as compressors and driers for compressed air, and supply units for other gases
- changing filters
- integrity test of sterile filters
- calibration of monitoring equipment
- leak testing
- analysis of gas quality at point of use and supply unit

One also should be aware that if a distribution system has been opened for alterations or repairs, it has been exposed to ambient air. Though steel is impermeable, this does not mean

Engineering and Maintenance	User	Quality Assurance
Operation and maintenance of systems – purchasing the gas supplies from a vendor	Assuring use of gases with correct specifications for different applications	Ownership of gas specification
SOP's for operation and maintenance	Ownership of sampling of gas including plan for sampling	Auditing and approving external suppliers
Qualification of process gas systems	SOP's for use of gas	Approval of the analyses of gas samples including the sample plan
Maintaining systems in change control	Periodical process review	Periodical process review and release of the gas utility
Periodical process review	Comments on impacts from OOS	Approval of SOPs
Out of specification (OOS) handling		OOS handling

Table D. Responsibilities and roles for process gas distribution systems.

that it is not hygroscopic. The NPL recommends flushing distribution systems with dry gas. For instance, if the dewpoint of the gas is -70°C (-94°F), it should be flushed for at least two hours. Copper used as piping material is far more hygroscopic than steel or even PTFE. In view of this, copper piping should be flushed for at least four hours if the dry gas has a dewpoint of -60°C (-76°F).[12]

Testing for bioburden in pressurized gases is very challenging. The requirement for a sterile manufacturing system will be <1 cfu/m^3 (<0.028 cfu/ft^3)of air for the most critical applications.[15,16]

It has not yet been possible to develop a validated method for these acceptance criteria for the following reasons:

- Testing requires pressure regulation, which cannot be proven to be 100% sterile before use.
- Testing at system pressure is not possible as filters or agar will be damaged at the relatively high pressure of 7 bar (101.5 psi).
- It is not possible to produce a reference gas for the method validation with an exact amount of 1 cfu/m^3 and for the contaminants to be equally distributed.

Change Control

Like any other qualified utility system a qualified process gas distribution system should, of course, be subject to change control. All changes to the system require a change request, but some exceptions can be made if the change does not affect the qualification and use of the equipment, such as:

- planned and preventive maintenance, including change of wear parts with identical specifications
- a "like to like" change of spare parts (spare parts with the same capacity, function, accuracy and identity)
- moving of equipment if this does not affect the equipment itself

Whenever performing maintenance or changes to a process gas system, the integrity of the system should always be kept in mind and respected. If the system is opened to ambient air, purging must be performed and gas quality must be verified at critical points of use.

If process gas systems are qualified and commissioned according to a risk-based approach, it is easier to implement minor changes to non-critical parts of the system. Re-qualification activities can be replaced by commissioning activities that do not require QA approval.

Responsibilities and Roles

Since the use of a gas system often includes several departments and vendors, it is a good idea to visualize the different responsibilities and roles in a matrix, see Table D, and relate them to existing written agreements on cooperation.

Conclusion – Trends and Future

The FDA's risk-based approach promotes a deeper knowledge of drug manufacturing processes and finished drug products. An impact assessment tool helps to reduce qualification activities and documentation to promote commissioning. This decreases the amount of actual testing conducted during the qualification of gas systems to include only critical component and parameter verifications. Risk-based qualification includes a greater focus on critical issues, such as gas quality, alarm testing, capacity, and leak testing. Non-critical issues should be commissioned, making it easier to implement minor changes to non-critical parts of the process gas system.

Authorities are interested in rationales and documentation supporting the choice of gas quality and traceability level. Traceable process gases are not medicinal gases, and need not be produced and handled according to cGMP. When submitting a drug registration file, manufacturers should avoid specifying medicinal gas if not necessary. The gas specifications should first of all fulfill production requirements. The pharmacopoeia monographs can give useful guidance.

The user of the gas must always identify threats to the quality of gases. Critical parameters must be identified and possible risks of contamination of the gas should be addressed. The most commonly identified pollutants are water, particles, hydrocarbons, and microorganisms. As long as the gases are kept in piping systems and pressure vessels of steel, stainless steel, or aluminum, they are practically invulnerable since these materials are impermeable.

The general rule for designing a distribution system is *Keep It Simple*. Dedicated (separated) systems for critical and non-critical applications should be considered. The design of the process gas system should always correspond to the desired gas specification. Stainless steel should be the material of choice.

The key challenge for gas users is to keep up with authority requirements, as there is a wide range of regulations and standards, which are often ambiguous. A further challenge is to maintain a focus on criticality as seen from the products' perspective. It is clear that the authorities focus on critical process gases and related utilities. The pharmaceutical industry would definitely benefit from standardized guidelines regarding gases and process gas distribution systems.

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PHARMACEUTICAL ENGINEERING Interviews

Uri Boneh, Director of Engineering, Global Generic Resources Group, Teva Pharmaceutical Industries Ltd.

by Nissan Cohen, Co-Chair, *ISPE Pharmaceutical Engineering Committee*

The Director of Engineering of the Global Generic Resources Group for Teva Pharmaceuticals discusses how solid management, strategic thinking, and proper execution have helped make Teva one of the top 20 pharmaceutical companies and one of the largest generic pharmaceutical companies in the world.

Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary branded pharmaceuticals, and active pharmaceutical ingredients. Teva is among the top 20 pharmaceutical companies and among the largest generic pharmaceutical companies in the world.

With more than a century of experience in the healthcare industry, the company enjoys a firmly established international presence, operating through a carefully tailored network of worldwide subsidiaries. Headquartered in Israel, 80% of Teva's sales, which totaled $8.4 billion in 2006, are in North America and Europe. Teva has more than 26,000 employees worldwide and production facilities in Israel, North America, Europe, and Latin America.

Q What led you into a career in manufacturing?

A Strictly by chance. I was an engineer and Teva was looking for a maintenance engineer. I applied and got the job.

Q How, why, and when was Teva founded?

A 1902. (Editor's note: Teva was established 46 years before there was a State of Israel.)

Q Where are your major facilities located?

A We have around 35 locations around the world, including Israel, Argentina, Chile, Mexico, Peru, Venezuela, UK, Holland, France, Ireland, Poland, Czech Republic, Hungary, Lithuania, China, Canada, and the United States.

Q What types of products and what therapeutic areas are you currently involved in? What products do you currently manufacture?

A We are currently producing APIs, oral solid dosage forms, respiratory products, and injectables.

Q What factors do you believe contributed most to Teva's success and growth in the generic market?

A I believe that sound management and the execution of our strategies have contributed to Teva's success and growth.

Q What is your strategy for long term growth?

A We are designing new plants, integrating improved technology for manufacturing, investing in R&D, developing new products, and continually integrating acquisitions quickly and efficiently.

Q What do you see as the major growth area for generics?

A I believe the major growth area for generics is oral solid dosage forms.

Q Why do you think the generic market has grown?

A Some of the growth in the generic market is natural, and some of the growth can be attributed to the increasing generic options to pharmaceutical labeled drugs.

Q What are some of the biggest issues in manufacturing generics?

A In my opinion, some of the biggest issues in manufacturing generics are quality, regulation, and compliance. Regulatory bodies will be with us for a long time. International harmonization is important to help with the globalization of manufacturing.

Q What are some of the key factors you are seeing in terms of globalization?

A I'm seeing a number of factors influencing globalization, including, a combination of market, market share, cost of labor, and management.. We are always concerned about cost of production. These influences are important.

Q What impact does government support or investment have on your growth/expansion plans?

A It helped with the Jerusalem facility as we are located in a high technology park with government incentives, as are also in Hungary and the Czech Republic. But overall, most of our foreign operations have little or no government support.

Q What sets Teva apart from other generic or pharmaceutical manufacturers? What do you do differently from the competition?

A We have good management, strategic thinking, and excellent execution everywhere. Teva is constantly looking at reducing costs.

Q What do you see as the challenges or barriers to achieving the goals Teva has set for its global pharmaceutical manufacturing operations?

A We have good management, we execute our strategic plans very well, and we are always looking at efficiency and cost reduction. The challenges and barriers are minimized by our strategies and the way we execute them.

Q What are Teva's long term goals?

A Teva's long term goal is to be the largest manufacturer with the largest market share of generic products in the world.

Q How does the current political situation in Israel affect Teva?

A The current political situation in Israel does not directly affect us.

Q What is your involvement with ISPE? When did you first encounter ISPE?

A My involvement with ISPE started about 17 years ago with facilities issues and reading articles from *Pharmaceutical Engineering*. I attended meetings in Philadelphia and Tampa. PE

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GAMP 5 – Enabling Innovation

by Sion Wyn

The new GAMP 5: *A Risk-Based Approach to Compliant GxP Computerized Systems* provides pragmatic and practical industry guidance that aims to achieve compliant computerized systems that are fit for intended use in an efficient and effective manner, while also enabling innovation and technological advance. The revised Guide describes a flexible risk-based approach to compliant GxP regulated computerized systems, based on scalable specification and verification. A robust quality risk management process based on ICH Q9 principles is central to the approach. GAMP 5 also contains new information on outsourcing, electronic batch recording, end user applications (such as spreadsheets and small database applications), and patch management.

Changing Environment – Regulatory and Industry Initiatives

The pharmaceutical industry is responding to the challenge of significantly improving the way drug development and manufacturing is managed. New concepts are being developed and applied, including science based risk management approaches, a focus on product and process understanding, and the application of Quality by Design concepts.

Many of these ideas are defined and described in the FDA 21st Century Initiative, new ICH documents, such as Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System, ISPE's Product Quality Lifecycle Implementation (PQLI) initiative, and various supporting industry consensus standards, such as ASTM E2500 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*.

As these new ideas and ways of working are being established, the industry will for some time be in a *period of transition*.

GAMP Guidance must evolve to meet the needs of the changing environment and integrate fully with ISPE initiatives, such as PQLI and the revision of the ISPE C&Q Baseline® Guide. There is both a need and an opportunity to make activities related to all types of computerized systems efficient, effective, and focused on patient safety.

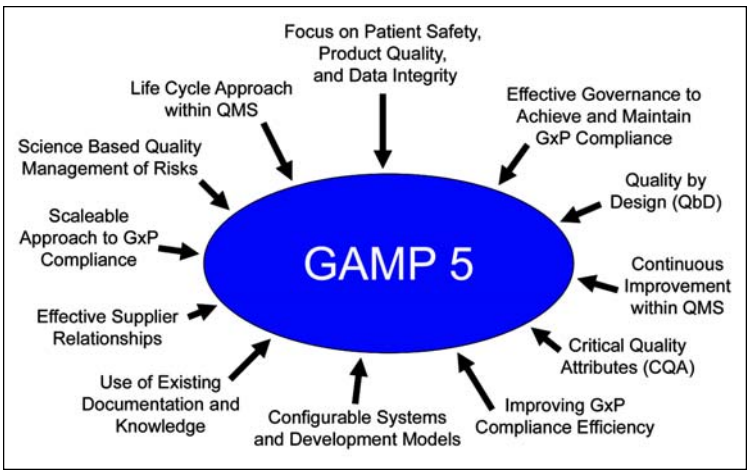

Figure 1. Drivers for GAMP 5.

