Real-Time Response from an Online Microbial Analyzer

To Monitor the Health of the Water System

Good Manufacturing Practice (GMP) guidelines are essential in the pharmaceutical industry to maintain product quality and safety. To help ensure compliance with GMP principles, companies seek new Process Analytical Technology (PAT) instruments to improve safety and quality controls and identify compliance challenges before Out-Of-Specification (OOS) conditions arise. In the specific case of microbial enumeration in compendial water systems, the analytical response time of the traditional plate count method is measured in days. A more rapid response in identifying that compliance is being met is an opportunity to complement plate counts for bioburden monitoring.





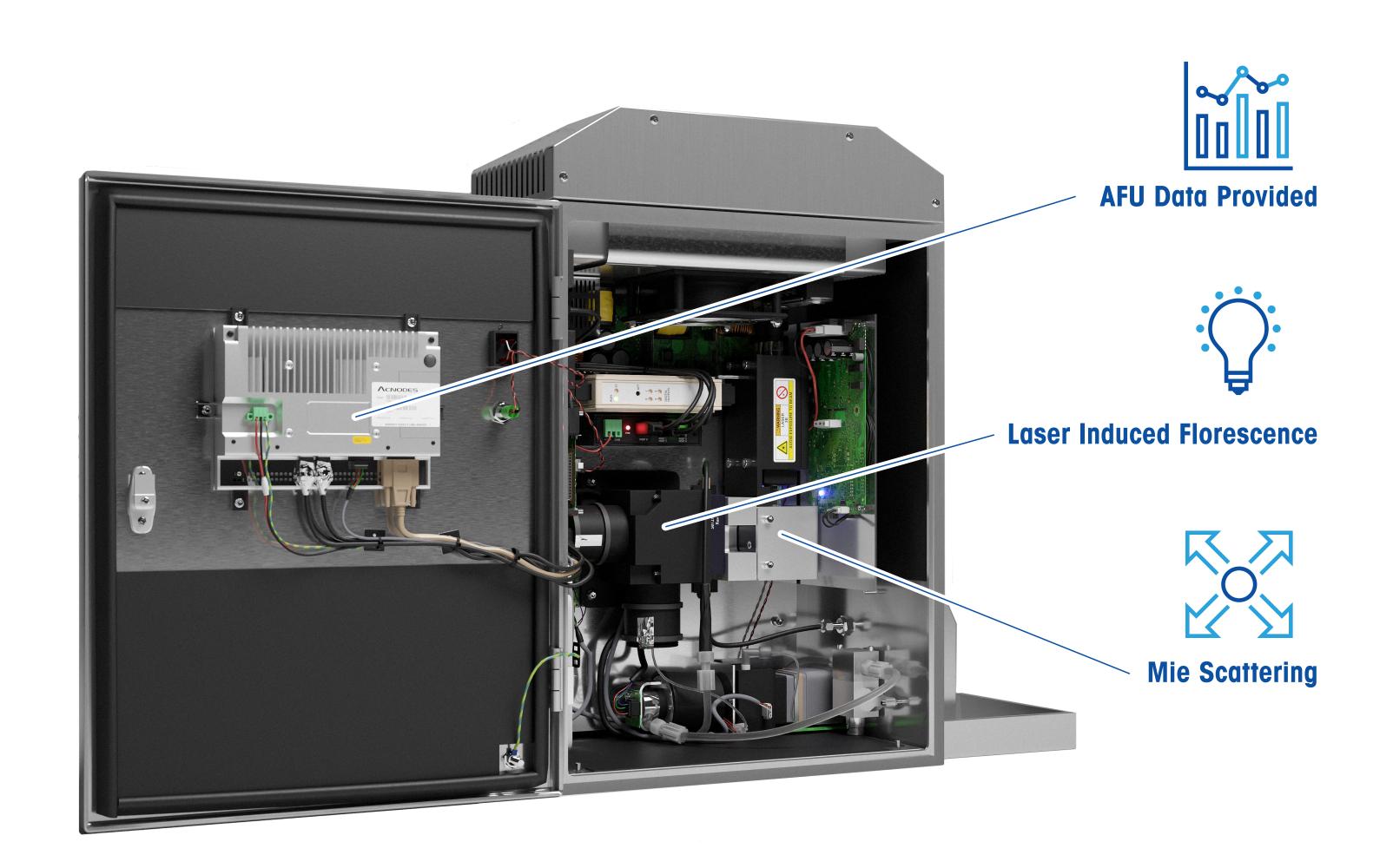


Introduction

The 7000RMSTM on-line microbial analyzer is an analytical tool to support PAT. The analyzer detects and measures bioburden in Purified Water (PW) and Water for Injection (WFI) systems in real time while the waters are being produced. Although regulators still require results from the traditional plate count method to release water for pharmaceutical manufacturing, the 7000RMS can be used as a real-time analytical tool in parallel to plate counts to assist in maintaining and managing water systems effectively.

Encouragement for PAT tool use

The FDA acknowledges real-time tools can generate large volumes of data which is relevant to routine quality assurance and regulatory decisions. Measurements do not need to be absolute values but must detect relative differences.



7000RMS

Conduct a side-by-side analysis to understand the difference between the two bioburden measurements

