QbD, PAT, and the Future of Microbiology

Environmental monitoring with RMM

By **Michael J. Miller, Ph.D.**
Microbiology Consultants, LLC

For many years, our industry has successfully provided pharmaceuticals and biopharmaceuticals to the public using batch processing with laboratory testing conducted on collected samples to ensure product quality. However, our current practices are not sustainable, and we must better understand our processes and the impact our processes have on our products and patients, reduce variability, waste and wasteful activities, and increase our manufacturing capacity and capabilities. Therefore, significant opportunities currently exist for improving the efficiency of manufacturing and quality assurance through the application of modern process analytical tools.

Quality by Design (QbD) encompasses a systematic approach to developing pharmaceutical dosage forms and their associated manufacturing processes to ensure a predefined expectation of product quality. Furthermore, QbD emphasizes product and process understanding and process control, sound science, quality risk management, and a continuous improvement model. Because one of the basic fundamentals of the GMPs is that quality should be built-in or should be by design, release testing should seldom result in an out of specification result. Additionally, if we properly design and validate our processes and include analytical testing points throughout manufacturing, *release testing can be reduced or eliminated*. This is the basis for Process Analytical Technology (PAT).

PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring predefined product quality at the end of the manufacturing process. It should also be noted that the term "analytical" is viewed broadly to include chemical, physical, mathematical, risk analysis, and *microbiological*.

Therefore, from a microbiological control perspective, our industry can benefit from utilizing QbD and PAT principles to:

- design robust processes that prevent contamination,
- ensure that a state of microbial control is maintained,
- develop more effective strategies to correct a contamination problem,
- continually improve our processes and products, and
- assess the potential impact of failing results on the patient.

This is where rapid microbiological methods, or RMMs, come into play. RMMs are novel technologies that provide microbial detection, quantification and identification results much faster than conventional or pharmacopoeial methods. They offer

Michael J. Miller, Ph.D. is president, Microbiology Consultants, LLC and owner of Rapidmicromethods.com. For more than 22 years, Dr. Miller has held numerous R&D, manufacturing, quality, consulting and business development leadership roles at Johnson & Johnson, Lilly, Bausch & Lomb, and Pharmaceutical Systems, Inc. He can be reached at mjm@microbiologyconsultants.com.

increased accuracy, reproducibility and sensitivity, and for some rapid method technologies, results in real time. Additionally, a number of systems are now fully automated, miniaturized and provide high-throughput processing. For the first time, we have an opportunity to move microbiology testing out of the laboratory and onto the production floor, with the goal of demonstrating and understanding how well we are in control while actively manufacturing product. Simply put, the future of microbiology testing will include realtime in-process bioburden analyses, sterility verification at the point of filling, and real-time environmental monitoring. From a product quality standpoint, this represents a model of continuous improvement and *realtime quality assurance and quality control*, which is at the heart of FDA's *cGMPs for the 21st Century: A Risk-Based Approach, and ICH Q8 and Q9*.

One RMM that is currently available already meets the goals I have outlined above, and provides a real-time and continuous assessment of our manufacturing environments while production is occurring. The core scientific principle behind the technology is optical spectroscopy, and because there is no need to wait for microbial growth in order to detect the presence of airborne microorganisms, the results are obtained almost instantaneously. BioVigilant Systems, Inc., developed the technology, and the instrument is called the IMD-A. This novel method represents the next generation in environmental monitoring and is directly aligned with the goals of a PAT-based microbiological control strategy. But is there really a need to move from conventional environmental monitoring to a real-time capability such as the IMD-A? This author believes so, and there are compelling reasons for moving in this direction.

The Issues with Conventional Environmental Monitoring

Available viable air sampling systems are currently limited in their ability to deliver on the expectations of a robust environmental monitoring program. For example, sampling technologies for the continuous and real time assessment of nonviable particles are utilized today; however, the pharmaceutical industry continues to rely on single-point, growth-based methodologies for the detection and quantification of microorganisms in volumetric air samples. One of the most commonly used sampling methods employs the process of particle impaction: airborne microorganisms are forcibly deposited onto an agar surface where (under the right growth conditions) they replicate, and develop into colony-forming units (CFUs), which are subsequently enumerated. For many years this practice has provided the industry with an understanding about

the state of microbiological control in critical manufacturing environments.

There are, however, significant limitations to this growth-based methodology, including a significant time delay between the point when the air sample is initially acquired to the point when CFUs are visually detected and enumerated on an agar plate (e.g., 3–5 days). In some cases, confluent growth may hamper efforts to accurately report the true number of CFUs that were in the original air sample, and some laboratories are discovering that airborne microbes—when stressed due to nutrient deprivation, or damaged following exposure to sub-lethal concentrations of chemical or physical antimicrobial agents, such as preservatives, disinfectants, heat or decontaminating gases—may not replicate and form CFUs when cultured on artificial media.