New and Innovative Approaches

Where a computer system is regarded as one component of a wider manufacturing process or system, particularly in an integrated Quality by Design environment, specific and separate computerized system validation may not be necessary. This environment requires both complete product and process understanding and that the critical process parameters can be accurately and reliably predicted and controlled over the design space. In such a case, the fitness for intended use of the computer system within the process may be adequately demonstrated by documented engineering or project activities together with subsequent Process Validation or continuous quality verification of the overall process or system. The same principle applies to the adoption of Process Analytical Technology (PAT).

These innovative approaches are available and useable now if the appropriate pre-requisites are met. While acknowledging that not all regulated companies will be in a position to, or will choose to, fully embrace the new approaches immediately, GAMP 5 is intended to encourage the adoption of such approaches and in no way to be a barrier.

Improving Quality Practice

During the period of transition, the industry continues to need practical guidance based on current good practice – giving practitioners the tools to do the job today, while building a bridge to new approaches. GAMP 5 aims to describe current good prac-

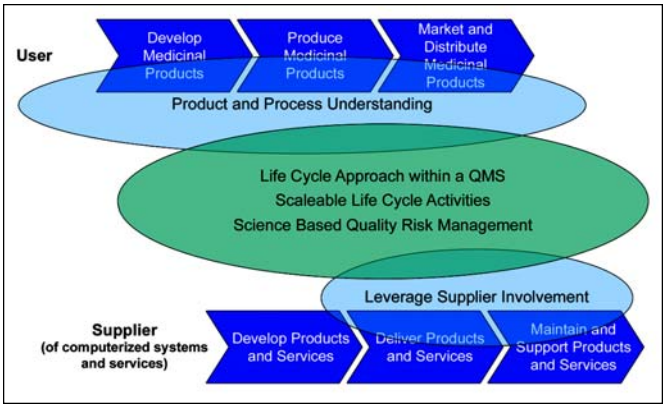

Figure 2. Key Concepts of GAMP 5.

tice in order to satisfy the needs of the majority of practitioners involved with computer systems, while also enabling new and innovative approaches, e.g., for process systems in a Quality by Design environment. These innovative approaches and the application of principles to specific system types will be explored in detail in subsequent documents.

In the meantime, key aspects supportive of ISPE PQLI and ASTM E2500 are addressed immediately to make current activities as effective and efficient as possible. These include:

- focusing on aspects critical to the patient
- avoiding duplication of activities (e.g., by fully integrating engineering and computer system activities so that they are performed only once)
- leveraging supplier activities to the maximum possible extent, while still ensuring fitness for intended use
- clarifying the roles of Subject Matter Experts and Quality Assurance
- scaling all lifecycle activities and associated documentation according to risk, complexity, and novelty
- clarifying that traditional linear or waterfall development models are not the most appropriate in all cases

These are reflected in Key Concepts upon which GAMP is based, and in the detailed contents - *Figure 2*.

GAMP 5 is deliberately flexible with regard to terminology – focusing on value-added activities and avoiding unnecessary activities is the main intent, and different regulated companies and suppliers may choose to use a wide range of different terms. In line with the principles of ASTM 2500, GAMP 5 adopts *specification* and *verification* as overall terms describing specific life-cycle activities, but does not discard the general lifecycle validation framework to reflect current industry practice for companies that decide to maintain these practices rather than applying the new concepts.

Extended Scope and Application

Coupled with these initiatives in development and manufacturing, a wide and ever-increasing range of local and global networked computerized systems are being used throughout the product life cycle. Many of these are fundamental to GxP activities.

Accuracy and integrity of records and data is essential throughout the product life cycle, from research and development through pre-clinical studies, clinical trials, production and quality control to marketing. The GAMP Good Practice Guide: *A Risk-Based Approach to Compliant Electronic Records and Signatures* provides further guidance on this topic, and should be read in conjunction with GAMP 5.

Achieving compliance and fitness for intended use for all GxP regulated systems in a pragmatic and efficient manner is essential. GAMP 5 aims to address the need to safeguard public health, product quality, and data integrity while at the same time enabling innovation and technological advance.

Focusing on Patient Risk

While previous GAMP guides provided an overall life cycle framework for systems and controlled equipment, they recognized that the practicalities are different for different system types. As a result, a series of Good Practice Guides were produced to support the understanding of these differences and provide more practical detail.

Many pharmaceutical companies undertake complex, time consuming and expensive qualification practices. There are aspects of qualification that can add value in terms of ensuring the equipment and systems are fit for intended use, but there are other aspects that often do not add this value. Some of the prescriptive and rigid conventions and practices that surround qualification as often practiced can detract from its overall value. GMP regulations provide the basis for the activities that are called qualification, but no specific requirements that relate to how qualification is practiced.

By focusing on the risk to the patient and leveraging the expertise of the supplier and subject matter experts based on Good Engineering Practices, verification is considered as a set of integrated activities that can replace the activities previously called IQ and OQ. Regulated company IQ and OQ activities may then be omitted or limited to an assessment of the supplier's activities and documentation, and if necessary, performing mitigation activities to close gaps. This eliminates much of the costly duplicated testing which does little or nothing to protect the patient.

Finally, the overall performance and fitness for intended purpose can be ensured through Performance Qualification or Verification, which focus on critical-to-quality attributes. Overall, this will demonstrate that the equipment or system is performing satisfactorily for its intended purpose, the process with which it is involved is controlled, and the risks to the patient have been effectively managed, thus meeting the regulatory requirement for validation.

It is important to select the right tool for a specific need, such as design review, inspection or testing (e.g., Commissioning, Qualification, IQ, or OQ). The term verification is

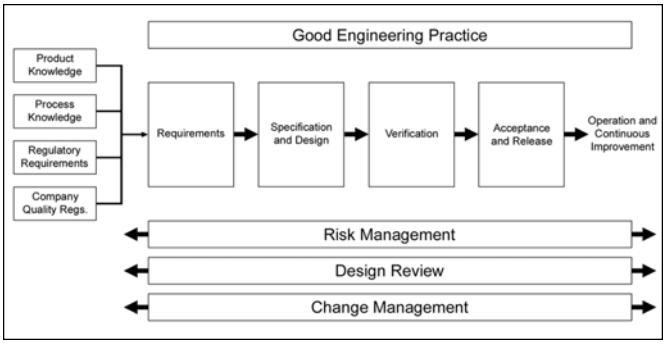

Figure 3. The specification, design, and verification process.

used in ASTM 2500 and aims to promote flexibility in choosing the right approach - *Figure 3*.

A science- and risk-based approach is inherent in the thinking behind verification, where the level and extent of verification is based on scientifically-assessed risk to the patient from specific processes, equipment, and systems. This is directly in line with the principles described in ICH Q8, Q9, and the forthcoming Q10 documents for the development, quality risk management, and quality management of pharmaceutical products throughout their life cycle. It is, of course, still appropriate to create a plan describing and justifying the approach taken to ensure the equipment is fit for use in a GxP regulated environment, and to have a report available providing the necessary evidence to support this claim.

Different Types of Computerized Systems

For integrated manufacturing systems or equipment where a computer-based system is part of the overall functionality, a specific and separate computerized system validation may not be required.

For example, where the computer controlled equipment can be regarded as one component of a wider manufacturing or process control system the verification can be an integrated part of the overall process validation effort. The verification of fitness for intended use may be adequately demonstrated by documented integrated engineering or project activities together with subsequent Process Validation – and the overall approach may be defined based on each regulated company's policies and preferences.

Validation is the common term used in regulations worldwide to describe a process that demonstrates that systems are fit for intended use. Some computerized systems are intimately involved in many regulated business activities outside the manufacturing area, and are critical for the health and protection of the patient. Examples include the collection of clinical trials data, the management of donor details in blood collection, the recording of adverse events and complaints, the release of product for sale, and the recall of defective product.

Such IT systems have no direct correlation with the manufacturing and release of the product. Consequently, there is no direct parallel with the manufacturing process and associated process validation. Acceptance of the system is dependent on the satisfactory completion of a functional test, such as the traditional OQ or equivalent tests, prior to a controlled cut over into the live environment. (Some further testing, e.g., stress or performance testing, may be necessary which some organizations call PQ but it is not an activity parallel to the PQ testing of controlled process equipment).

The principles described in ASTM Standard E2500 should be interpreted with attention to the special characteristics of particular systems, and suitable verification that the critical-to-quality requirements of the system have been met should be completed before the computer system can be approved for use in a GxP-regulated environment.

The ideas that led to the development of ASTM E2500 are applicable to all computerized systems. GAMP 5 describes a process which follows the same principles:

New and Revised Material

Particular emphasis is given in GAMP 5 on providing a cost effective approach to compliance and demonstrating fitness for intended use. To support this, new and updated guidance is given on the following aspects:

- a complete system life cycle approach as part of a Quality Management System (QMS), from concept to retirement
- a scaleable approach to achieve and maintain GxP compliance driven by novelty, complexity, and risk to patient safety, product quality, and data integrity
- clarifying the role of the Quality Unit, and introducing the roles of Process Owner, System Owner, and Subject Matter Experts.
- in the GMP environment, stressing the importance of clear requirements based on a thorough understanding of the science and of the Critical Quality Attributes (CQAs) of the development and manufacturing process and drug products, to facilitate the adoption of a Quality by Design (QbD) approach
- the leveraging of supplier documentation and knowledge, wherever possible, and subject to satisfactory supplier assessment to avoid unnecessary duplication
- improving efficiency by promoting practical and effective interpretation of GAMP guidance
- maximizing use of documentation from activities such as development and commissioning as verification evidence
- the importance of effective governance to achieve and maintain compliance
- identifying opportunities for process and system improvements based on periodic review, root-cause analysis, and Corrective and Preventive Action (CAPA)

New information is provided in specific appendices on the following topics of special interest to industry:

- alignment with ASTM E2500
- organizational change
- outsourcing
- electronic batch recording
- end user applications such as spreadsheets and small databases
- patch management

- the requirements of the system should be clearly defined
- requirements critical to the health and protection of the patient (critical-to-quality requirements) have been identified and the risks identified and controlled
- the principles of GEP are applied throughout
- the testing carried out and documented by the supplier should be leveraged as much as possible
- the critical-to-quality requirements are appropriately verified and reported by the regulated organization in line with regulatory expectations

It is also recommended that a plan describing and justifying the approach taken, and a report supporting the claim that the system is fit for intended use, are created.

Performed in this way, the process described above for computerized systems meets all the GxP regulatory expectations for validation.

Terminology

Since GAMP 5 covers both systems involved in manufacturing of pharmaceuticals and systems for other critical types of IT applications, this Guide uses terminology that enables appropriate selection of the relevant life-cycle activities, depending on the specific context.

Some organizations have already taken the decision to adopt the term "verification" and apply it to both computer and control systems. Others have indicated that they will stay with the words "qualification," but adopt the principles described in the ASTM Standard 2500. Still others have changed to verification for controlled process equipment, but retained "qualification" for computer systems.

The GAMP Community of Practice aims to strongly support and promote innovation. GAMP Guidance is neither mandatory, nor prescriptive, but aims at enabling innovation in a compliant and cost effective manner.

Descriptions of current industry practices in GAMP 5 should not be read as constraining in any way the development and adoption of other approaches. Individual companies should and will decide what terms and precise approach they will use.