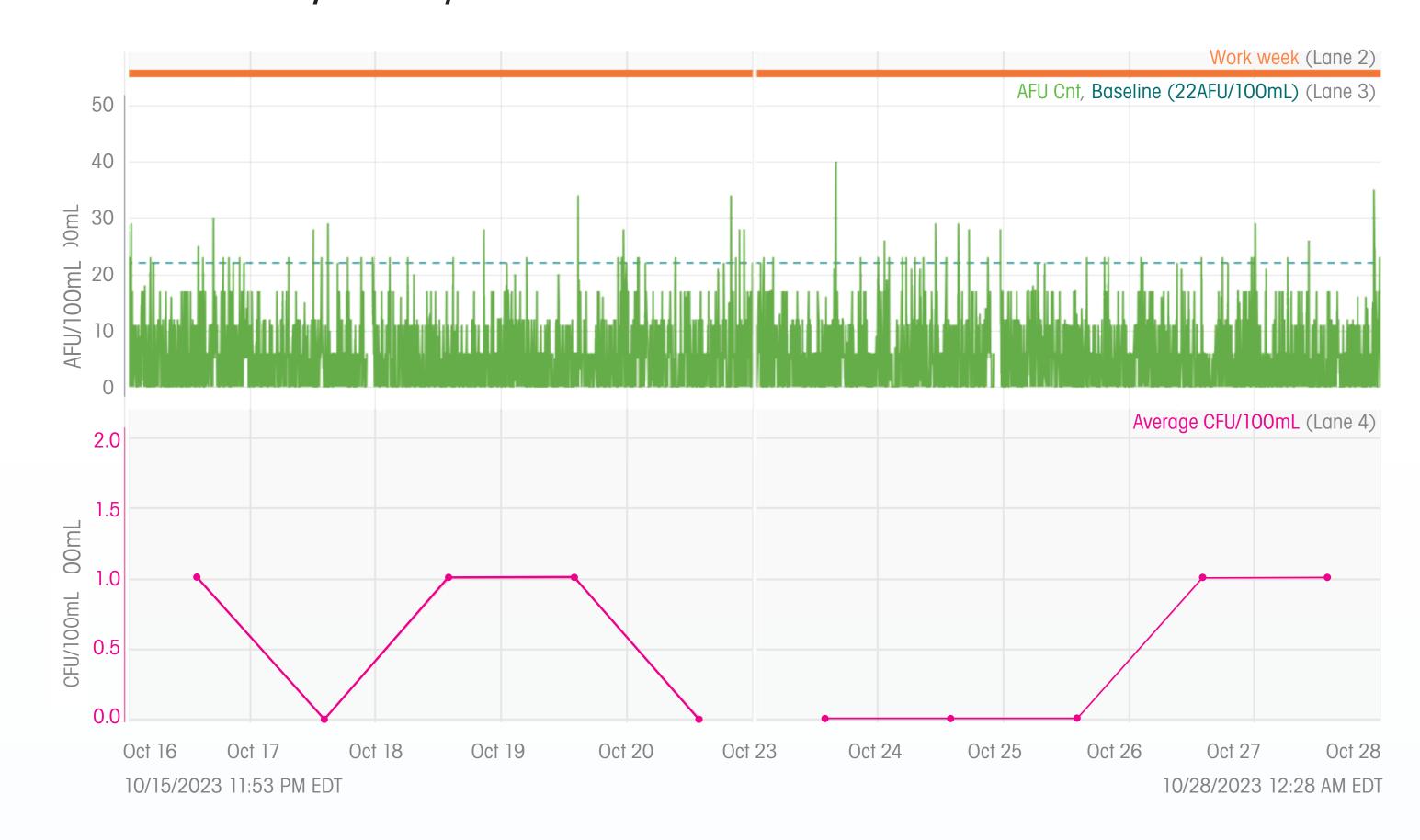


Figure 1: Top: AFU trend with baseline (22 AFU/100mL) and established alert level (172 AFU/100mL), bottom: CFU trend with the site's alert level (12 CFU/100mL)

A side-by-side study illustrates the difference between the AFU and CFU measurements by comparing the trends of the results when the water was measured. Figure 1 shows a consistent and stable AFU trend at the return location of a water system during routine

2. Evaluate the reliability of both measurements in detecting microbial contamination and their effectiveness in identifying potential issues

It is important to note that AFU measurement cannot be correlated to CFU measurement due to the differences in detection technology, fluorescent particles and visual count of colonies, respectively. However, the non-equivalency of AFU and CFU is not a barrier to adopting the 7000RMS. The AFU measurement from the 7000RMS is more reliable due to its constant detection and measure ment. In addition, the 7000RMS detects all organisms (both viable and non-viable) while water flows through the device. This fuller picture of bioburden levels allows users to make better GMP decisions. The CFU results, on the other hand, are related to the water samples co lected at POUs at the time of collection and the capability of microorganisms to form colonies under the defined growth conditions.

While the AFU results are more relevant to the production and processing of water within the water system 24/7, the CFU results are used to measure water quality in terms of the visual count of microorganism colonies under several factors that are unrelated to the water

Once a facility has assessed the AFU and CFU trends during routine operation of their water system, the AFU trend can be used alongside CFU-based limits as the baseline of the water system in process control to detect potential issues more effectively and efficiently. Since the AFU measurements are reported in real time, a facility can rely on the 7000RMS's data to detect an out-oftrend event and advise the QC microbiology department rective actions need to be taken. Using Figure 1 as an samples and not of the entire water system. example, albeit that the CFU data is below the alert level,

172 AFU/100mL and 12 CFU/100mL. some companies would still want to understand where the contamination came from. In such a case, facilities

engineers and QC microbiologists can decide whether

to investigate the CFU results if the AFU trend shows a

stable baseline during operation.

