Instantaneous Microbial Detection: 21st Century Process Control Tool for Pharmaceutical Water Systems

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Modern technologies that enhance process knowledge and process control have been developed for use in pharmaceutical manufacturing. The adoption of such technologies has been encouraged in guidance such as FDA's 2004 Guidance for Industry on Process Analytical Technology (PAT), and the adoption of Quality by Design (QbD) principles. Rapid Microbiological Methods (RMMs) are a subset of such technologies permitting the rapid detection of microorganisms, in contrast to traditional culture-based methods in use in the pharmaceutical industry for the past century. One class of RMM instrumentation utilizes intrinsic, laser induced fluorescence (LIF) to detect the presence of microorganisms in air or water. It provides results in real-time, enables continuous monitoring, and doesn't require stains or reagents for detection. As applied to pharmaceutical water quality, this method of instantaneous microbial detection offers enhanced process control across a number of applications through its real-time and continuous bioburden monitoring capabilities.

Laser Induced Fluorescence

With LIF, a light source such as a laser is used to excite fluorescence in a material. Fluorescence is the luminescence that occurs with the absorption of light at one wavelength followed by the emission of light at a longer wavelength. Light absorption by a material is dependent upon the composition of the material and the excitation wavelength utilized. A laser of appropriate wavelength and intensity can induce fluorescence emission in microorganisms because of internal chemical components, or fluorophores, like tryptophan, nicotinamide adenine dinucleotides (NADH), and flavins that are capable of light absorption. Non-biologic materials such as plastics, rubbers and paper can also fluoresce at a range of excitation wavelengths. Therefore, an excitation wavelength is chosen that excludes as many non-biologic materials as possible while inducing sufficient fluorescence intensity in the target materials or fluorophores.

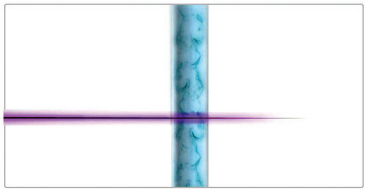
LIF-Based Instantaneous Microbial Detection

LIF-based RMMs are capable of the instantaneous detection of microbes without the need for consumables or the limitations plaguing traditional growth-based methodologies such as improper media selection and poor incubation conditions. LIF-based systems rely on light emission instead of microbial growth for detection. The chosen excitation wavelength is based on the excitation spectra of target microbial fluorophores. In this application, 405 nm is optimum.

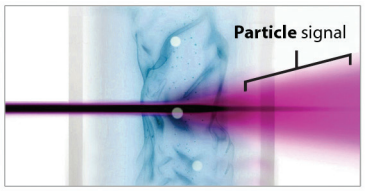
A commercially available example of a LIF-based RMM system for ultrapure water (UPW) and water for injection (WFI) is BioVigilant's IMD-W™ system. In this system, 405nm laser light intersects the flow of water sampled by the system, as shown in Figure 1. If the water contains particles, each particle will scatter the laser light as it passes through this laser interrogation zone. The scattered light is detected by the system's particle detector and provides information on the particle's size. If the particle is biologic, it will also have a fluorescence signal due to the laser-induced intrinsic fluorescence emitted by the particle. Detection and correlation of the particle scatter and two fluorescence signals, combined with advanced algorithm assessment, provides real-time information on particle presence and biologic status.

Process Control Monitoring Benefits

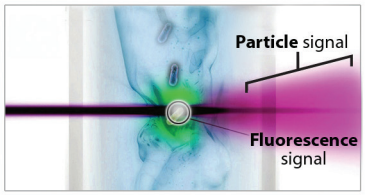
LIF-based RMMs for pharmaceutical waters deliver significant benefit as process control monitors. As described in FDA's 2004 guidance, the goal of PAT is to "enhance understanding and control the manufacturing process." The IMD-W system enhances this understanding by providing inert and biologic particle data in real-time, on a per-second and per-volume basis. This permits



Laser intersecting water flow



Inert particle being detected
No fluorescence = **Inert** particle



Biologic particle being detected

Figure 1. IMD-W scientific principle.

continuous water bioburden and particulate monitoring with a granularity and sensitivity not possible with the intermittent and imperfect sampling of traditional culture-based methods. The IMD-W method of detection described earlier is often more sensitive than traditional growth-based methods and, as a result, higher counts may be observed. This increased sensitivity, coupled with a continuous flow of data creates a robust data set not limited by the zeros and intermittence of data typical of the traditional method. This significant baseline data set and continuous data enables focused process analysis and trending for better confidence and control in the manufacturing process.

IMD-W Installation on Facility Water Loop

The IMD-W system supports a number of Critical Control Point (CCP) monitoring applications within a pharmaceutical water processing system. This includes water quality monitoring for clean-in-place (CIP) applications, pretreatment and reverse osmosis (RO) effectiveness, storage tank water monitoring, and point-of-use sampling. A common IMD-W application is system installation on a UPW line's loop return. Although recirculation is often utilized to reduce the potential for biofilm formation in storage tanks, changes in the microbial quality of the water or integrity of redundant filters and gaskets upstream may occur. In this location, the IMD-W system provides continuous particle and biologic count data that can provide information on microbial levels and the overall health of the process.

Figure 2 shows an example of how the IMD-W system can be utilized as a trend and process control monitoring tool. In this plot, daily biologic count averages per 100mL, taken from three months of IMD-W data on a line loop return, is shown with the one-month average and one and two standard deviation levels. Beginning on July 5, the IMD-W daily average biologic counts per 100mL starts to trend upward. Although daily average values do not surpass two standard deviations, there is indication of change. The IMD-W data can be assessed at higher granularity, with future data monitored closely to ensure process control on an hourly or daily basis, and the overall process assessed in real-time to determine a root cause.

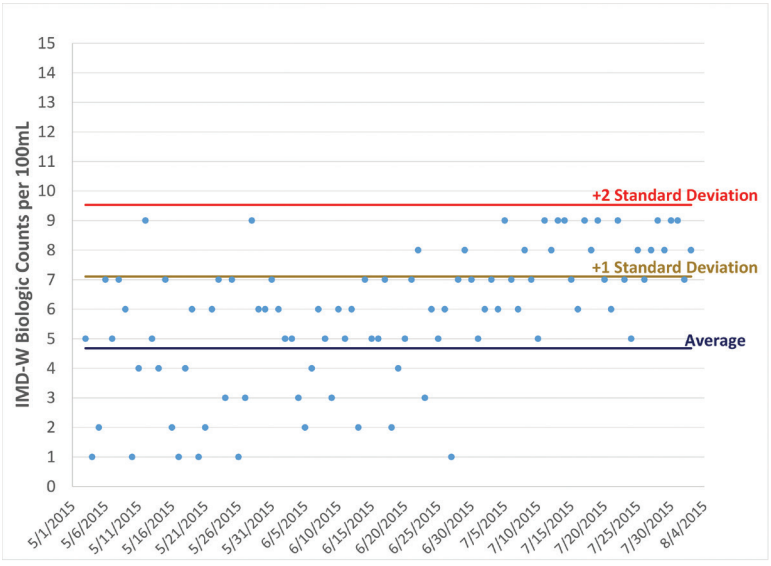


Figure 2. IMD-W daily average biologic counts.

Conclusion

LIF-based RMMs such as BioVigilant's IMD-W system outfit pharmaceutical engineers and microbiologists with a means to measure and monitor bioburden in real time and continuously and, as a result, elevate the state of process control in place to assure the overall health of pharmaceutical water systems.

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