This case study presents early contamination detection in an established WFI and PW system through the use of on-line particle counters.

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On-line Particle Counters Provide Detection and Control in Water for Injection (WFI) and Purified Water (PW) Systems

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Creating an effective water system to provide Purified Water (PW) or Water for Injection (WFI) in a life science application is a careful adjustment of design, materials, monitoring, and maintenance. By convention, certain parameters must be monitored in a WFI system: endotoxin levels, conductivity, TOC, and microbial (CFU) values.[1,2] In the EU, other parameters that must be monitored are nitrates and heavy metals.[3] It has been common in the past to obtain grab samples of the water at a predefined frequency and to later perform a laboratory analysis for the key parameters. In recent times, some of the instrumentation for these parameters, for example, TOC, has allowed continuous on-line measurement to be accomplished. Determination and monitoring of particulate levels in WFI systems are not required by regulation, but can provide an enhanced degree of control, as described in this article, resulting in early detection of potential breaches in the integrity of the water system.

The water system in Building S166 at the Schering facility in Berlin provides PW to an oral dosage forms manufacturing area and PW and WFI to a parenteral area for manufacturing clinical trial supplies. In 2000, an on-line particle counter was installed on the WFI system - *Figure 1.* The instrument was connected to monitoring software that provides water system information from three different buildings - *Figure 2*. The software includes operational details of various parameters such as the system temperature and pressure in the various piping systems on the campus. Based on the performance of the initial analytical monitoring system on the WFI system, a second particle counting system was installed in 2005 on the PW system in Building S166.

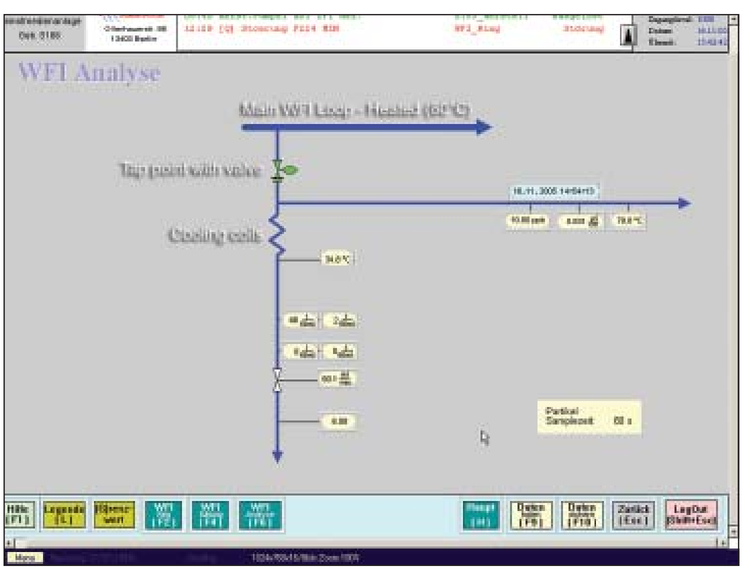

Figure 1. WFI system with instrumentation and valves.

As with most WFI systems, the water is circulated in a continuous flow loop at an elevated temperature of at least 80°C (176°F) to exclude bacterial growth. Neither the pH sensor nor the particle counter are designed to operate in this temperature range so a heat exchange system is positioned up-