operation. In contrast, the plate count's CFU trend often

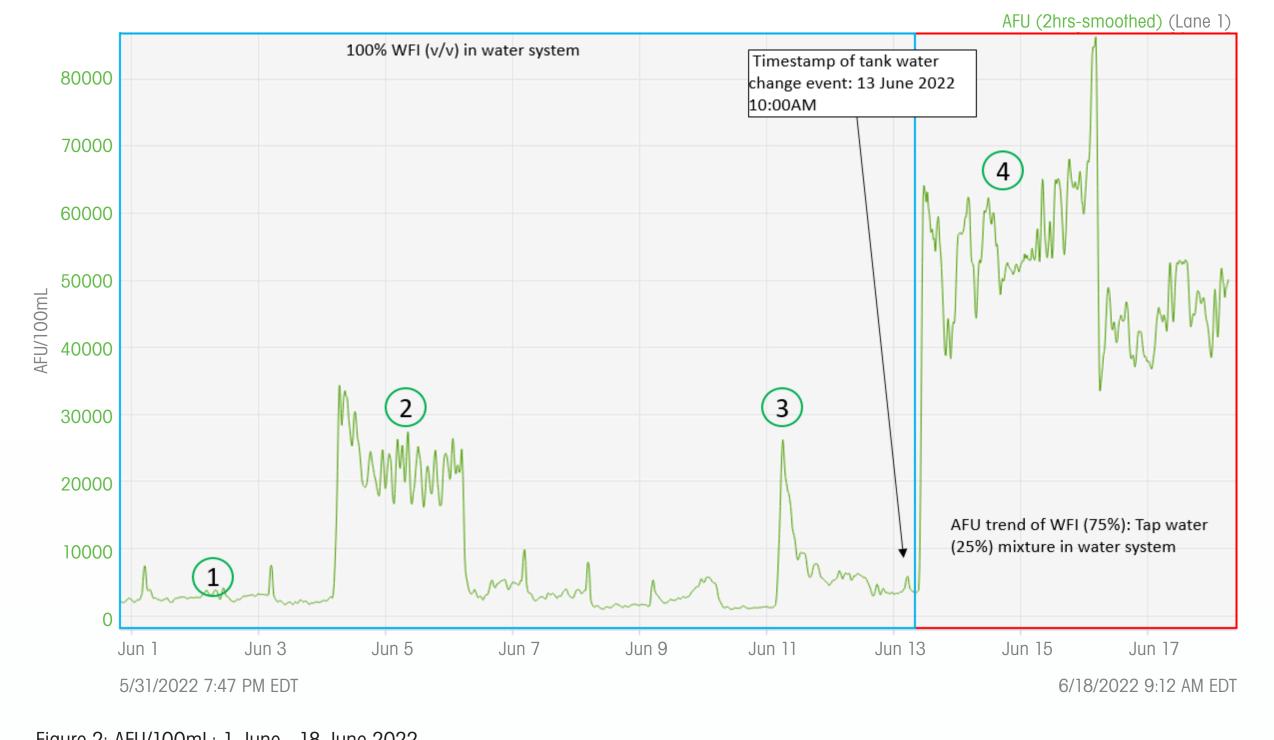
shows a zero measurement. Both measurements indi-

cate water quality below the corresponding alert limits of

