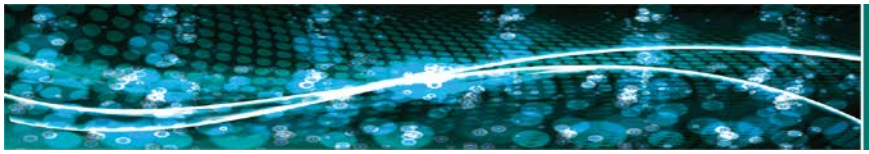

Applications Concept:

Reducing Manufacturing Risk during Cleanroom Maintenance and Downtime with Instantaneous Microbial Detection™

Major Benefit:

- Assess Risks during Unique Production Situations
- Can Accelerate Return to Production by Three to Five Days

Introduction

Cleanroom product manufacturing is common across multiple industries including pharmaceutical, biotech, ophthalmological, and food and beverage manufacturing. The procedures, acceptable practices, and quality metrics during periods of production are often clearly delineated within industry standards documents or internal SOPs. Environmental Monitoring (EM) is typically a key element of production, as manufacturing in controlled environments would be unnecessary were it not important to the final product quality. Even within the best manufacturing environment, however, there are periods of downtime. The causes may be planned, such as shutdown during holiday or scheduled maintenance, or unplanned, such as from equipment malfunction or product quality issues.

Regardless of the cause, manufacturing downtime is a shift from nominal cleanroom state and processes. Particularly given the unique activities which may occur during downtime, including equipment maintenance, investigations, or construction, risks not typically expected within the cleanroom environment and standard procedures can exist. While a thorough cleaning and disinfection is performed prior to returning a room to its production state, there is a need to maintain environmental quality within controllable levels.

Unfortunately, traditional environmental monitoring techniques (e.g. growth-based air samplers) are often too burdensome, retrospective, or expensive to be effective in mitigating these atypical risks during short periods of planned or unplanned downtime. In particular, the time required to detect microbial colonies (three to seven days or more) can delay manufacturing start-up. As a result, these techniques and results are only used typically as a required stage-gate to proceeding with manufacture.

Cutting-edge techniques such as Instantaneous Microbial Detection, however, offer the opportunity to bridge these traditional limitations and provide a practical solution to assess and proactively manage risks to the manufacturing environment during downtime.

IMD-A Systems: Ideal Monitoring Tools

Azbil BioVigilant's IMD-A systems instantaneously detect and report the presence of airborne microbes and inert particles, continuously and in real-time, using an optically-based system that requires no culturing, staining or reagents. Both the IMD-A 300 (sample flow of 1.15 lpm) and IMD-A 350 (sample flow of 28.3 lpm) instruments are 21 CFR Part 11 compliant and validated to USP<1223> and EP 5.1.6 guidance.[A]

IMD-A system features include[B]:

- Instantaneous detection of microbes and inert particles
- Simultaneous detection of particle number, size and biologic status
- Reporting of real-time results with the PharmaMaster® software interface
- Video camera and synchronized data playback functionality
- Marker function enabling activity tracking and display in data files and reports

IMD-A systems display results in real-time using the IMD-A PharmaMaster software (Figure 1). The display options include a graph that plots counts for biologics, particles ≥ 0.5 µm, and particles ≥ 5 µm every second while the air is sampled, as well as updating total and average counts for each particle type so changes in contamination levels are easily noted. In addition, each IMD-A system is supplied with a small video camera that can be used to record and display activity in the room during sampling. The software features a playback function that allows a review of videos for completed samples as they were collected, replayed in synchrony with the recorded data.

[A] Azbil BioVigilant, USP<1223> and EP 5.1.6 Validation Testing of IMD-A 300/350 Systems, LI-007.
[B] Azbil BioVigilant, Product Specifications: IMD-A Series, LI-005.

BioVigilant® Instantaneous Microbial Detection

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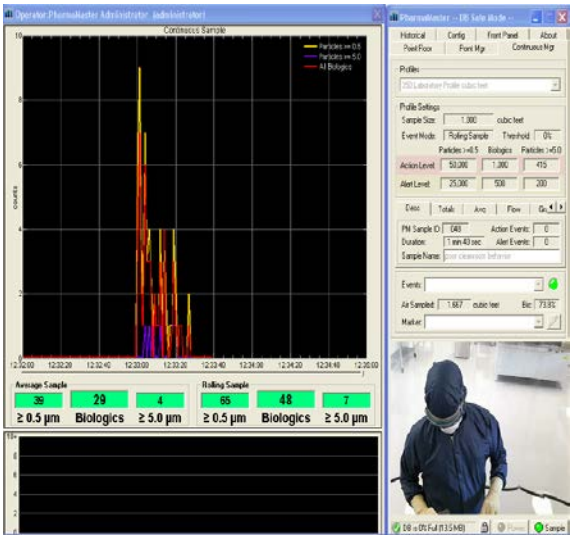

Figure 1: IMD-A System's PharmaMaster software interface provides immediate feedback.

Atypical risks to the manufacturing environment during downtime call for unconventional methods to mitigate them. With IMD-A technology, quality and manufacturing personnel have the unique ability to get immediate feedback about the state of the manufacturing environment and the potential risks present. For a specific location such as a critical zone in a cleanroom, the continuous and real-time information provided by the IMD-A 300 about the airborne bioburden can empower informed decision-making. In many cases, the IMD-A 350 system is especially suitable because the higher flow rate enables monitoring of a larger cleanroom footprint and quicker detection of a change in cleanroom control.

Example: Equipment Maintenance and Calibration

Nearly all manufacturing equipment and instrumentation will require adjustment, maintenance, or calibration. Often, it is either impossible or impractical to move the equipment/instrumentation for these activities, and the work must be done in place. Not only do these activities represent a change from the nominal cleanroom procedure, but the mere presence of the technician to perform them is likely atypical.