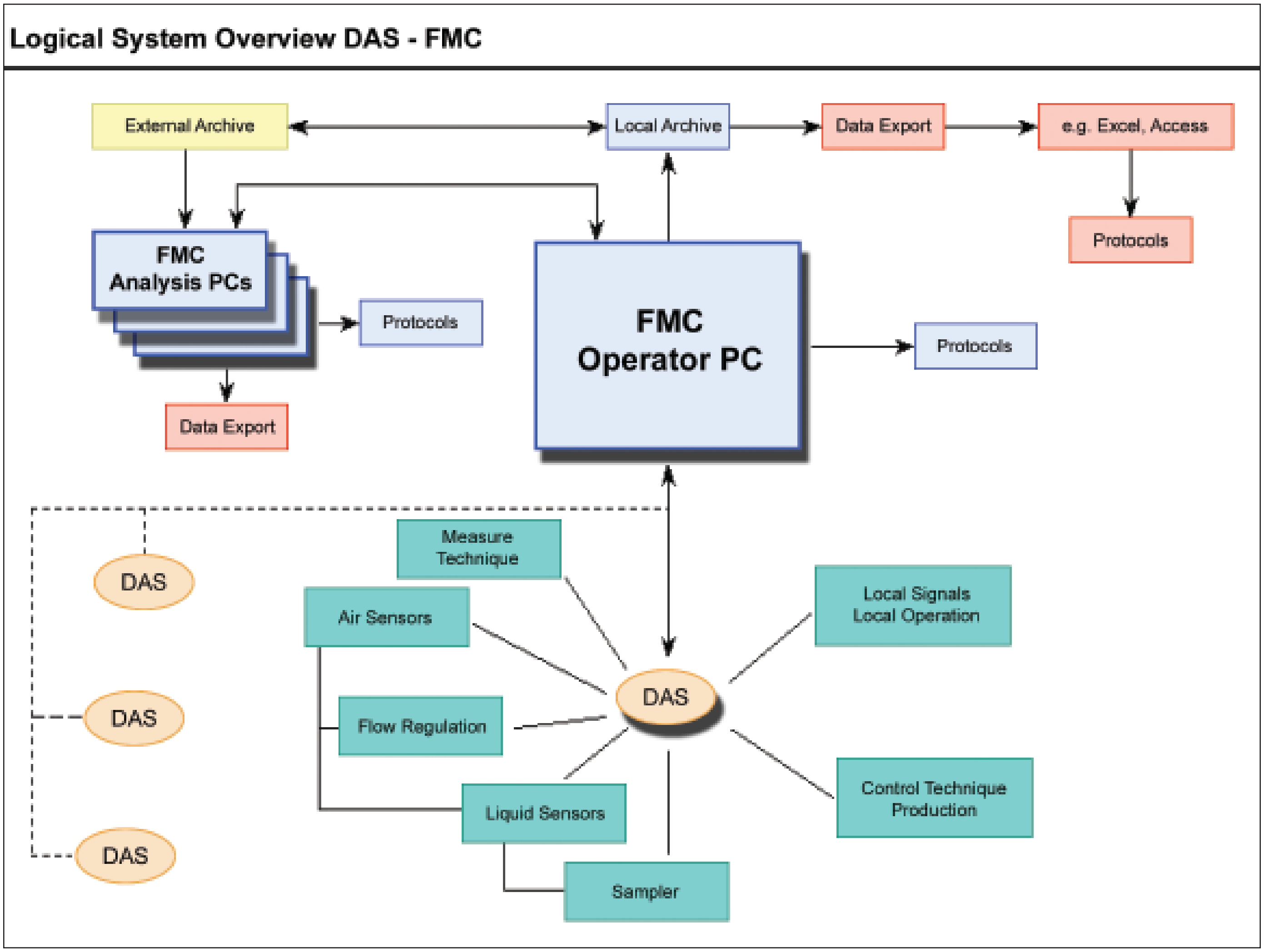

Figure 2. Overview of DigiPlan FMC-DAS software architecture.

stream from the counter to reduce the temperature of the sampled water to approximately 35°C (96°F) - *Figure 3*. The cooled water flows through the particle counter with the flow controlled to 60 milliliters per minute (0.95 gallon/hour) and then through the pH meter. It is then sent to drain. Sending the sampled water to drain avoids potential introduction into the WFI system of chemical contaminants such as the reagents used in the pH sensor.

At this time, alarm indications in the monitoring software are provided only for conductivity and TOC pending establishment of appropriate limits for the pH and particles through further monitoring.

Conductivity, TOC, and temperature are measured directly on the heated loop. Separate temperature transducers are used to monitor the temperature in the main loop and in the sample line following the heat exchange unit. Downstream from the particle sensor is a flow controller, followed by the pH sensor. The output of the pH sensor goes to drain.

Particle Detection

The sensor provides detection of particles starting at approximately 2 µm through 400 µm. The counter updates the particle count data each minute in each of four size channels: ≥5, ≥10, ≥25, and ≥50 µm. The data is shown on the monitoring system screen in terms of "counts per 60 ml" in each of the four size ranges (channels). During steady-state operation, some counts are observed in the first two size channels (≥5 and ≥10 µm), usually less than 100 counts per 60 milliliters at 5 microns. Counts are rarely seen in the upper two size ranges (≥25 and ≥50 µm) during steady-state operation - *Figure 4*.

Observed count values of particles with this system are well below 1% of the USP limits [25 counts per mL at ≥10 microns and 3 counts per ml at ≥25 microns] for Large Volume Injectables (LVI). Care has been taken to monitor not only peaks in particle count values, but also changes in the baseline readings. Peak readings convey information on system performance that previously were never recorded with grab sample methods at Schering due to their once-per-week schedule. Today, the consistent and minute-by-minute data readings of the on-line system permit relevant data to be gathered for trend analysis and even SPC methods in the future.