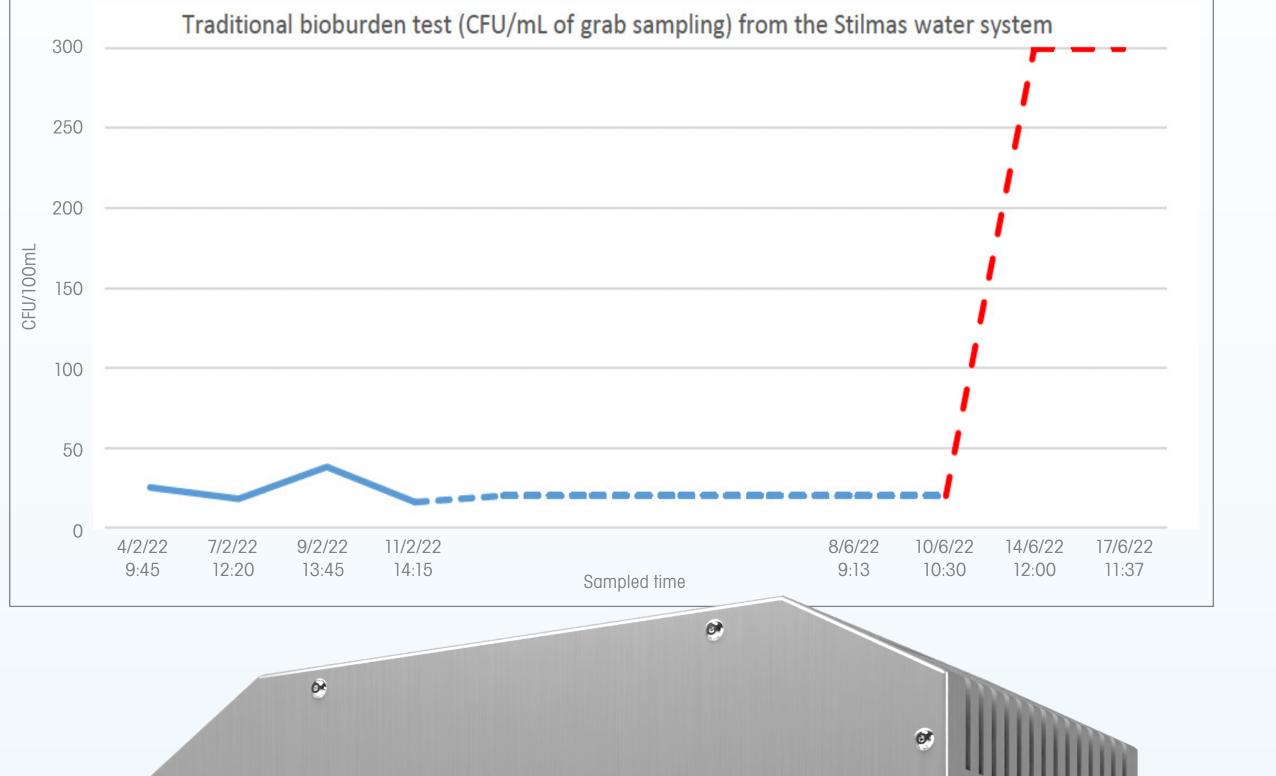
3. Analyze the cost effectiveness of both measurements and their impact on process improvement and product quality