For example, performing operations such as modifying line speed or adjusting fill volumes requires a fine adjustment of controls, which necessitates personnel activity in close proximity to the manufacturing line. Using an IMD-A system near the operations provides assurance that activities near the filling line do not impact the overall quality of the environment while critical adjustments are made.

For periodic activities, while the equipment may have received periodic CIP/SIP treatment since the last maintenance cycle,

…What happens when the covers are removed and components are adjusted or replaced?

…Are abnormally large numbers of particles, including microbes, being released from the inside of the equipment?

Placing the IMD-A system on a cart with the rest of the technician's tools provides immediate feedback and a level of assurance that the necessary maintenance activities aren't creating unnecessary risk to the environment. If contamination is released, the IMD-A system can monitor remediation and indicate the effectiveness of cleanup without the three to seven (or more) day delay required for standard plate-based air samplers.

Example: Facility Construction

It is quite common for manufacturing facilities to receive periodic upgrades or expansion. While these activities are certainly planned and their impact to production minimized, it is usually preferable to try and execute them in a way that allows some level of manufacturing in parallel.

Once again, there may be myriad risks inherent in these activities despite careful logistical planning and execution. Facility engineers do their best to segregate building systems (e.g. HVAC) of areas under construction from those which remain in operation, but complete segregation may not be possible. Furthermore, construction activities typically require personnel from outside the company to be present for extended periods in and around the manufacturing environment.

…Do these personnel strictly adhere to the procedures for cleanroom gowning and conduct?

…Is the mere presence of increased personnel for construction adding risk that wasn't assessed during a facility's validation?

Placing an IMD-A system in a hallway or in a cleanroom transition zone can provide continuous information about whether these expansion and improvement activities are expanding the risk to the process. Furthermore, the synchronized video camera feedback within PharmaMaster interface can help pinpoint the root cause for increased particles and bioburden if they are detected.

Example: Resuming Production after Shutdown

Manufacturing facilities may cease production for both planned and unplanned reasons, perhaps most commonly because of company holiday. Certain building and control systems may be reduced or turned off during this period to save money, or atypical activities may occur during cessation such as from quality investigations. Regardless, returning to production after these periods often requires certain cleaning and environmental verification steps. Quick and efficient verification will be necessarily delayed, and incur additional cost, if the cleaning and disinfection are not successfully verified on the first attempt.

Using an IMD-A system in parallel with traditional EM techniques to confirm efficacy of the cleaning and disinfecting process will generate environmental results instantaneously. This IMD-A data can provide confidence in the environment's suitability while the traditional EM results are confirmed, enabling three to seven additional days of manufacturing ability than what was previously possible.

Conclusions

Within many controlled manufacturing environments, it is natural for regulations and SOPs to focus on environmental monitoring and risk assessment during the expected "typical" manufacturing state. However, there are multiple situations when atypical activities or environmental states may generate unique and unforeseen risks. While traditional EM techniques are used in certain cases to confirm the transition back to an acceptable and typical state, it is often done with a penalty of delay. In other cases, these risks may remain unknown until effects upon quality are caught later in the process with a greatly increased penalty. Rapid technologies such as the IMD-A offer the distinctive ability to rapidly assess both expected and unexpected risks in the manufacturing environment, maximizing your operation's production, quality, and bottom line.

Support

Please contact Azbil BioVigilant's Applications team or your sales executive for additional assistance.

We can assist with:

- On-site and remote support by our Field Applications Scientist team
- Complete evaluation protocols and data analysis tools
- Custom protocol development including a sample training protocol

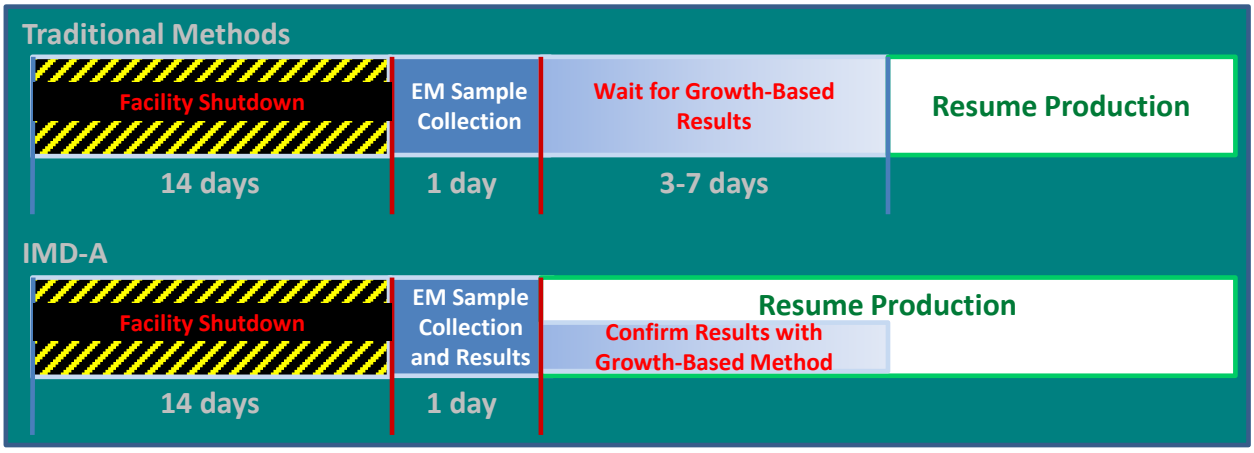

Figure 2: Accelerating return to production: A potential savings of 3-7 days when applying IMD-A to the process.

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