GAMP 5, like previous versions of GAMP, supports good quality management practices. The enhanced focus on science and the increased focus on risk to the patient are important to the future of the pharmaceutical industry. GAMP will continue to support evolving good practices for the pharmaceutical industry at large, its regulators, and suppliers.

GAMP 5 is scheduled to be released at the ISPE Conference on Manufacturing Excellence, 25-28 February 2008 in Tampa, Florida, US. Please visit www.ISPE.org/manufacturingexcellence for more information.

About the Author

Sion Wyn, Director, Conformity Ltd., is an acknowledged expert in computer system validation and compliance and international regulations in this field. He is currently assisting the FDA with its re-examination of 21 CFR Part 11, and is a member of the team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He is the technical content expert for the FDA's ORA Virtual University on-line training modules on computerized systems validation and compliance. He has received the FDA Group Recognition Award for work on Part 11. Wyn is the editor of ISPE's *Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems,* and is a member of the ISPE GAMP Council and the GAMP Europe Steering Committee. He has extensive experience in all aspects of computer systems validation and compliance, including managing validation projects, validation planning, specification and testing of systems, performing site and system compliance audits, writing SOPs, performing 21 CFR Part 11 assessments, and supplier audits. Wyn's expertise as a specialized computer validation consultant covers all stages of the lifecycle approach to validation of computerized systems and most system types including MRPII, manufacturing execution, electronic document management, EBRS, process control and monitoring, environmental monitoring, manufacturing equipment, and laboratory systems. At Conformity Ltd., Wyn provides computer validation and compliance consultancy to the pharmaceutical and other regulated healthcare industries. Wyn received the 2006 ISPE *Professional Achievement Award*, which honors an ISPE Member who has made a significant contribution to the pharmaceutical manufacturing industry.

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AL-6XN® Weld Discoloration and Effect Corrosion Resistance

by John Tverberg and Ken Kimbrel

This article identifies the source of discoloration that can appear on sanitary welds of AL-6XN material and its effect on the corrosion resistance of the material.

Introduction

It is a well known fact that weld discoloration is detrimental to the performance and life span of austenitic stainless steels. Discoloration can lead to premature material failure by promoting pitting and crevice corrosion. As buffer solutions become more aggressive, it has become necessary to look beyond the traditional austenitic steels such as 316L. One such material gaining popular usage in pharmaceutical and other sanitary applications is the super-austenitic 6% molybdenum containing material AL-6XN.

A common characteristic observed when welding 6% molybdenum materials either by automatic weld machine or by hand is the appearance of light and dark spots on both the inside and outside of the weld bead. Figure 1 shows two sections of 0.065' minimum wall 20 RA polished AL-6XN tubing automatic fusion welded together utilizing an alloy 625 weld insert ring. Clearly visible, these colors may appear with or without the use of a weld insert ring which is used to over-alloy the weld for the purpose of enhanced corrosion resistance, and appears different than the standard oxide discoloration typically experienced due to improper purge practices.

Figure 1. Visual discoloration on welds.

AL-6XN (UNS N08367) is a low-carbon, nitrogen containing super-austenitic stainless steel and is one of the most corrosion resistant iron-based austenitic steel produced.[1] Originally marketed for seawater environments, AL-6XN has recently gained wide acceptance for use in sanitary applications for the food, pharmaceutical, and biotech industries due to its exceptional resistance to general corrosion, pitting, and intergranular corrosion.

For this study, alloy 625 (UNS N06625) is used as the over-matching composition welding product. Super-austenitic stainless steels are susceptible to chemical segregation in the weld area and therefore subject to preferential corrosion attack in severe corrosive environments. In order to compensate and offset the segregation of the molybdenum within the heat-affected zone of welds which will not undergo post-weld heat treatment, three different types of consumables are recommended by the manufacturer of AL-6XN. These are Alloy 625, Alloy C-22 (UNS N06022), or Alloy C-276 (UNS N06276). Each of these is a nickel alloy with higher levels of molybdenum than AL-6XN. Inconel 625 contains 9% Mo, Hastelloy C-22 contains 13% Mo, and Alloy C-276 contains 16% Mo. C-22 has the highest chromium content (22%) of these. The higher content of the Alloy 625 welding products offsets the effects of elemental segregation in the weldments which can result in preferential weld corrosion.[2]

Test Methodology

In an effort to identify the origin of and effect the spots may have on the corrosion resistance of the welds, the following analytical techniques were used to evaluate the discoloration:

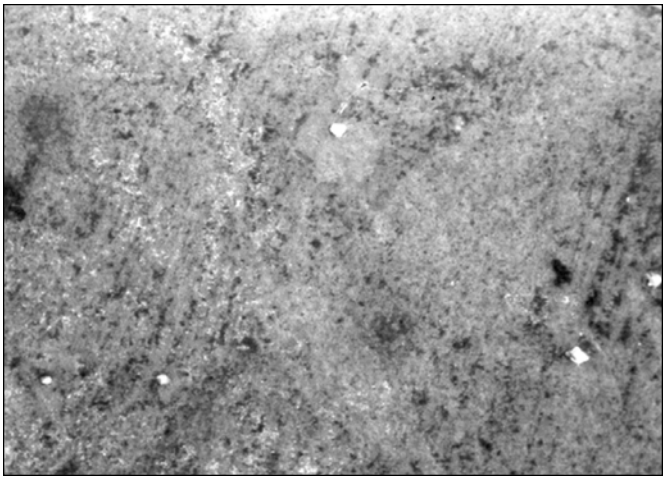

Figure 2. Low magnification view (470X) of dark area on inside of tube weld.

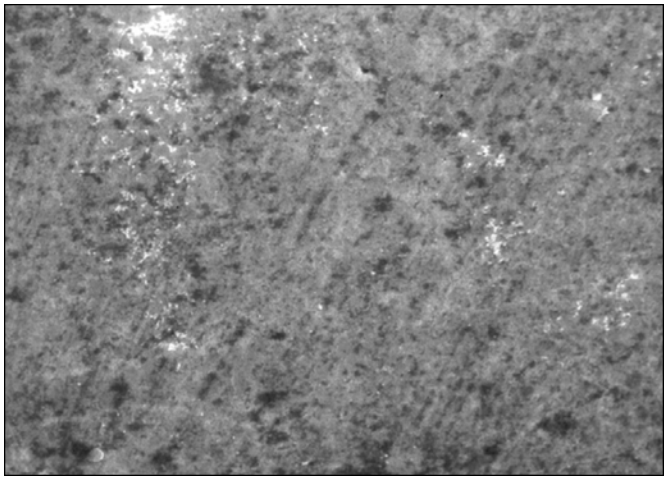

Figure 3. High magnification view (1000X) of dark area on inside of tube weld.

1. Scanning Electron Microscopy (SEM) to determine what the surface "looks like" and to determine those areas for evaluation with microprobe analysis.
2. Energy Dispersive Spectroscopy (EDS), sometimes called microprobe analysis, to determine the approximate composition of any areas in question.
3. X-Ray Photoelectron Spectroscopy (XPS) to determine the molecular composition of areas or compounds present and to provide light element detection.
4. Accelerated corrosion testing in a modified ASTM G 48 solution to identify areas of potential corrosion attack. This test is explained further in the corrosion section.

Test Samples

- AL-6XN Tube 1.5" × .065" wall Ht. #4100039
- Alloy 625 Washer Style Insert Ring Ht #RL75
- Automatic welds made with 100% Argon

The following summarizes the results obtained from this testing.

Scanning Electron Microscopy

Four areas of the weld, designated as dark and light, were selected for Scanning Electron Microscopic (SEM) evaluation. One pair was located on the inside and one pair on the outside of the tube. These areas were examined at 470 and 1000X, and are included in this article as Figures 2 to 9. One of the major advantages of SEM examination is the relative ease of performing microprobe analyses; therefore, anomalies found during examination may be identified and traced to their origin.

Figure 2 is a low magnification view (470X) of a dark area on the inside of tube weld. The dark areas are non-conductive and will not hold an electron charge, and most likely represent refractory oxides such as aluminum oxide. The white crystals are more highly conductive areas and probably represent some type of ionic compound or the corner of a sharp surface formation, such as the edge of a crystal face.

Figure 3 is a high magnification (1000X) view of the dark area of the weld on the inside of the metal tube. The dendritic pattern of the weld is clearly seen. The white areas are the metal free from any oxides, visible through the thin oxide/nitride coating.

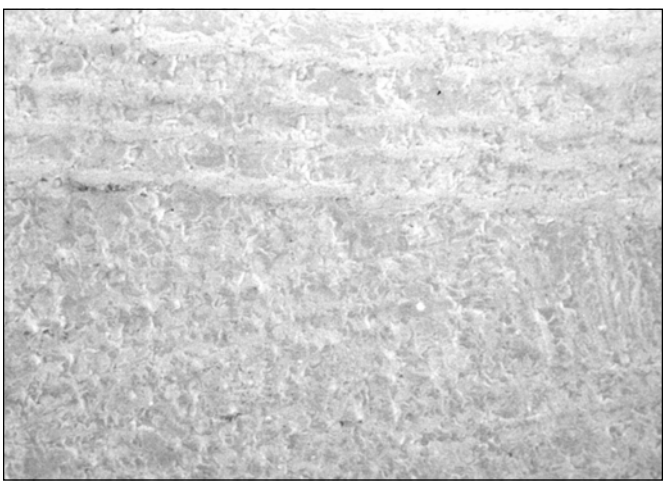

Figure 4. Low magnification view (470X) of light area on inside of tube weld.

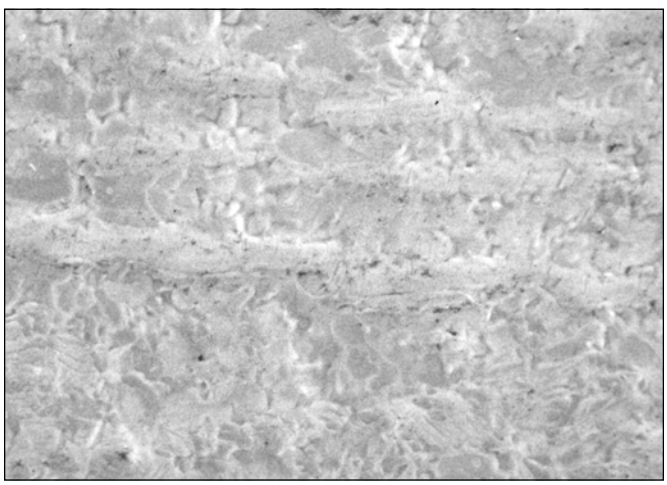

Figure 5. High magnification view (1000X) shows small particles of refractory oxides on the edges of the dendrites.

