Applications Concept:

Speeding Investigations Using Instantaneous Microbial Detection™

Major Benefit:

- Enables expedient investigation and remediation of out-of-specification events
- Accelerates return of production facilities to operational levels

Introduction

Many pharmaceutical, biotechnology, ophthalmology and food and beverage companies manufacture and package their products in cleanrooms or other highly controlled environments using operating procedures designed to minimize or preclude microbial contamination of products. If an out-of-specification event occurs, then finding the root cause, taking remediation steps, and getting the manufacturing line back to full operational level becomes critically important.

Traditionally, the investigative tools and processes available to companies are retrospective, time-consuming, and may provide only circumstantial evidence supporting one or more root causes of microbial contamination. Growth-based methods using agar plates require three to seven days or more to incubate before meaningful results are obtained. This can cause a multi-day delay in every step of the process requiring microbial detection, including:

- Initial detection of microbial contamination
- Investigating root cause/probable cause
- Implementing remediation and corrective environmental control activities
- Verifying effectiveness of corrective and preventative actions

Combined, weeks of valuable manufacturing time may be lost waiting for results. This can lead to a significant financial impact for the company.

IMD-A® systems are aptly suited to facilitate expedient investigation and remediation when out-of-specification events occur. With the ability to detect inert and biologic aerosol particles simultaneously and in real-time, the IMD-A system is an ideal assessment tool for facilitating investigations. When investigation activities are complete, results may be included with a user's quality documentation, as the IMD-A system meets all pharmacopoeial guidelines for equivalence to existing methods, and the software assures data traceability through 21 CFR Part 11 compliance.

IMD-A Technology and Features

Azbil BioVigilant's (ABV) Instantaneous Microbial Detection™ systems 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. The IMD-A system can detect bacteria, yeast, mold, vegetative cells and spores without the need to culture the microorganisms on media, thereby increasing the accuracy and speed of the results obtained. Both the IMD-A 300 (low flow) and IMD-A 350 (high flow) instruments are 21 CFR Part 11 compliant and validated to USP<1223> and EP 5.1.6[A]. The IMD-A 350 system is particularly suited for investigations because the higher sample flow rate of 28.3 LPM[B] enables sampling larger volumes of air during time-sensitive investigations.

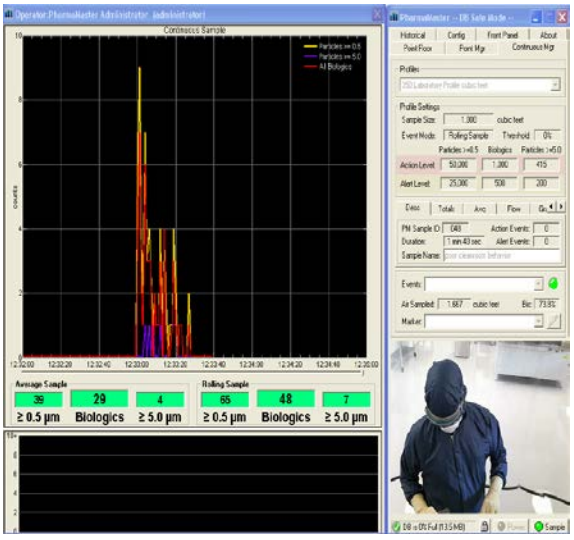

Figure 1: IMD-A System's PharmaMaster software interface displays real-time results.

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

[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.

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 area during sampling, a feature of particular value during investigation. Playback of data with the synchronized video function allows one to see what interventions, anomalies, or continuing events are occurring that contribute to contamination. This gives the ability to assess the risk to the product, isolate the root cause, and provide confidence in taking remedial action. The reporting function of the PharmaMaster software also allows you to define and automatically track 'events' as they occur during data collection. These features enable quick and deterministic correlation of data and video during use of the software playback function.

IMD-A system features for investigations include:

- Instantaneous detection of microbes and inert particles
- Real-time reporting of particle number, size, and biologic status within the PharmaMaster software interface
- Synchronous video/data collection and playback
- Automated 'Event' and manual 'Marker' software functions enable activity annotation, tracking, and display in data files and reports

Example: The IMD-A System as a Tool in the Investigation Process

The IMD-A system is a proven tool for facilitating quick and efficient investigations, capable of providing time-saving and actionable data when used during steps of an investigational process requiring microbial detection and quantification. These benefits can significantly reduce downtime and financial impact when contamination occurs.