Because the system is still regarded as being in the investigative stage regarding particle counts, alert and action levels have not been set. Particle count changes are

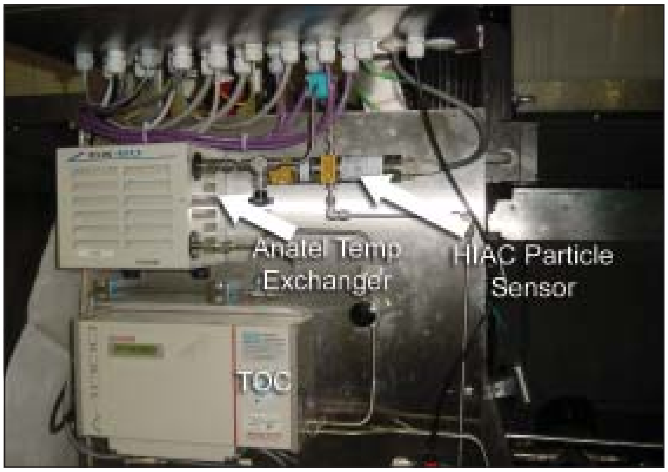

Figure 3. Instrumentation panel with HIAC HRLD sensor.

monitored by the Quality Group, evaluated, and then reported and discussed with both the Production Group from Clinical Supplies and Engineering. Elevated readings are now used to initiate maintenance and repair of the systems in cooperation with the Engineering Department.

Detected Particulate Matter in the WFI System

One of the major reasons for investing in an on-line particulate monitoring system was the significant variance in the data obtained from the hand-drawn grab samples Schering had previously employed. Often, these variances were false positives due to sample handling. In one incident, Raman microscopy was successfully used to determine that the probable source of high readings of particles larger than 5 microns in the grab samples was particles generated from a polyethylene component of the screw-on caps of the jars used for the grab samples.

The on-line system avoids false positives caused by manual sample gathering technique and materials. Note that sample point valves are another notorious generator of particles and potential false positives; grab samples should be drawn only after waiting long enough for the particles generated by the opening of the valve to be flushed out of the sample port.

A further impetus for the on-line system installation was the reduction of manpower needed to obtain samples from the water system. Previously grab sampling was carried out on a weekly basis and the results of the sampling were delayed by the time needed for the laboratory analysis. The on-line monitoring system now provides current data minute-by-minute at an estimated annual savings of at least one man-month of labor.

Within Schering's water system, high-purity membrane valves are used to control flows. The membranes of these valves are exposed to the circulating WFI. Particle shedding from compromised membranes will therefore also show up as baseline rise in the detected particle levels. A significant improvement in the valve system was triggered by the detection of black particles in the WFI; it was discovered that the initial EDPM membrane material was deteriorating more quickly than expected in the hot WFI and clean steam systems. Changing the contact surface to a Teflon-coated EDPM material and establishing scheduled annual or bi-annual replacement [depending on use and application] of these membranes eliminated this particle source.

In another incident, particles recovered from the system following detection of increased counts were determined through Atomic Absorption Spectroscopy (AAS) to be metallic particles from the piping system itself. Recent construction and repairs to the piping system were identified as the probable cause. After the data was brought to the attention of the maintenance group and contractors, procedures were initiated both to reduce the amount of particulate matter generated during maintenance and to more effectively clean repaired sections before they were re-connected to the system.

High Flow Demand Triggers Particulate Release

An on-line system can show events that grab sampling would be unable to detect; on-line systems also permit the possibility of correlation to other parameters of the system in order to help establish the root cause of the abnormal readings.

Figure 4 shows the normal, steady-state values. Compare this to the screen capture Figure 5 that recorded episodes of elevated counts following both a sudden reduction of the level of water in the WFI holding tank by high rapid demand and also two successive events of rapid refilling action by the still.

The red line in the graphic display represents the output of the level detector for the WFI tank. The supply system (WFI still) works to keep the tank from dropping below approximately 70% of 3000 liters (793 gallons). Upon reaching the trigger value, the supply system adds water from the still and brings the tank level back to a nominal "full" value of approximately 74%.

The green trace shows the particle counts obtained in the first channel (≥5 µm) of the particle counter. Although some counts are present during normal circulation, the rapid drop in level (marked as **1**) caused the detected counts to jump significantly.

Figure 4. Chart with typical steady-state or "normal" values.

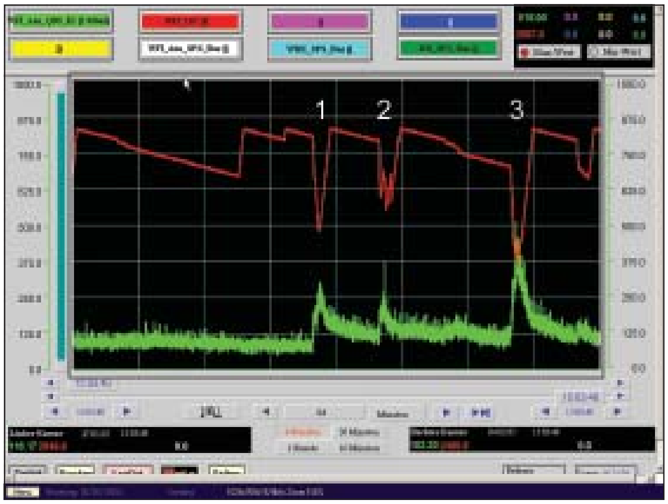

Figure 5. Particle surge as result of rapid drop in level of WFI holding tank.