	1a, ID	1b, ID	2a, ID			2b, ID			
	General	General	General	Dark Inclusion	Light Inclusion	General	Light Inclusion	Dark Platelet	Dark Inclusion
Spectrum	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Micrograph	*7353 a, b*	*7354 7355*	*7350 7351*	*7350 7351*	*7350 7351*	*7347 7349*	*7347 7349*	*7347 7349*	*7347 7349*
Mg	-	0.5	-	-	6.0	-	-	-	0.4
Al	2.1	0.3	3.3	41.7	57.8	0.1	0.4	-	0.2
Si	0.5	0.5	0.5	2.7	1.1	0.7	0.6	0.6	0.4
S	-	-	-	-	-	-	-	-	-
Ca	0.4	0.1	0.9	49.2	17.0	-	0.2	0.2	0.1
Ti	0.1	-	-	1.0	0.2	-	-	0.2	0.2
Cr	21.5	22.6	20.8	2.6	5.7	22.6	20.5	23.6	21.8
Mn	0.5	0.5	0.3	0.2	-	0.3	0.4	0.4	0.6
Fe	46.3	44.0	45.3	2.3	7.2	44.9	48.1	42.4	44.9
Ni	22.3	21.9	22.3	0.5	3.2	22.3	23.1	20.7	24
Cu	-	0.2	-	-	-	-	0.4	-	0.3
Mo	6.3	9.5	6.5	-	1.9	9.1	6.4	11.9	7.2
Chemical Composition Wt. %									

Table A. EDS analytical results. Sample 1a is the "Dark" area of the weld on the inside of tube, 1b the "light" area, 2a the "dark" area on the outside of tube, and 2b the "light" area.

Figure 4 (470X magnification) is the light area of the weld on the inside of the tube. It is very uniform in appearance and indicates little or no oxide or nitride on the surface. The dendritic structure of the weld is clearly visible.

Figure 5 (1000X magnification) shows small particles of refractory oxides on the edges of the dendrites. The lack of any oxide film makes the dendrites clearly visible. The clarity of the structure indicates the weld cover gas, in this area, was excellent.

Figure 6 is a (470X) magnification of a dark area of the weld on the outside of the tube. Large black particles are seen which appear to be refractory compounds, probably inclusions from the steel that were melted during welding and redeposited as slag. Several crystals are present on the surface, again most likely some ionic compound that contaminated the surface after welding, representing secondary contamination. The darker gray color is a continuous oxide or nitride layer on the surface of the weld.

Figure 7 is a high magnification (1000X) view of the same area. Here, the layer appears to be more crystalline, most likely a chromite spinel or a simple chromite. Also in this view, it is possible to see the areas where microprobe analyses (EDS) were performed. These show up as white dots in the inclusions.

Figure 8 (470X magnification) is the light area of the weld on the outside of the tube. The black particles are refractory oxides or nitrides and the white spots are the high-energy peaks of the dendrites. Very little oxide or nitride coating of the metal is present. The crystalline surface layer is not visible at either magnification. These micrographs appear darker because the voltage was decreased to obtain more contrast.

Figure 9 is a high magnification (1000X) SEM micrograph of the white area of the weld on the outside of the tube. The white dots in the dark platelet – upper left; the light inclusion – center, and dark inclusion – lower right are spots where microprobe analyses were made.

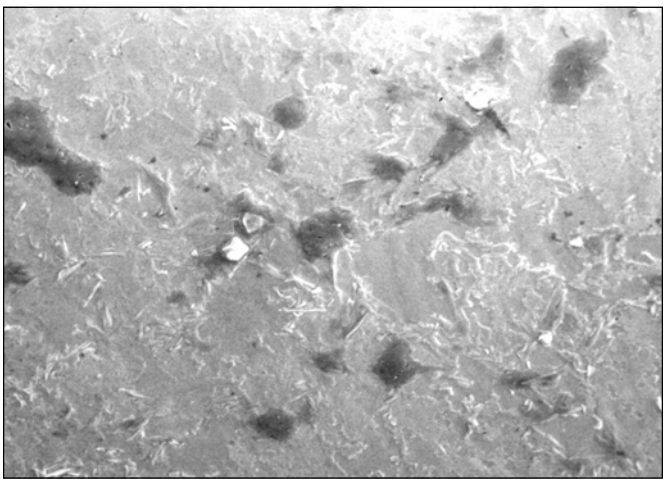

Figure 6. Low magnification view (470X) of dark area on outside of tube weld.

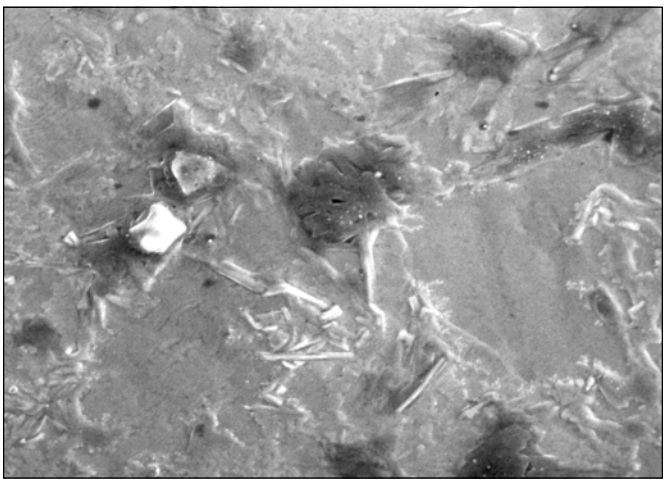

Figure 7. High magnification view (1000X) of dark area on outside of tube weld.

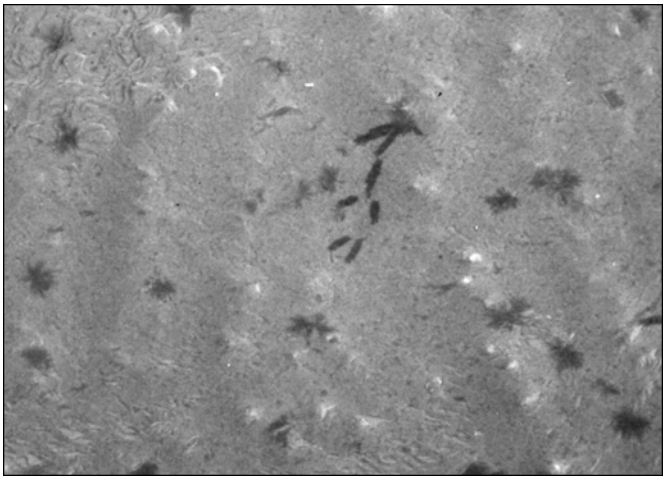

Figure 8. Low magnification view (470X) of light area on outside of tube weld.

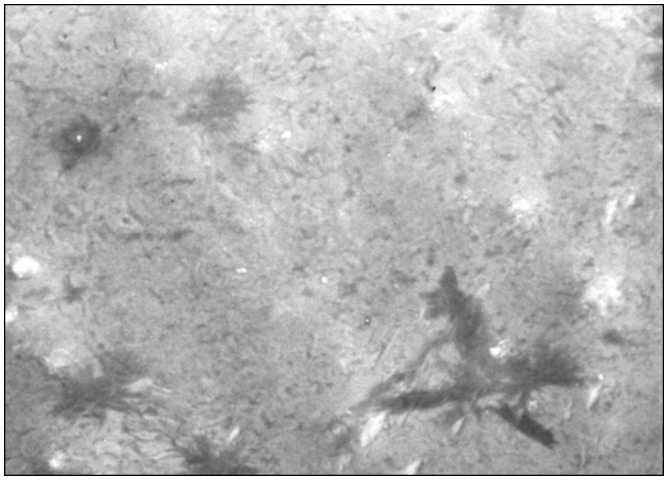

Figure 9. High magnification view (1000X) SEM micrograph of white area on outside of tube weld.

Energy Dispersive Spectroscopy

Energy Dispersive Spectrographic (EDS) or microprobe analyses were made of several areas during SEM examination of the welds. These results are summarized in Table A and the energy spectra are included as EDS Spectra 1-9.

The dark areas on the outside of the weld are very high in aluminum, calcium, and titanium. Because EDS analyzes to a relatively deep level compared to XPS this layer is reasonably thick. The origin of the aluminum and titanium is the deoxidation practice following AOD, and the calcium comes from the AOD/caster slag. These oxides/nitrides are in the metal as inclusions and are remelted during welding and form a slag on the surface of the weld. The light areas of the weld have magnesium and copper. Magnesium probably comes from the refractory brick of the arc melting furnace, AOD convertor, the casting ladle, or the tundish at the continuous caster. Copper is a tramp element that comes from the scrap used to compound the melt. Silicon was slightly higher on the outside of the weld in the dark inclusions, indicating that it was a slag component from the steel itself, floating on the surface of the weld. There is less silicon in the light color areas of the weld. Silicon is added to the steel as a deoxidizer and to increase the fluidity of the molten metal.

The chromium, nickel, molybdenum, and iron are in the correct range for AL-6XN stainless steel.

X-Ray Photoelectron Spectroscopy

Four areas were selected for examination using XPS. These were the same areas used for SEM and EDS examination.

The system used for this analysis was a Physical Electronics Model 5802 Spectrograph with a monochromatic aluminum anode. The spot size was approximately 0.8 × 2.0 mm (0.032 × 0.078 inches) and the depth of analysis was approximately 40Å (1.6×10^{-7} inches). The chamber pressure during analysis was 10^{-9} Torr (1.9×10^{-11} psi). Each specimen was washed in isopropanol prior to examination to reduce the potential for contamination and filament burn-out. After the initial scan, each major element was analyzed in high energy resolution mode to determine the compounds present and their degree of oxidation.

Table B summarizes the elemental surface composition of each of the four areas as obtained with XPS. These data are illustrated in Spectra 1-4. No boron was detected in any of the areas analyzed. Therefore, if boron was added at the continuous casting operation to control sliver formation during hot rolling, it remained in solid solution and the quantity was below the detection limit of the spectrograph and is not part of a weld slag component.

Ratios were calculated for Si/Fe, Cr/Fe, and Mn/Fe from the data in Table B. These are presented in Table C. The Cr/Fe ratio is greater than 1.0 in all areas except one, the dark area on the weld ID, and greater than 4.0 on the OD surfaces. The Si/Fe and Mn/Fe ratios are likewise high on the OD surfaces. This is logical since these are light oxides or silicates that tend to float on the surface of the weld puddle.

Table D summarizes the molecular composition of the elements on the surface of the welds. Area 1b, the light or white area on the weld ID, is unique in that it contains elemental chromium and iron, while the other areas were

	Spectrum	C	N	O	F	Na	Mg	Al	Si	Cl	Ca	Ti	Cr	Mn	Fe	Ni	Zn	Mo	Ag	W	Pb
1a	*1*	44.0	3.6	39.9	-	0.5	-	6.6	1.1	Tr	0.7	-	1.2	-	1.6	0.3	0.3	0.1	-	-	-
1b	*2*	48.4	-	35.5	-	0.2	-	0.9	3.6	-	0.3	0.7	5.1	0.1	3.7	0.8	0.3	0.5	-	-	-
2a	*3*	39.8	4.9	34.3	3.7	0.3	0.5	4.8	3.6	-	1.2	0.1	5.0	0.4	1.0	-	0.1	-	0.1	0.1	-
2b	*4*	62.4	2.0	22.4	-	0.5	0.2	2.8	3.1	0.4	1.0	-	3.1	1.2	0.7	-	0.2	-	-	-	0.1
Chemical Composition Wt. %				1a - Dark area on ID of weld 1b - Light or White area on ID of weld									2a - Dark area on OD of weld 2b - Light or White area on OD of weld								

Table B. Summary of the elemental surface composition, in atomic percent, within 40Å of the surface.

	Si/Fe Ratio	Cr/Fe Ratio	Mn/Fe Ratio
Sample 1a	0.7	0.8	-
Sample 1b	1.0	4.0	0.0
Sample 2a	3.7	5.1	0.4
Sample 2b	4.4	4.4	1.7

Table C. Ratio of silicon, chromium, and manganese to iron.