Initial Detection of Microbial Contamination—The most efficient investigation is the one which never occurs. The IMD-A system provides the unique ability to detect contamination events as they happen within the manufacturing environment, immediately alerting operators of unacceptable conditions and risk to the product, as opposed to days or weeks later. The IMD-A system's ability to run continuously with pre-programmable measurement profiles (including alert and action levels) empowers proactive monitoring to limit the impact of contamination and the extent of any ensuing investigation. Corrective action can be taken immediately, saving time, materials, and expense. For example, a microbial excursion within an aseptic filling area can have devastating consequences, especially if it is only detected downstream during a quality check (e.g. Sterility Test). If detected immediately with the IMD-A system, the data and correlated video can show the extent and exact timing of contamination. If the event is temporally short (e.g. caused by a manual intervention within a filling line), corrective action may be as concise as segregating and discarding only product exposed during the excursion. While continuous monitoring of controlled manufacturing environments with the IMD-A system is not the focus of this application note, the value of immediate detection and proactive control to prevent investigations should not be diminished.

Investigating root cause/probable cause—When out-of-specification environmental conditions are retroactively detected (e.g. exceeding an Alert or Action level for environmental monitoring), a formal investigation is likely to ensue. Often this investigation is triggered by a single data point (e.g. one CFU on an agar plate), collected during a short sample time during an eight-hour shift, leaving few clues for the investigational team. Performing a thorough and definitive investigation to ensure quality product is often constrained by the pressures for a quick resolution. In these critical situations, the IMD-A instrument is an invaluable tool that can be used like an aerosol "sniffer" in the compromised environment and surrounding areas. Unlike particle counters, the IMD-A system is able to accurately differentiate between inert particles and biologics in real-time, and quantify the counts of each.

If the extent of the contamination is great or there are multiple potential sources, one of the first steps may be to perform some type of room mapping and risk analysis within the affected room or area. The data can be useful to help isolate potential root causes and to determine whether investigation outside the immediately affected area is warranted. In this setting, the IMD-A system can be set up (e.g. on a rolling cart) and programmed to take multiple, discrete samples at different locations.

In Figure 2 (next page), the data shows the most likely routes of contamination ingress and the associated root cause. For example, elevated counts near a doorway or similar threshold can indicate that pressure differentials between areas are improperly balanced, potentially allowing air from a 'dirtier' adjacent room to flow into the affected environment. In addition to the discrete samples collected for spatially 'mapping' an environment, the IMD-A system also can be used to more precisely scan potential sources. A length of inlet tubing attached to the IMD-A system allows an operator to scan walls, doorframes, filters, workstations, instrument panels, drains, and equipment for sources of unusually high counts or unexpected 'spikes' in biologic or inert particles. For example, unexpected or hidden sources such as compromised HEPA filters or mold growing within the walls can be quickly pinpointed.

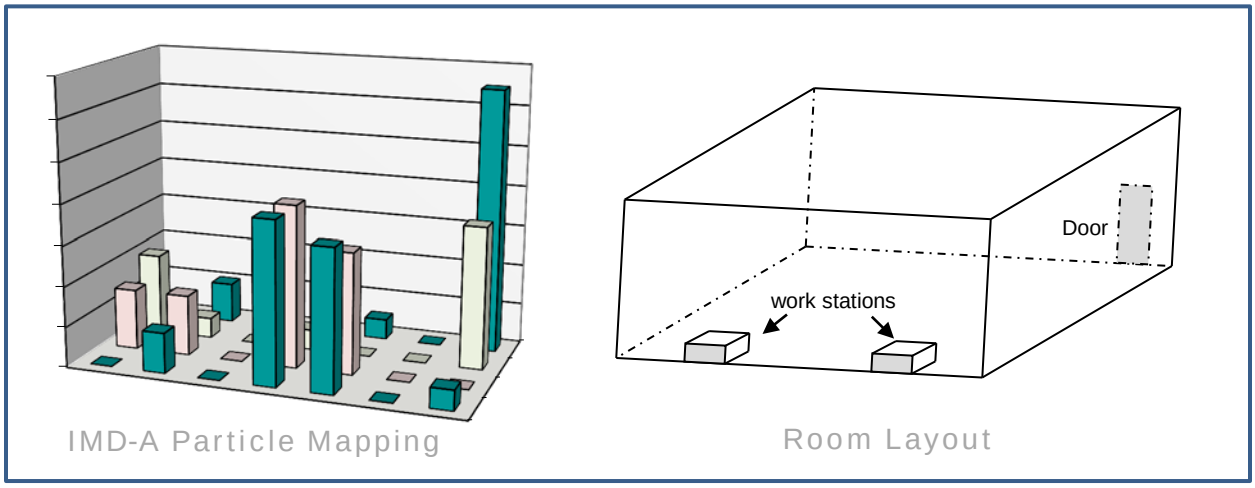

Figure 2. IMD-A data characterization of room.