One explanation for this observed lack of growth might be attributed to the collected organisms being in a viable but non-culturable (VBNC) state, in which the artificial medium and/or incubation conditions are not optimal for the resuscitation and subsequent proliferation of the captured microbes. Additionally, currently available bioaerosol samplers are limited by their design with respect to their collection methods and subsequent recovery of microorganisms. For example, the aerodynamics of many air samplers limits the efficiency and consistency of capturing microorganisms on an agar plate.. High airflow rates, shearing forces and/or desiccation may damage microorganisms, resulting in reduced or no microbial growth. For these reasons, the modern microbiological laboratory should look towards developing innovative approaches to the detection and quantification of CFUs or microorganisms in environmental monitoring samples. This is where the IMD-A comes into play.

The Next Generation of Active Air Monitoring

The BioVigilant IMD-A is an optical spectroscopic technology that simultaneously detects, sizes, and enumerates both viable (biologic) and nonviable (inert) particles in real time. The system relies on Mie-scattering, whereby airborne particles intersect a 405-nm laser beam and scatter light which is concentrated in a forward direction and proportional to the particle size. Airborne particles that enter the instrument are quantified and sized within a 0.5 to ≥15 µm range. At the same time, the 405-nm laser causes particles of biological origin, such as vegetative bacteria, yeast, and bacterial and fungal spores to autofluoresce, due to the presence of specific cellular markers (i.e., NADH, riboflavin, and dipicolinic acid). The resulting fluorescent signals are registered as biologic particles. The data is acquired almost instantaneously and the system is capable of analyzing a single volumetric air sample, such as 1 cubic meter,, or operating in a continuous monitoring mode. The latter is especially useful in understanding the environmental state of control over the entire course of a manufacturing campaign.

To illustrate how the system can be used to support a true, PAT in-process monitoring program, we assessed the ability of the IMD-A to simultaneously and continuously detect viable and nonviable particles in a variety of static and dynamic manufacturing isolator operating conditions, including the transfer of sterile components from an autoclave and depyrogenation oven into a filling isolator, during an aseptic liquid filling campaign, and during filling interventions that may be encountered during routine manufacturing and/or during process simulations (media fills). Additionally, the IMD-A was used to monitor an isolator environment in the location of a simulated mouse hole (i.e., where filled product would leave the isolator enclosure) and when a breach in isolator glove integrity was artificially created. In all cases, this rapid method successfully demonstrated that the isolator operations were virtually free of contaminating microorganisms, unless there was a significant breach in the enclosure integrity, at which point viable microbes were detected in real-time. A more comprehensive review of these studies may be found in our previous publications (see References).

In a time when the pharma industry continues to rely on single-point measurements and century-old methods for the detection of microorganisms, the introduction of a real-time microbiology solution for environmental monitoring is long overdue. Today, there are significant limitations for the use of conventional microbiological methods for environmental monitoring in an isolator, including the fertility of media, the effect of exposure of agar plates to the decontamination process, and accidental contamination of plates due to handling. Additionally, environmental monitoring methods do not always recover microorganisms present in the sampled area, and low-level contamination can be particularly difficult to detect. For these and many other reasons, the industry should look toward the introduction of a more sensitive, real-time, and continuous environmental monitoring technology with the ability to track and trend an increased incidence of microbial contamination over a period of time.

The implementation of the next generation of rapid microbiological methods represents significant progress toward the acceptance of microbiological PAT solutions for the industry, and is directly aligned with the expectations for pharmaceutical manufacturing, quality, and operational excellence in the 21st Century. The BioVigilant IMD-A is one example of a PAT tool that will help us achieve these goals. I predict that within the next five years, the availability of additional real-time, in-process RMMs will provide the scientific and regulatory framework for completely eliminating the need for finished product release testing, and embrace microbiological parametric release for all dosage forms, even aseptically-filled product. These are truly exciting times for pharmaceutical microbiologists! ■

References

Portions of this article were adapted from two of the author's previous publications on this subject:

1 2009. Miller, M.J.; Lindsay, H.; Valverde-Ventura, R.; O'Connor, M.J. Evaluation of the BioVigilant IMD-A, a novel optical spectroscopy technology for the continuous and real-time environmental monitoring of viable and nonviable particles. Part I: Review of the technology and comparative studies with conventional methods. PDA Journal of Pharmaceutical Science and Technology 63(3): 244-257.

2 2009. Miller, M.J.; Walsh, M.R.; Shrake, J.L.; Dukes, R.E.; Hill, D.B. Evaluation of the BioVigilant IMD-A, a novel optical spectroscopy technology for the continuous and real-time environmental monitoring of viable and nonviable particles. Part II: Case studies in environmental monitoring during aseptic filling, intervention assessments and glove integrity testing in manufacturing isolators. PDA Journal of Pharmaceutical Science and Technology 63(3): 258-282.