Element	Spectrum	Summary
C	5	Mixed hydrocarbon and carbon/oxygen species; due to atmospheric exposure and isopropanol washing
N	6	Nitrides on Sample 2a, 2b (OD); organically bound on 1a, 1b (ID)
O	7	Mixed oxides – assignment difficult due to number of oxide species
F	8	Teflon on Sample 2a; none in other areas
Al	9	Oxide on all surfaces, but also major Al intermetallic on Sample 1a
Si	10	Silicates on all surfaces
Ca	11	Calcium oxide and probably calcium silicate
Cr	12	Primarily Cr_2O_3; 5% Cr° on 1b, hydrated oxide on 1a
Mn	13	Mn O_2 on Samples 2a, 2b (OD)
Fe	14	Primarily Fe_2O_3; 10% Fe° on 1b
Zn	15	ZnO
Mo	16	MoO_2

Table D. Summary of molecular form of elements on the weld surface.

Temperature, °C	Weight Loss, grams	% Weight Loss
50	0.9200	11.03
35	0.0011	0.013

Table E. Corrosion test results.

totally oxidized. These data indicate a high level of oxygen in the weld zones. In addition, there are high levels of calcium, silicon, and manganese.

Teflon on the outside of the tube appears to be from secondary contamination after welding. Keep in mind that XPS analyzes the top 5 to 8 atoms on the surface of the metal. High energy spectrum charts from which these data were obtained are included as Spectra 5-16.

Corrosion Testing

The remaining section of the submitted sample, not consumed in the preceding analyses, was submitted for corrosion testing. The specimen was cut into two equal pieces so that a portion of the weld center line was exposed to the corroding solution in both pieces. AL-6XN is a superior austenitic stainless steel that has proven to be resistant to standard tests for typical austenitic steels such as 316L. Therefore, the test used for this study was a modified ASTM G 48 corrosion immersion test. The solution is 6% $FeCl_3$ + 1% HCl. Two temperatures were selected, 35° C and 50°C each for a 72 hour duration. The 50°C corrosion test is more severe than the normal acceptance test for AL-6XN. The normal acceptance test is a crevice corrosion test in 6% $FeCl_3$ at 35°C. Normally, the crevice corrosion test is more severe than a pitting test, but because of the near impossibility to make a plastic crevice former to fit a circular weld, the test is modified to make it into a severe pitting test that approximates the same corrosion sensitivity. The higher temperature and 1% hydrochloric acid makes this test much more severe so it will indicate if the component will behave differently than the base alloy. Table E presents the corrosion results for the two temperatures.

The weight loss is substantial for the 50°C test. Examination of this corroded specimen shows severe attack in the heat affected zone of the AL-6XN stainless. This is caused by the formation of secondary phases formed in the heat affected zones of welds during the cooling period after welding, which is vulnerable to attack in severe corrosion environments. The 35°C sample shows no corrosion pits, indicating the test takes place below the critical pitting temperature. Neither specimen showed any evidence of attack on or around the oxide film on the weld or heat affected zone which was the focus of this test.

Summary

Visual examination of the two areas selected for evaluation, namely the light and dark areas of the weld on both the inside and outside of the tube, shows a heavier surface oxide or nitride layer in the dark areas and little, if any, coating in the lighter areas. The dark areas had large patches of black compounds. The coating is essentially nonexistent in the light areas. Figures 5 and 6 indicate the surface in the dark area appears to be covered with a crystal that is either chromite or chromite spinel based on the XPS analyses.

The high calcium and aluminum in the dark particles come from melting the inclusions in the steel. Argon-Oxygen Decarburization (AOD) is a refining process used to adjust the final chemistry of the steel to very precise levels and to remove essentially all of the carbon and sulfur from the molten steel. Calcium and magnesium silicate is used as a protective slag in the AOD refining process and may be entrapped in the molten steel. A short radius caster was used which is very prone to capturing slag particles on one side of the ingot. Following the AOD operation, aluminum, titanium or both, are added to remove the excess oxygen from the AOD operation. Unfortunately, all of these additives may show up in the finished product as slag inclusions and cause problems during welding.

Usually, the dark brown to blue-black colors on the weld and heat affected zones indicate contaminated gas coverage or decomposition of complex oxides present in the inclusions. At the high temperature of the welding torch, it may be possible to reduce the oxides to a substoichiometric species, thus, providing oxygen to allow further oxide formation. This is fairly common with reactive metals like zirconium and titanium where the substoichiometric oxides are black and corrosion resistant, but once the oxide becomes stoichiometric, rapid corrosion occurs. This mechanism would account for oxygen when no oxygen appears to be present.

The 35°C (95°F) corrosion test shows no evidence of corrosion susceptibility although the 50°C (122°F) had excessive attack in the heat affected zone because of chi phase in the

AL-6XN. No attack took place in the weld area. The presence of the chi phase is a problem with the formulation of the AL-6XN alloy and is caused by the alloy's low nickel content. There is little you can do to prevent its formation. The alloy needs at least 45% Ni to prevent chi formation and AL-6XN stainless has only 24%. Chi forms in the temperature range of 1750 - 2050°F, a zone of which will exist in both heat affected zones of every weld. Its formation can be minimized by extracting the heat as fast as possible, perhaps by using water cooled weld rings. Changing filler alloy to either C-22 or C-276 will have little impact on chi phase formation in the AL-6XN stainless although it will make a difference in the solidification structure of the weld.

Although the weld and heat affected zones show discoloration, the discoloration should have little effect on the performance of the weld in service. The oxides appear to be stable and do not dissolve even at very high temperatures and in an extremely corrosive solution. Therefore, it appears that the current welding practice may be used in the field without concern of early corrosion failure.

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Automatic Pill Bottle Opener

by Jorge DaSilva, Jay Peterson, Murat Kocak, William Indoe, and Richard Berkof

This article describes the design of an innovative Automatic Pill Bottle Opener, which was a Senior Design Project in the Mechanical Engineering Department at Stevens Institute of Technology, completed in May 2007.

Project Background

Like most fourth year engineering students, four mechanical engineering students at Stevens Institute of Technology in Hoboken, New Jersey began their senior design project in September 2006. This may not sound significant, but the final body of work more closely resembled a new product development project than your standard undergraduate design project. With a funding grant from ISPE and a total project cycle time of eight months, these students attempted to do what many professionals could not: Find a market need, design a product to meet this need, and transform the final design into a new product reality.

Given the problem statement of designing and developing a semi-autonomous electromechanical product to assist the elderly, the original problem statement was about as vast as the Atlantic Ocean. But before the team could narrow down the scope, it needed to understand its market. The results from the subsequent market research were not surprising. The domestic elderly care and assistance market is one of the fastest growing markets in the world. Within the next 15 years, another 32 million new customers from the older baby boomer demographic will enter this market representing a total spending power of $2.1 trillion.[1] Currently, Americans age 65 or older account for approximately 12.6% of the total population, or roughly 36 million people, with an average expenditure of $3,588 per person on healthcare. This represents a total healthcare spending of $129 billion.[2]

Now that the team had a fairly good understanding of its overall market, a preliminary needs assessment was conducted. Desperately trying to capture the voice of its customer, the team vigorously pursued all avenues. Focus groups held at senior citizen homes, one-on-one interviews with elders, and internet searches for elderly products all yielded several plausible opportunities, particularly in the areas of personal mobility, medication delivery, and memory assistance. Finally with input from potential customers, data captured from market research and lengthy brainstorming sessions, the group identified a need for an automated medication container opener.

The automated medication container opener was targeted at individuals suffering from arthritis, cerebral palsy, muscular dystrophy, or any other cause for general muscle weakness and reduced grip strength. Such individuals tend to have difficulties opening standard childproof closures found on most medication containers. Thus, the team's new objective was to facilitate the opening of medication containers through the development of an electromechanical consumer device. The goal was to provide a universal solution for removing these medication container closures.

In addition to simply fulfilling a need, the team felt that this product also presented a great market opportunity. Consumer models

Poster Contest Team at Contest: (l-r) Richard Berkof, Jorge DaSilva, Murat Kocak, William Indoe, and Jay Peterson.

Poster Contest Team at Engineering. Day: (l-r) Richard Berkof, Murat Kocak, William Indoe, Jorge DaSilva, and Jay Peterson.

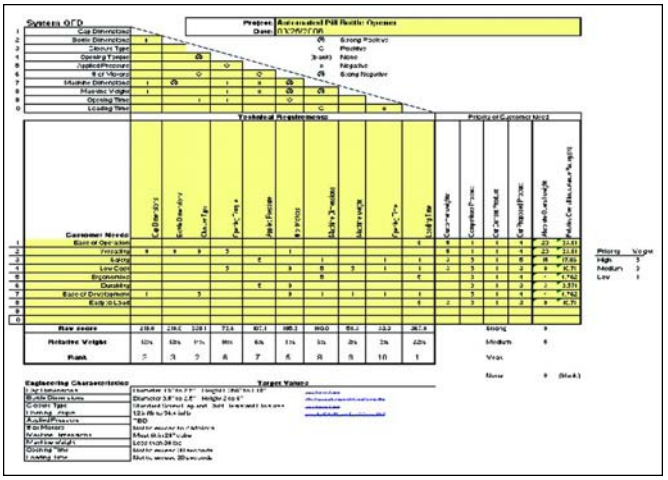

Figure 1. House of Quality matrix.

that exist in the current market are not fully automatic. Most consumer models are simple manually assisted devices that require a large amount of dexterity and strength from the user. If a fully automatic device could be designed and built, it would enjoy a huge competitive advantage as being the first such product to market.

Preliminary Design

With a customer need and market opportunity identified, the team could now enter the initial design phase. Knowing how important customer satisfaction is to the success of a consumer product, the team needed to ensure that the final design would satisfy the customer's needs and wants. To achieve this, the team developed a House of Quality Matrix - *Figure 1*. The matrix takes engineering characteristics listed in the top row of the matrix and compares them to the customer requirements listed in the leftmost column. In the cell where the customer requirement intersects the engineering characteristics, the level of interdependence is denoted by a symbol or number. Ranking the customer requirements in order of priority and then seeing which engineering characteristics correspond to the higher ranking requirements, the team is able to identify areas of the design in which to focus. For this project, the top three ranking customer requirements were ease of use, cost, and appearance.

Now that important engineering characteristics were identified, the next step in the process was to develop a product scope and specifications for the design. With the original goal of developing a universal fully automatic device, the team tried to make the scope as wide as possible without biting off more than they could chew. Thus, they decided to include all types of medication containers they could. The types of containers included in the scope were child safety, standard screw off, and pop top containers. The only containers omitted from the scope were the child resistant containers featuring two tabs on the side of the cap across from each other, which the user depresses in order to unlock the safety mechanism.

Specifications such as the cap and bottle dimensions and closure type were determined through researching the different types of medication containers that exist. The values were acquired from manufacturers of the medication containers. Specifications such as the machine dimensions, weight, opening time, and loading time were determined from feedback that was provided by the customers. The customer research showed that the consumers desire a product that is similar to conventional home devices such as a coffee maker or a microwave. The opening time must not exceed 30 seconds and loading time must not exceed 20 seconds. The remaining specifications such as opening torque and minimum down force were determined experimentally. After performing such experiments, it was found that in order to depress a standard child safety mechanism, a minimum of 11 pounds of down force must be applied. In addition, the minimum torque required to open a bottle was determined experimentally to be about 1.5 inch-pounds.