If contamination is suspected from a transient source such as people or processes, the IMD-A system is equally adept at excluding potential sources and highlighting those more probable. Collecting longer, continuous samples with the IMD-A system, particularly when coupled with the synchronized video capture, can be extremely effective. Furthermore, the ability of the IMD-A system to automatically tag the collected data with predefined out-of-specification 'events' makes analysis of long samples, even including overnight and over-the-weekend samples, quick and efficient. This synthesis of data, video, and automatic characterization of out-of-specification conditions makes correlation between certain time periods or events and changes in environmental control straightforward and definitive. For example, overnight samples can illuminate whether adherence to standard procedures is within compliance during third shift operations and which may contribute to increased microbial levels and risk. Perhaps night or weekend activities such as cleaning are actually causing periods of increased microbial counts which do not subside by the time manufacturing resumes in the morning. In some manufacturing facilities, construction activities may pose an unexpected risk that is hard to quantify during an investigation using traditional approaches. In this instance, the IMD-A system can be used within an aseptic manufacturing area to determine whether construction personnel performing activities outside the suite are creating an increase in bioburden or are compromising the environmental control strategies[C]. Once particular time periods or specific activities are correlated with increased counts, follow up spot samples with the IMD-A system can be taken to isolate the root cause. For example, increased microbial counts during routine cleaning may lead investigators to find that contaminated shoe covers from poor gowning technique are to blame. Or, this may quickly be ruled out as a potential root cause, leading investigators to pinpoint that a contaminated mop is the source of intermittent microbial excursions. Regardless, investigators can converge upon a root cause or probable cause with the IMD-A system in a fraction of the time traditionally necessary.

Implementing remediation and corrective environmental control activities— Once an investigation has been initiated, manufacturing cannot typically resume until the microbial source has been eliminated and/or the bioburden levels have returned to within specifications. If a definitive source has been identified, the IMD-A tool can be applied to immediately determine whether remedial actions are having the intended effect. For example, removal of mold from within a cleanroom wall or rebalancing of pressure differentials/air exchanges between controlled areas will yield IMD-A results in agreement. In cases where a microbial excursion is expansive or the definitive cause cannot be isolated, the IMD-A system can be used as a cost- and time-effective method to survey surrounding areas for spillover contamination or risk assessment. The facility's standard procedures may still require traditional growth-based samples be used as evidence in verifying remediation. These results will require a minimum additional three to five days, traditionally adding to the impact of the investigation. However, immediate confirmation of effective remediation with the system can provide the confidence necessary to

[C] Azbil BioVigilant, Reducing Manufacturing Risk during Cleanroom Maintenance and Downtime with Instantaneous Microbial Detection, LI-015.

resume manufacturing operation while the growth-based results are generated.

Verifying effectiveness of corrective and preventative actions —In an ideal situation, one of the benefits of a fruitful investigation is the clarity to implement preventative actions. A lack of clarity, such as no definitive root cause, can make preventative actions overly broad at best, misguided or even wasteful at worst. For example, a preventative action may be to increase the air exchange rate within a particular environment. While this may appear to produce the intended result of lower bioburden, this imprecise remedy also comes with increased energy cost. A more definitive root cause investigation may have indicated that simply improving gowning technique or operator cleanroom behavior could reduce the creation of bioburden in the first place. In a case such as this, the IMD-A system could be used to verify the appropriateness of preventative actions. For example, while the traditional EM sample ports may collect samples at the height of critical processes, the IMD-A system could be used to collect samples from the floor height both before and after the increased air exchange rate. Similar concentrations of detections on the IMD-A system may lead investigators to conclude that while increased exchange rates reduce the rate of microbial detection at product height, the preventative action is actually doing little to reduce the existence of bioburden and thus, risk within the environment. The IMD-A system can help produce knowledge and situational awareness that fosters informed decision making as opposed to guess-and-check decision-making.

Conclusions

The process of an investigation following product contamination or out-of-specification EM samples can be complex and burdensome. While traditional growth-based tools play an important part during stages of this process, their limitations in speed and sensitivity hinder a team's ability to quickly remedy the situation, or better yet, prevent a costly investigation in the first place. When time and product quality are of utmost concern, the IMD-A system can be an invaluable tool to speed the investigation with data-driven knowledge and produce clear and actionable results. The flexibility of the IMD-A system platforms for sample collection combined with the data-rich stream of count results and video allow the IMD-A system to play a key role in the investigation process, from prevention to preventative action.

Support

The ABV Applications Team offers a full range of support services and documentation for various IMD-A applications. For investigations requiring immediate attention, ABV is pleased to offer Emergency Investigation Services. The service includes an IMD-A system, on-site Field Applications Scientist, and final analysis/report—more details can be found in ABV's Real-Time Investigation Services flyer[D]. Please contact Azbil BioVigilant's Applications team or your sales executive to learn more.

[D] Azbil Biovigilant, Real-Time Investigation Services Using Instantaneous Microbial Detection, LI-014.

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