The large drop in the tank level could have been caused by a cleaning operation in the main facility or, for instance, the initial high demand of a vial washing machine.

Note that there also are significant increases in particle counts when there are rapid, but lower volume demands on the WFI system, causing a rapid activation of the refilling system. In these cases (marked as **2** and **3**), the refilling system had the capacity to return the holding tank to its "full" state, but the demand for WFI was maintained at a slow, but steady rate so that that the refilling cycle occurred at a high frequency. This activity also was accompanied by high counts. It has been determined that these spikes of counts are the result of the turbulence in the holding tank caused by the refilling action. Trapped particles or sediment on the bottom of the tank could be released into the WFI circulation - *Figure 6*.

This tank and the general piping system go through a scheduled maintenance including annual cleaning. If this annual cleaning event is delayed, the spikes of particles triggered by the high demand/refilling cycle increase in amplitude and continue until the cleaning is undertaken. Cleaning of the system causes a definite reduction of the baseline counts and of the spikes triggered by the refilling action. By analyzing the debris material removed from the tank during cleaning, it is expected that further improvements to the materials and the operation of the water systems will be made.

By comparison, the responses of the other instruments on the system during a refilling spike are not at all as strong as the response of the particle counter. In Figure 6, the green trace again represents the first size channel of the particle counter. The red trace is the tank level, the yellow one is the output of the conductivity sensor, the magenta one is the TOC data, and the blue is the pH value. The reaction of the other sensors is very muted compared to the very observable response of the particle counter clearly detecting the increased particle concentration.

The reaction of the particle counter correlates precisely with the rapid depletion of the holding tank contents.

The particle counter has become an excellent indicator of the resident particulate content of the tank and has been used to determine the frequency of the cleaning cycle necessary for this part of the WFI system, as well as a superior indicator of unexpected increases in baseline particle count levels.

Because of the positive experiences with the automated WFI analysis system, Schering AG has now equipped a PW loop with a similar system of sensors including particle measurement.

Evolution of the WFI Monitoring System

At this time, daily review of the on-line monitored parameters is conducted as a joint session attended by Quality personnel, the Production personnel for Clinical Supplies, and Engineering personnel during which any observations are reported and discussed. This investigative phase will continue through 2006, after which it is likely that automatic alarms will be initiated; SPC limits also may be implemented. Alert and action levels will be decided based on the ongoing observations of the baseline values and unique events that occur. Analysis of any sediment collected during annual tank maintenance cycles will lead to further improvements in the system and its operation.

On-Line Monitoring and the FDA's PAT Initiative

The increasing movement toward on-line sensing technology and automation in the pharmaceutical industry has the support of the main regulatory agencies worldwide. The growing interest in Process Analytical Technology (PAT) is due to the potential for improved control of the process, improved product quality, and shortened analysis times for In-Process Controls (IPCs). Minute-to-minute monitoring of the key utilities in support of production – such as WFI – can aid in the assurance of product quality and rapid release of product because there is more complete data to back up a decision for product release. Particle counters can assist plant operators in maintaining and assuring an appropriate quality of water for use as a rinsing agent and as an ingredient in a product.

Figure 6. Comparison of outputs from particle counter, TOC, pH, and conductivity during a particle spike event.

The FDA has provided encouragement and support for the conversion of existing processes into PAT processes. Data collected can at first be regarded as "research data" until the user has decided that the additional method is sufficiently robust.[4] This allows a PAT process to be developed by the addition of suitable analytical and control processes of which this might be one.

Conclusion

Real-time sampling helps avoid errors common in manual sampling, such as compromised cleanliness of glassware, contamination generated when sample point valves are opened, and contamination contributed by the screw caps of the sample jars.

If a product contamination event were to occur, the monitoring details from the WFI system would allow investigators to quickly determine if the WFI was a contributing element to the contamination. Generally, the root cause for a contamination event will be found to be something other than the quality of the WFI system, but with the continuous monitoring data available, investigators can be on solid scientific ground when they eliminate the WFI system as a suspect. And there is an economic benefit due to the reduction of labor required to obtain and analyze grab samples, in this case, estimated to be more than one man-month annually.

Particle counters can be placed in key positions of critical systems such as PW and WFI systems to assist in developing maintenance cycles and as "watchdog" instrumentation to monitor the continuing stability of the system. This technology, based on stable, field-proven light-extinction sensors, can be an affordable adjunct to existing monitoring systems by providing a highly sensitive and real-time reaction to perturbations in water systems.

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