During the next phase of the project, the team brainstormed several different concepts and developed hand sketches of these concepts, such as the one shown in Figure 2. Based on the highest ranking customer requirements and the important engineering characteristics identified in House of Quality, the team was able to perform a concept screening to choose the best concept. The sketch shown is actually the winning concept that was selected for further development. It features a crosshead that travels vertically downward to engage the child safety mechanism. The bottle is centered using the lower grippers and then the crosshead rotates to open the container.

Design Development

After two and a half months of work, several discussions, and a few disagreements, the team was ready to begin its detailed design. With the customer needs always in mind and focusing on the critical engineering characteristics, the team was able to utilize advanced 3D modeling software packages to develop a detailed design. Figure 3 shows an exploded view of

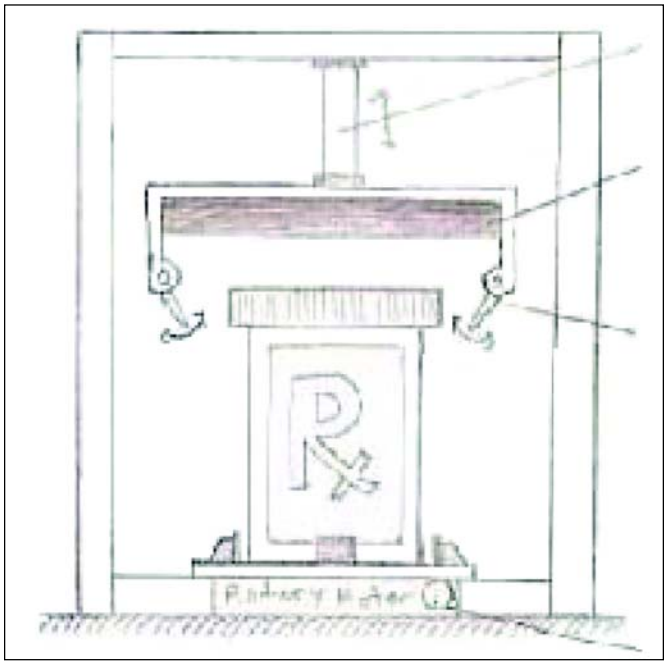

Figure 2. Early concept sketch.

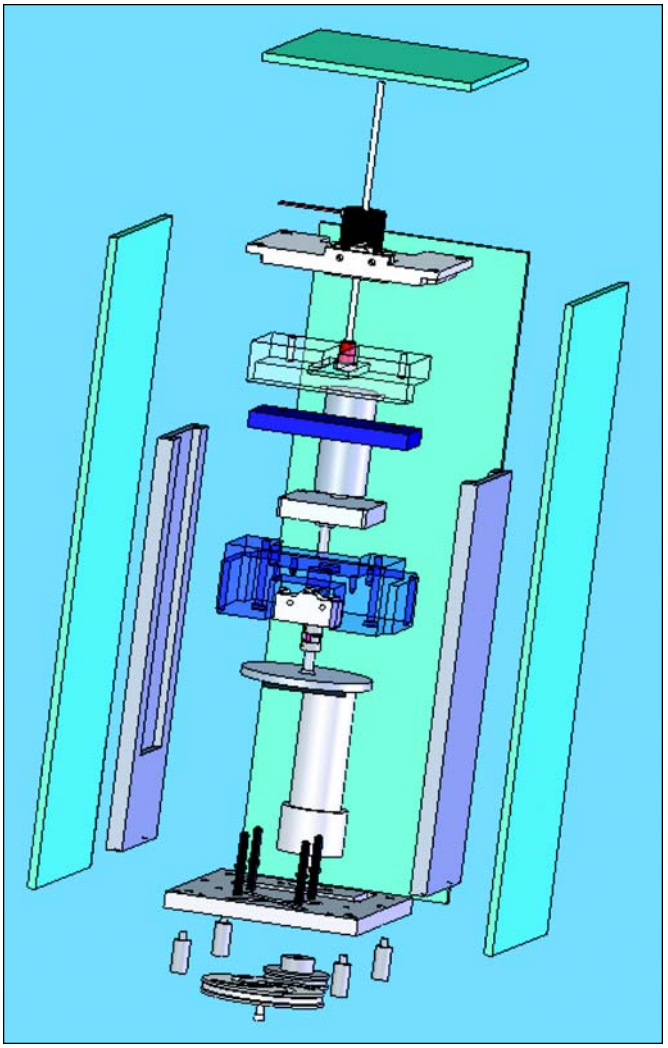

Figure 3. Detailed design – exploded view.

the final detailed design. Somewhat different from the original sketch, the final design does not use fingers to physically hold the cap after it is loosened. The team felt that a user would not want the machine to retain the cap after the bottle is opened. This also helped reduce complexity in the design as it reduced the number of moving parts.

The final design features a bottom gripper operated by the rotation of an internal cam. This gripper is only used to center the bottle and does not need to firmly grasp the bottle once the crosshead is engaged. A linear lead screw is used to raise and lower the crosshead as well as provide the necessary down force to depress the child safety mechanism. This linear lead screw is operated via a stepper motor. The final motion, which is the bottle rotation, is done at the crosshead and is powered by a standard permanent magnet DC motor.

The advantage of using a 3D modeling program is the ability to perform stress analysis on the various parts that make up the assembly. This allowed the team to verify the integrity of the design and make design changes quickly based on unfavorable results. The screen shot was taken from one of these analyses performed on the internal cam mechanism of the assembly - *Figure 4*. The team identified this component as having a high potential for failure; thus, the team used the software to verify that its design would not fail under the stresses and strains of operation.

Final Design, Fabrication, Assembly, and Integration

A final design was now in place, critical parts were identified and analyzed, and the team had four months remaining to fabricate and test the design. During these remaining four months, the team was able to order and receive all components, machine those that needed machining, perform a detailed electrical design, program a microcontroller, assemble all of the sub components, and test the machine's functionality. After a successful integration phase, the result of this effort is shown in a fully functional proof of concept device capable of gripping, engaging, and rotating caps off a wide variety of medication containers - *Figure 5*.

Industrial Design

The major aspiration of this project was design, build, refine, and test the proof of concept device to highlight the feasibility of our concept for an automated pill bottle opener. The team decided that it also needed to demonstrate that the concept has a marketable aspect to it. Thus, a consumer design was required to reveal the next rendition of the group's concept; the design incorporated all the knowledge of the mechanics of opening various caps that the group had learned from testing and refining the proof of concept design. The consumer model can be seen in Figure 6. Some major changes are the sleeker outer casing, which would be made of injection molded plastic. This helped significantly reduce the number of fasteners necessary for assembly, reducing assembly time. The casing also helped considerably reduce size and weight. The power transmission mechanism also was changed on the lower gripper of the consumer design from a belt and pulley to a gear train.

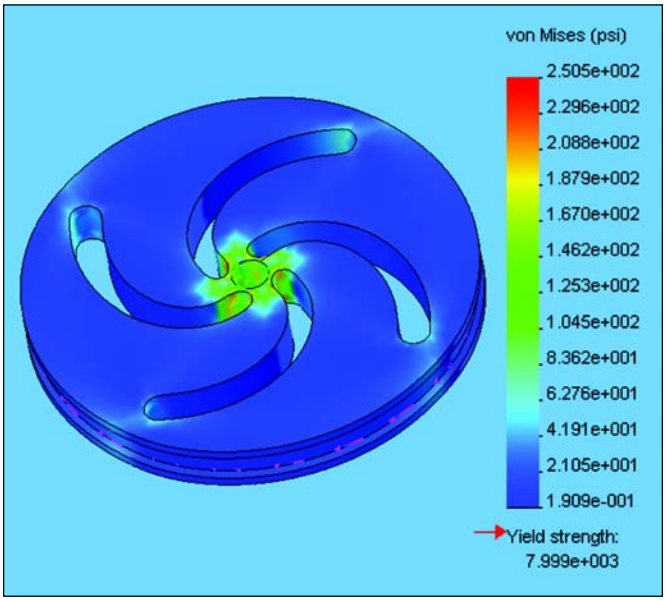

Figure 4. Stress analysis of cam.

Figure 5. Proof of concept demonstration device.

This consumer model also was important to help determine the economic feasibility of the project. Market research showed that price was the primary concern for consumers. It also showed that there was a willingness to buy the product if it could be offered at approximately $75. Based on revenue projections, manufacturing cost estimates, and start up expenses, this initial investment could generate an IRR of 33%, a Net Present Value of $1,778,000, and a payback period of 4.1 years. The cost of the product is reasonable, considering many devices on the market are manual and can cost up to $30.

As people age, they lose some of the physical functionality they had at younger ages. As this begins to happen, they become more dependent on others to help them complete daily tasks. This device will allow elderly individuals to retain a level of self-reliance, which could enhance their overall quality of life. Not such an insignificant accomplishment for eight months work from a group of highly motivated undergraduates.

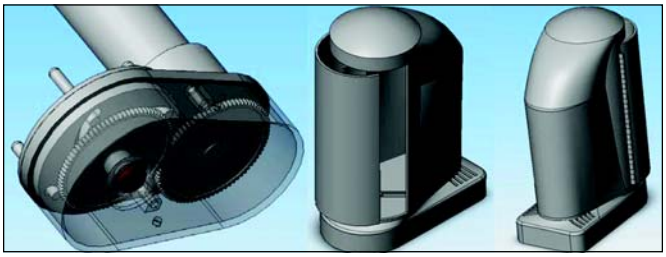

Figure 6. Industrial design – consumer model.

Note About the Project

This project was supported by a generous grant from the ISPE New Jersey Chapter, of which the associated Stevens Student Chapter is the active organization on campus. The Senior Design Project concept and working model were presented at the 2007 ISPE New Jersey Student Poster Contest, and won first place/top honors.

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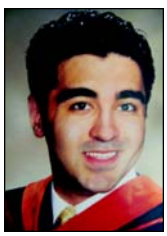

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PQLI at Forefront of Industry's Quest for Quality

by Rochelle Runas, ISPE Technical Writer

PQLI, the groundbreaking project to find practical, global approaches to implementing ICH guidelines, continues to gain momentum with more interactive sessions scheduled for ISPE's Copenhagen Conference in April.

The Product Quality Lifecycle Implementation (PQLI) initiative is an industry-driven effort lead by ISPE to find pragmatic approaches for those wanting to implement the high level ICH Guidelines Q8, Q9, and Q10.

With the encouragement of the US FDA, PQLI was launched in June 2007 at the ISPE Washington Conference, which featured highly interactive workshops with 50 FDA participants. PQLI has since been capturing the attention of industry leaders and regulators worldwide. In response to fast growing interest, PQLI sessions were held at the ISPE Berlin Conference in September 2007 in Berlin, Germany, and at the ISPE Annual Meeting in November 2007 in Las Vegas, Nevada.

At the Berlin Conference, Jacques Morénas, EU expert and Chairman of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), announced his support of PQLI. PIC/S is a cooperative arrangement between 30 regulatory authorities worldwide that enables active and constructive cooperation and sharing of information in the field of GMP.