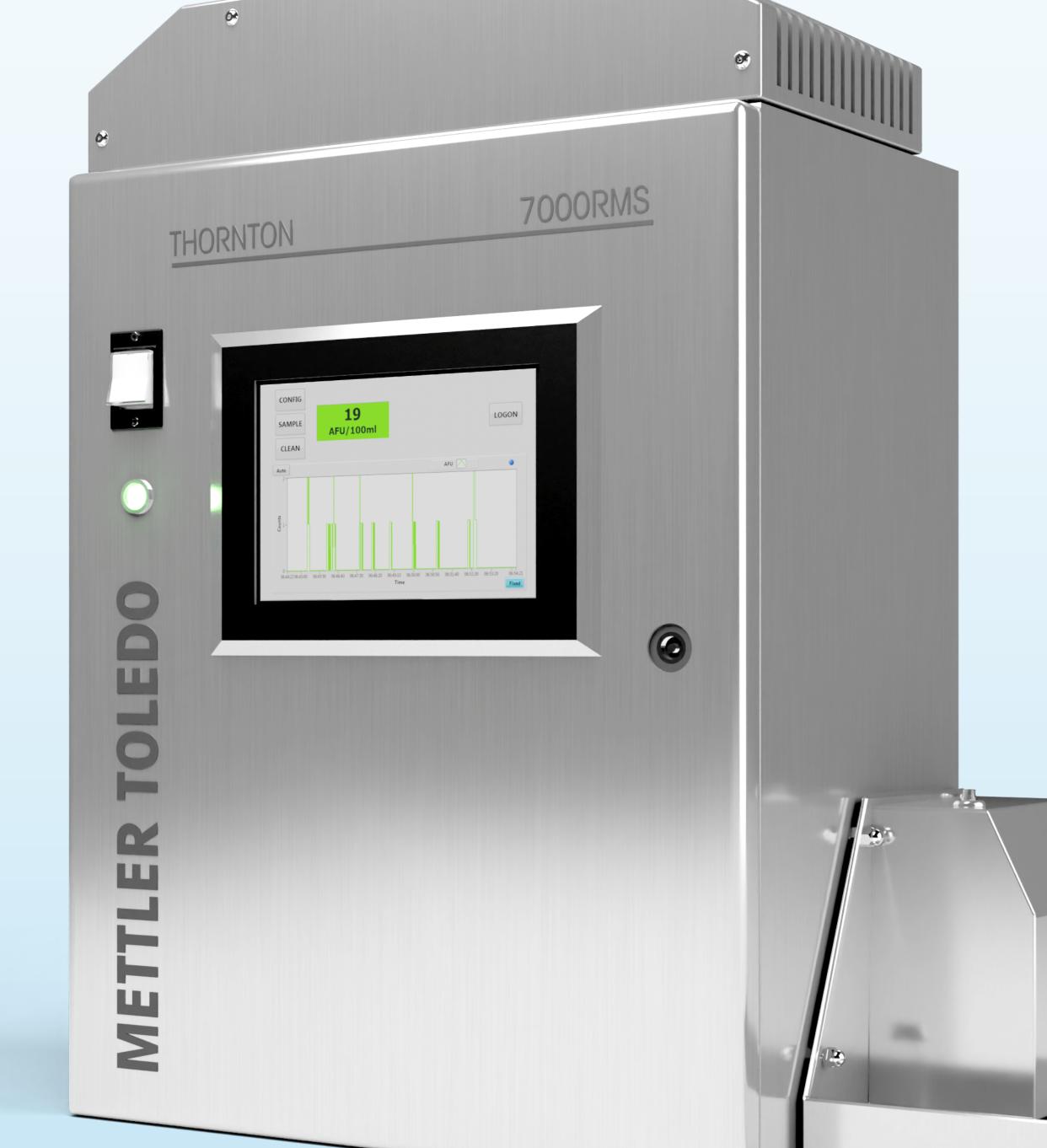
The 7000RMS measures at-line on the water system while pharma water is produced, used, recycled, and filled. The AFU measurements reflect all operations of the water system, including sanitization, maintenance, and water usage. However, the CFU measurements relate to water quality only in terms of bioburden growth in the samples. Although the two measurements can be assessed holistically to understand the risk of bioburden while water is being produced and used, the AFU measurements are more cost effective in providing data for water system management.