The ISPE Annual Meeting brought together regulators from the US FDA, Japan's MHLW, and the EMEA who actively engaged in PQLI educational sessions with conference attendees.

The next PQLI gathering will take place 9 - 11 April at the ISPE Conference on Innovation in Copenhagen, Denmark.

Background

ICH Guidelines

The ICH is a forum that brings together the regulatory authorities of the US, Japan, and Europe, and experts from the pharmaceutical industry to harmonize technical requirements for the registration of pharmaceutical products among the three regions.

In November 2005, ICH endorsed and recommended that the three regulatory authorities adopt the following two guidelines:

- ICH Q8 (Pharmaceutical Development) – provides suggested content for a particular section of a product registration application to regulatory authorities in the three regions. This section is intended to provide reviewers and inspectors a comprehensive understanding of the product and its manufacturing process.
- ICH Q9 (Quality Risk Management) – provides recommendations for a systematic approach to quality risk management. The guidance includes principles and tools for quality risk management that can be applied to all aspects of pharmaceutical quality throughout the lifecycle of drug substances, drug products, and biological and biotechnological products. The guidance is intended to enable regulators and industry make more effective and consistent risk-based decisions.

Currently under development is ICH Q10 (Pharmaceutical Quality System). This guideline is expected to describe a model for an effective quality management system for the pharmaceutical industry that can be implemented throughout the different stages of a product lifecycle. Implementation should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

The Big Picture – Why PQLI is so Important

PQLI plays an integral role in bringing industry and regulators together to find solutions to the challenges of implementing the high level concepts found in ICH Q8, Q9, and Q10 and QbD.

These concepts coincide with the industry movement toward building quality into pharmaceuticals from development through manufacturing; bridging gaps between pharmaceutical development and manufacturing; and using sound science to demonstrate and assure the product's safety, quality, and efficacy throughout its entire lifecycle.

If these concepts are implemented, it may streamline the way pharmaceuticals are developed and manufactured, resulting in cost benefits for the pharmaceutical companies, which they in turn, can pass on to patients in the form of high quality, affordable medicines.

Quality by Design

Around the same time ICH Q8 and Q9 were issued, the term Quality by Design (QbD) made its way into the industry's lexicon. It has been described in many different ways, including it being a concept, idea, approach, philosophy, or perspective that quality should be built into a product as opposed to being tested for after manufacture. Many of the concepts in Q8 and Q9 are elements of or are closely aligned with QbD.

Currently under development is ICH Q8 R1 (Pharmaceutical Development Revision), the annex to Q8 (Pharmaceutical Development). The document is expected to provide an official definition for QbD and its principles. The document is also expected to provide further clarification of key concepts (e.g., design space) and tools outlined in the core guideline and how they can be put into practice.

PQLI – Tying It All Together

"The ICH guidelines, especially Q8, Q9, and Q10, are unique because they

Continued on page 2.

PQLI at Forefront of Industry's Quest for Quality

Continued from page 2.

are more visionary," said Moheb Nasr, Director, Office of New Drug Quality Assessment, CDER, US FDA, in the December issue of the *Journal of Pharmaceutical Innovation*. "They are at a higher level, they are not very prescriptive, and do not provide a lot of details of how and what to submit in applications."

"Because of that, there is a need to develop more detailed technical guidance to facilitate the implementation of Q8, Q9, and Q10," Nasr said. "ISPE developed the PQLI program to do just that." PQLI also aims to provide more detailed technical guidance to implement QbD in regulatory submissions.

The main objectives of PQLI are to:

- Facilitate the understanding of the concepts contained in the ICH documents Q8, Q9, and Q10
- provide the technical framework required for the implementation of Quality by Design (QbD) in regulatory submissions
- enable Q8, Q9, and Q10 to become cross-functional tools valued by both the industry and regulatory authorities worldwide

While accomplishing the above objectives, PQLI envisions delivering to the industry a comprehensive and practical knowledge base that will include the following: white papers and similar publications, guidances, technical documents, an Enyclopedia of QbD, and education and training.

What has PQLI Accomplished So Far?

Much progress has been made in facilitating the understanding of QbD and the concepts in the ICH guidelines, including:

- Criticality (subtopics of critical vs. non-critical, attributes and parameters, and knowledge space)
- Design Space
- Control Strategy

These concepts are discussed in detail in the Draft PQLI Summary Update

The Next Step: Copenhagen

Copenhagen will feature highly interactive workshops with valuable input from 20 European regulators.

Copenhagen 2008 PQLI Workshop Draft Agenda

(Agenda Subject to Change)

Day 1 – Wednesday 9 April 2008 (Introductory workshop)			
Afternoon Session – Plenary – Introduction to Program			
Introduction to ICH and the way ICH works			
Overview of the ICH Guidelines			
Coffee Break			
ICH Implementation Work Groups and ICH Q8/9/10 Guidelines from an Assessors Perspective			
ICH Implementation Work Groups and ICH Q8/9/10 Guidelines from an Inspectors Perspective			
Wrap up and lead in to PQLI			
Day 2 – Thursday 10 April 2008			
Morning Sessions – Plenary			
Introduction to PQLI			
The Future Role of Pharmacopeias			
Coffee Break – Exhibition			
Establishing Release Specification – Current and Future *(An Assessor and Industry Perspective)*			
What Could be the Role of the Qualified Person in the Future – including Control Strategy and Batch Release *(Inspector and Industry Perspective)*			
Introduction to Workshops			
Lunch and Exhibition			
Afternoon Sessions – 4 parallel task teams. Workshop / Case Study Format			
Design Space	Criticality	Control Strategy	LegacyProducts
Coffee Break – Exhibition			
Design Space	Criticality	Control Strategy	LegacyProducts
Reception and Exhibition			
Day 3 – Friday 11 April 2008			
Morning Sessions – 4 parallel discussions. Workshop / Case Study Format			
Future Role of a Qualified Person	Submission vs. Inspection Data	Specifications	Real Time Release
Coffee Break – Exhibition			
Future Role of a Qualified Person	Submission vs. Inspection Data	Specifications	Real Time Release
Lunch and Exhibition			
Afternoon Sessions – Plenary			
Reports and feedback on Workshops			
Coffee Break – Exhibition			
Panel Discussion and Q&A – All Region and Key Speakers from Industry and Regulators + Industry Speakers			
Conclusions and Wrap-Up: Way forward for PQLI			

First of Its Kind Joint ISPE-PIC/S Workshop a Success

by Robert M. Tribe, ISPE Regulatory Affairs Advisor, Asia-Pacific

ISPE joined with PIC/S to co-host the Workshop "Systems Approach to Quality Risk Management," which was the first time that PIC/S had collaborated with an industry organization to arrange the training of regulatory GMP inspectors alongside industry representatives.

The Workshop, held 22 – 23 November 2007 in Singapore, was attended by 226 participants, comprising 65 regulators and 161 industry participants from 34 different countries. The Workshop provided updates on ICH Q8, Q9, and Q10, as well as the risk management methodologies that the industry can use to enhance manufacturing efficiencies. Examples of the use of risk management approaches, in the form of actual case studies, were presented by a French regulator and an industry representative.

Regulators and industry representatives also worked together in small breakout groups to discuss and seek solutions to two fictitious manufacturing problems using risk management tools and methodologies. These workshop exercises revealed that regulators and industry generally reached similar conclusions when solving manufacturing problems, using similar risk management approaches.

There was enthusiastic participation and interaction between regulators and industry, not only during the Workshop sessions, but also during the less formal coffee and lunch breaks and evening networking reception.

PIC/S has reported in a press release that "the Workshop was a success and it is expected that more joint workshops will be organized with professional and industry associations in the future."

Bruce Davis, Chairman of ISPE, has indicated, "We in ISPE were proud to have been the first industry organization to be invited to co-host such a prestigious event in such a dynamic part of the world and, as Chairman, I was delighted to be able to open the Workshop along with Mr. Jacques Morénas, Chairman of PIC/S."

PQLI at Forefront...

Continued.

Report, V04, by PQLI Technical Writer Sion Wyn, which can be found at www.ispe.org.

White papers and articles are being developed for publication this year in *Pharmaceutical Engineering* and the *Journal of Pharmaceutical Innovation*.

Mark Your Calendar with these ISPE Events

February 2008

5	Nordic Affiliate, Conference on Product Security and Protection Oslo, Norway
9	ISPE Southeast Student Leadership Forum, McKimmon Center, Raleigh, North Carolina, US
9	ISPE West Coast Student Leadership Forum, Embassy Suites, Walnut Creek, California, US
12	**ISPE Webinar: Successful Training of CTM Professionals**
14-15	**INTERHEX *Puerto Rico*, Puerto Rico Convention Center, San Juan, Puerto Rico**
20	Carolina-South Atlantic Chapter, Student Career Fair, NC Biotech Center, Research Triangle Park, North Carolina, US
21	Rocky Mountain Chapter, Annual Vendor Expo and Workshops, Millennium Harvest House, Boulder, Colorado, US
21	New Jersey Chapter, Clean Room Overview and Comparison of FDA and EU Regulations, Somerset, New Jersey, US
21	San Diego Chapter, Dinner Meeting, Topic: Business Continuity, San Diego, California, US
25 - 28	**ISPE Conference on Manufacturing Excellence, Hyatt Regency Tampa, Tampa, Florida, US** Topics include: Biotechnology processing, validation, aseptic processing, PAT, GAMP®5, advanced automation and process control, critical utilities, disposables, and operational excellence
28	San Francisco/Bay Area Chapter, Vendor Night, South San Francisco Conference Center, South San Francisco, California, US
28	UK Affiliate - Central Region, Seminar on Risk and Quality Management, AZ, Loughborough, United Kingdom
28 - 29	**ISPE Classroom Training, Auditing for GMP, Tokyo, Japan**

March 2008

4	Carolina-South Atlantic Chapter, Annual Technology Show with local Chapter Student Poster Competition, RBC Center, Raleigh, North Carolina, US
12	Carolina-South Atlantic Chapter, Joint CASA/ASHRAE Event, BioContainment, McKimmon Center, Raleigh, North Carolina, US
12	Nordic Affiliate, Conference on Biomanufacturing Excellence, Copenhagen, Denmark
12-13	Indonesia Affiliate, Conference, Indonesia
13	France Affiliate, Conference on Single Use Devices, Paris, France
17	Argentina Affiliate, Workshop Topics include GAMP Validation, Qualification, Risk Analysis, Buenos Aires, Argentina
18	Central Canada Chapter, Toronto Breakfast Seminar: Biotech Session, Toronto, Ontario, Canada
19	Central Canada Chapter, Montreal Breakfast Seminar: Biotech Session, Montreal, Quebec, Canada
20	Central Canada Chapter, Quebec City Breakfast Seminar: Biotech Session, Quebec City, Quebec, Canada
20	New Jersey Chapter, Dual Track Program on RFID and AIA Contracts, Somerset, New Jersey, US
26-28	**INTERPHEX*2008*, Pennsylvania Convention Center, Philadelphia, Pennsylvania, US**
28	Turkey Affiliate, Seminar on GAMP 5, Istanbul, Turkey

Dates and Topics are subject to change.

ISPE – CCPIE Partnership Aims to Advance China's Pharmaceutical Industry

by Rochelle Runas, ISPE Technical Writer

With China's entry to the WTO expected to open the floodgates of the country's pharmaceutical industry along with stiffer pharmaceutical standards, the joint ISPE and CCPIE inaugural GMP Conference held in Shanghai couldn't have been timelier.

More than 150 industry leaders, government officials, and academics attended the conference, held 28 October 2007 at the Parkview Hotel, Shanghai, China.

The Conference was a joint collaboration between ISPE and the China Centre for Pharmaceutical International Exchange (CCPIE), a division of the China Safe Food and Drug Administration (SFDA).

The Conference was held the day before the 12th China International Pharmaceutical Industry Exhibition and the China International Pharmaceutical Industry Forum and just days after China's State Food and Drug Administration issued revised good manufacturing practice inspectional guidelines.

According to an article in PharmaAsia, the new guidelines, effective 1 January, replace GMP inspectional guidelines that were implemented in 1998. The revised guidelines are meant to increase quality systems standards for pharmaceutical manufacturers, expanding "drug makers' technical requirements for personal qualifications, production processes, quality control, and validation documentation."

The inaugural GMP Conference included sessions addressing the latest trends in the Chinese pharmaceutical industry, including policies, regulations, industry guidelines, and technical criteria.

Some of the topics discussed included the Use of Science and Risk-Based Approach and Quality by Design in Pharmaceutical Engineering and Manufacturing, and an in-depth look into the PricewaterhouseCoopers report *Pharma 2020: The Vision – Which Path Will You Take?*

The GMP Conference is a result of a three-year Memorandum of Understanding (MOU) signed by ISPE and CCPIE October 2007. Under the MOU, ISPE and CCPIE will collaborate to oversee the production of conferences, exhibitions, and training programs, both for the pharmaceutical industry in China and the SFDA.

By introducing training programs and educational events to qualified professionals, ISPE hopes to share global best practices and knowledge with China's pharmaceutical industry. This will contribute to the advancement of technical efficiency of pharmaceutical professionals in China, such as engineers, microbiologists, chemists, QA/QC, production, process development, pharmacists, regulatory and training personnel, academia, and suppliers. ISPE also aims to keep industry professionals updated on the latest technological and regulatory trends that are occurring on the international scene.

International Call for Articles

Pharmaceutical Engineering is the Global Information Source for Pharmaceutical Manufacturing Professionals and is the official magazine of ISPE. ISPE members include individuals participating in multiple fields relating to pharmaceutical manufacturing. This audience encompasses engineering staff, operators, scientists, and compliance staff from biologics and pharmaceutical operating companies; vendors supplying equipment and services to these industries; regulators and government officials; academic scholars, professors, and students.

Pharmaceutical Engineering is seeking articles with a global perspective for the issues listed here.

JULY/AUGUST 2008
Theme: Process Development
Manuscripts Due: 3 March 2008 **Publishes:** 21 July 2008

Potential articles in this issue will focus on process development topics, including process research and innovation, process modeling, scale-up, and the design, construction, and operation of pilot plants and laboratory units. This issue could explore technology transfer, manufacturing optimization, operational excellence, and the use of PAT to achieve new efficiencies and increase process knowledge and control. Additional topics could include design space, combined products, continuous processing, ICH Q8, Q9, Q10, Quality by Design, and fast response facilities.

SEPTEMBER/OCTOBER 2008
Theme: Oral Solid Dosage (OSD)
Manuscripts Due: 2 May 2008 **Publishes:** 22 Sept 2008

Potential articles in this issue will focus on the processes and equipment used in a typical Oral Solid Dosage (OSD) facility. Case studies will attempt to demonstrate PAT application, better process control strategies, and automation in an OSD environment. Articles featuring the latest in OSD packaging technology, including robotics, RFID, and vision systems will be sought. Additional topics could include advancements in combined products, production, tabletting, containment, and risk assessment. An update and application of the ISPE Baseline Guide will be featured.

NOVEMBER/DECEMBER 2008
Theme: Decontamination/Containment/Sterilization
Manuscripts Due: 3 July 2008 **Publishes:** 20 Nov 2008

Potential articles in this issue will focus on the latest in Decontamination/Containment/Sterilization technologies and their applications in the pharmaceutical industry. Case studies could explore how these systems are incorporated into pharmaceutical processes and facilities. Additional topics could focus on how to effectively utilize a Risk Management process to determine the decontamination/containment/sterilization needs, in addition to sampling issues, aseptic sampling, cleaning, PAT application, and process control strategy. Articles on the newly updated ISPE Baseline Guide for Sterile Manufacturing Facilities as well as updates and applications of various ISPE technical documents, including the Water and Steam Baseline Guide Revision, HVAC Good Practice Guide, and the C&Q of Pharmaceutical Water and Steam Systems Good Practice Guide will be featured.

For further information, please visit our Web site at **www.ISPE.org**, and then connect the following links: Publications, Pharmaceutical Engineering, How to Submit an Article, and then Author Guidelines.

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Veolia Water Solutions & Technologies, Global Headquarters, L'Aquarène – 1, place Montgolfier, 94417 Saint-Maurice Cedex, France, www.pharma.veolia waterst.com, E-mail: pharma-info@ veoliawater.com. See our ad in this issue.

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International

A report of the 11th conference of the **Global Harmonization Task Force** SG1 held 3 to 4 October 2007 in Washington DC, USA have been available on their Web site[1] since 19 October. Presenter's slides are also available.

In November 2007, Global Harmonization Task Force SG4 posted[2] draft guidelines on regulatory auditing of quality management systems of medical device manufacturers for general comment by 14 May 2008. The document is intended to provide nonbinding guidance on the regulation of medical devices, and has been subject to consultation throughout its development.

Europe

The **European Commission** has launched a public consultation on proposals to simplify variations regulations and make them less burdensome on manufacturers. The document[3] is the second part of a two-part consultation that proposes revisions to the EC regulations. Proposal for change to requirements are considerable and include:

- flexibility to manufacturers where modern (e.g. ICH) quality tools have been put in place
- simple notification procedures for Type IA variations
- treating changes not explicitly recognized as Type IA, II or line extensions as Type IB variations by default and no longer as Type II
- introducing generic definitions of variations and replacing the current annexes with detailed guidelines on the classification of variations
- outlining cases where grouping of variations under a single submission could
- be allowed
- clarifying exactly when change is allowed to be implemented by a marketing authorization holder

The European Directorate for the Quality of Medicine & Healthcare (EDQM) has announced via its Web site[4] that at an October meeting of the Pharmacopoeial Discussion Group in association with ICH Expert Working Groups harmonization had been achieved on 9 of the 11 General Chapters identified by the ICH Q6A Guideline, including the newly signed off general chapters on sterility, disintegration and X-Ray Powder Diffraction In addition, the monograph for Sucrose and revisions to the monographs for Corn Starch, Potato Starch, and Wheat Starch were signed off. At present, therefore, 25 of the 35 General Chapters and 36 of the 62 excipient monographs have been harmonized.

In November 2007, the European Pharmacopoeia announced on the same Web site that it would like to extend the deadline for manufacturers to send their comments on practical aspects of the application of the new method for *Uniformity of dosage units (2.9.40)*. The European Pharmacopoeia at present has two sets of general chapters concerned with dosage uniformity: 2.9.5 *Uniformity of mass of single-dose preparations and 2.9.6 Uniformity of content of single-dose preparations*, and 2.9.40 *Uniformity of dosage units*. The latter has been developed as a harmonized chapter following a request from the ICH Steering Committee related to the Q6A Guideline and contains tests for uniformity of both mass and content. Comments (with data) should now be provided by end June 2008

The **Committee for Medicinal Products for Human Use (CHMP)** has published reports[5] from its September, October and November plenary meetings held on 17-20 September, 15-18 October, and 2-15 November 2007 respectively.

The following relevant guidelines[6] have been prepared or adopted by the Quality Working Party:

- Guideline on Radiopharmaceuticals for 6-month public consultation (EMEA/CHMP/QWP/306970/2007)
- Revised Guideline on Medicinal Gases for 6-month public consultation (EMEA/CPMP/QWP/1719/00 Rev 1)
- Guideline on Declaration of Storage Conditions has been adopted (CPMP/QWP/609/96/Rev 2)

The following relevant guideline[6] has been prepared by the Biologics Working Party:

- Draft Guideline on allergen products: Production and quality Issues for 6-month public consultation (EMEA/CHMP/BWP/304831/2007)

The **Committee on Herbal Medicinal Products (HMPC)**[7] has published their monthly meeting reports for the meetings 7 September and 31 October 2007. No new relevant information was noted.

The **Paediatric Committee (PDCO)** has published their monthly meeting report[8] for the meeting on 21-23 November 2007. No new relevant information was noted.

The **Committee for Orphan Medicinal Products (COMP)** has published their monthly meeting report[9] for the meeting held 24 to 26 October 2007. No new relevant information was noted.

The **Committee for Veterinary Medicinal Products (CVMP)**[10] has published their Monthly Reports of Application Procedures, Guidelines and Related Documents for September and October 2007. Each includes an accumulative summary of the opinions issued by the CVMP in the current year and a list of adopted Guidelines and other public documents.

At their September meeting,[11] a revised Guideline on Stability Testing: Stability testing of existing active substances and related finished products (EMEA/CVMP/QWP/846/99-Rev.1) was adopted for release for a 6-month period of public consultation. The aim

of this revision is to update provisions in line with the recently updated VICH guideline on stability (GL3).

The Committee adopted a questions and answers document regarding application of the so-called 'sunset clause' to centrally authorized veterinary medicinal products (EMEA/CVMP/120559/2006) following the close of the public consultation. This document addresses questions that a Marketing Authorization Holder may have on this topic and on how EMEA will monitor any centrally authorized veterinary medicinal products.

Ireland

The **Irish Medicines Board (IMB)** has published a guide to batch specific requests (BSRs) for human medicines on its redesigned Web site.[12] Essentially, BSRs will only be accepted for authorized medicines to ensure maintenance of supply when supply of product in a fully compliant product is temporarily and unavoidably unavailable, and will normally cover sufficient batches for three month's supply to the market. The BSR procedure can also be used in such instances where a variation has been approved and the PA holder is unable to meet the required timeline for implementation.

IMB further advises that BSRs should not be submitted for batches which have been deemed by the Qualified Person to meet the terms of the reflection paper on dealing with minor deviations from the detail in the Marketing Authorization (EMEA/INS/GMP/71188/2006) available on the EMEA Web site.[13]

Israel

The **Israeli Ministry of Health** has issued new requirements[14] for the labeling of medicinal products covering the outer packaging, immediate packaging and package inserts. The aim of the guideline is to prevent prescription, dispensing or handling errors by medical professionals. To this end, requirements are designed to enable easy identification and differentiation of similar products and also ensure their proper use.

Russia

Russia (**Roszdravnadzor**) has announced[14] a plan to complete good manufacturing practice (GMP) certification of all drug manufacturers registered in the country by 1 January 2010. The majority of domestic pharmaceutical companies in Russia founded during the Soviet era or in the early 1990s have not yet started modernization procedures that would make their drug manufacturing processes GMP compliant. However, as over 1200 factories located outside the Russian Federation are involved in drug manufacture, Roszdravnadzor plans also to inspect foreign drug manufacturing sites.

Implementation of the plan will include consultations with stake holders and amendments to the Russian Drug Law.

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