Due to the real-time response by the 7000RMS, AFU measurements can be used to assess the risk of bioburden throughout the entire water system operation, including process changes that may affect the bioburden level in the water. The AFU measurements can provide qualitative and quantitative data related to sanitization, filling of water tanks, pressure changes during distribution, and more. Water system engineers therefore gain previously unavailable visibility into the water system and can make data-driven decisions based on system operation activities without waiting for CFU results. It is worth mentioning again that water samples collected for CFU plate counting after maintenance and engineerto perform a CFU analysis of the water and decide if cor- ing changes can only show the bioburden level of the



Microbial content removed from heat sanitization: 12,500 AFU/100ml 4. Average AFU due to the microbial excursion: 51,222 AFU/100mL





- REAL-TIME PROCESS CONTROL
- 2 IMPROVED PROCESS EFFICIENCY
- 3 RISK REDUCTION BENEFITS
- 4 DATA ANALYSIS
- 5 PROCESS SIGNATURE

AFU for process control in support of CFU

Significant differences in AFU vs CFU measuring rates and detection capabilities. AFU measurements provide continuous profile of bioburden while CFU measurements provide a snapshot of the water system. CFU result is still not comparable to AFU due to the low measurement frequecy.

To understand AFUs as a process measurement signal for bioburden monitoring in GMP environments (USP <1223>), facilities must compare the 7000RMS's AFU with traditional CFU measurements for overall control.

Conclusion

Using the 7000RMS microbial contamination analyzer as a PAT tool can fill the gap in the need for continuous measurement of bioburden levels in pharmaceutical waters. The AFU data from the 7000RMS is more relevant to a water system's process understanding and process control than CFU data. When used in parallel with the plate count method, the 7000RMS analyzer allows users to make informed decisions regarding the operations of a water system. The process-related AFU measurements provide confidence in decision making regarding water quality, while waiting for plate count method results.

Continuous AFU measurements give users high visibility into a water system, which serves as an investigative tool when plate count methods produce elevated CFUs. Therefore, the 7000RMS can significantly improve decision making in GMP environments, enhance product quality, reduce costs, and help companies make data-driven decisions to meet regulatory requirements. By evaluating the use of PAT tools and traditional off-line measurements side by side, pharma manufacturing facilities achieve a holistic process control and improvement.

Author: Arundhati Samanta

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