WHITE PAPER
Environmental Monitoring

Pharmaceutical MANUFACTURING

The State of Pharmaceutical Environmental Monitoring:

Avoiding the Dire Risks of a Poorly Executed Program

What is Environmental Monitoring?

Environmental Monitoring (EM) is a strategic, scheduled sampling that is predefined with respect to its frequency and scope. More sampling is required, meaning the frequency and number of samples taken is higher during manufacturing processes; whereas routine sampling will occur regardless of the manufacturing schedule.

Samples are typically taken at predefined locations within the manufacturing suites including walls, floors, equipment and utilities, air, as well as the people that work within the manufacturing suite. Regardless, the most important part of any successful environmental monitoring program is that it is standard operating procedure (SOP) driven. The SOP should dictate sample frequency, locations and overall procedure. Sampling locations often indicate what type of sample needs to be taken.

With respect to environmental monitoring, its necessity should be clear to most. If a company is to release its product, the Food and Drug Administration (FDA) requires environmental monitoring samples to be taken, data collected and then analyzed to determine whether or not there is any contamination that could preclude the product from being shipped — or worse, recalling a product that has already been shipped. Even at the highest management levels, environmental monitoring is an important operational priority within any pharmaceutical company. Delayed product release and shipping means millions, or more likely, hundreds of millions of dollars in lost revenues.

Survey Says

To better understand the challenges managers' face every day when it comes to environmental monitoring programs, BIOVIA (previously Accelrys) recently conducted a survey in collaboration with *Pharmaceutical Manufacturing* magazine.

Approximately 100 leading pharmaceutical, biopharmaceutical, contract manufacturers, and generic pharmaceutical manufacturers were identified and invited to participate. Ultimately, 121 quality assurance, quality control (QA/QC) manufacturing, operational, and compliance executives completed the survey.

Environmental monitoring programs generate a lot of samples from a variety of sample types — from swabs, finger dabs, contact in settle plates, and air-sampling apparatus, to the utilities used in the manufacturing process. Although one might contend that an environmental monitoring program is sample-centric, actually the sample is just one part of an environmental monitoring program's sample-type workflow. The sample-type workflow is instrumental in ensuring that samples are taken, received and reconciled, incubated at appropriate temperature — percent, humidity, duration — as well as the reading to determine if the growth is that of a specific Colony Forming Unit (CFU) level where an action or alert is required.

Impact Can Be Dire

The corporate SOP response for an alert or action level will dictate what actions a microbiologist will take. In some cases, secondary testing will occur. Under drastic circumstances, a production line can be shut down and/or product quarantined. A 483 issued in December 2012 highlighted a very important part of the environmental monitoring sample workflow, which is the reconciliation of the samples that are a part of the sampling plan. The FDA's 483 stated approximately 846 environmental monitoring samples were not collected in the class 100 and class 10,000 areas for March 2010 to February 2012 during the manufacturing of sterile products.

In extreme cases, the results of a poorly implemented or executed environmental monitoring program can be dire, and the impact is felt across the entire company. This particular example resulted in the company closing its doors. In large pharmaceutical companies, employees lose jobs, products are recalled, and fines can be levied, which can be in the billions of dollars.

The typical FDA responses to poorly implemented and executed environmental monitoring programs are 483 warning letters. Although FDA inspections are usually focused on the quality control manufacturing labs, environmental monitoring programs are a part of the overall SOP for releasing finished products. The environmental monitoring data needs to be included in the batch record and certificate of analysis, which opens up the environmental monitoring program to scrutiny by FDA auditors.

The FDA data on Figure 1 is interesting given that the greatest challenge for the environmental monitoring program is inventory management. All of the other items are an integral part of an environmental monitoring program, but inventory management typically sits outside of the environmental monitoring program and cannot be overlooked given the large number of consumables used within environmental monitoring.

Figure 1. 2013 FDA Observations Top 5 Related to Environmental Monitoring

Cite ID	Ref No	Frequency	Short Description	Long Description
1361	21 CFR 211.100(a)	106	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.
3603	21 CFR 211.160(b)	99	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.
1215	21 CFR 211.67(b)	77	Written procedures not established/ followed	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.
1451	21 CFR 211.113(b)	76	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed].
1213	21 CFR 211.67(a)	71	Cleaning / Sanitizing / Maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product.

If the tracking of these consumables is all on paper, there can be considerable gaps where needed data might not be available — such as expiration dates for media used to create the agar plates, or the qualification vapor contact in settle plates. This inventory information is all vital data needed to execute a sampling plan accurately and effectively. One surprise is how far down the list central reconciliation is. Why the surprise? At a recent PDA conference on pharmaceutical microbiology, BIOVIA asked booth visitors what their biggest challenge was when it came to their environmental monitoring programs. Everyone queried unequivocally answered "sample reconciliation." Several explained that if the sampling plan called for 25 plates, what was received, more often than not, were 23 or 28 plates. Of course, this causes additional work to find out where the extra plates needed to go or from where missing plates needed to be collected.

Responses to the question "Are Your Currently Using Paper-Based Methods" speaks volumes to the greatest challenges listed on Figure 3, ranked by respondents from most to least. Forty-eight percent of those responding said they used paper for all or part of their environmental monitoring program. As most can understand, paper-based environmental monitoring programs are often wrought with gaps that cause inaccurate environmental monitoring data, which can ultimately lead to the FDA issuing a 483. The use of environmental software combined with an inventory management application to manage consumables (with respect to the environmental monitoring program combined with the lab execution system for the testing and identification of the colony forming units) provides a robust environmental monitoring program mitigating the common issues found in the paper-based environmental monitoring program.

The good news is that for the majority of respondents (76.5 percent), management of actions and alerts are handled by an electronic system, all but eliminating the introduction of human error found in paper-based systems. Therein lies the problem, because the remaining respondents do not use an electronic system to manage actions and alerts. Managing actions and alerts on paper exposes the environmental monitoring program to human error. For example, if one is reading the plates for CFU, and documents the results as 22 CFU for a particular plate sampled from a specific location, there's a good chance that person is not going to know what the action or alert levels are, given the numerous sampling locations within a sampling plan.

Figure2. Are you currently using paper-based methods to fulfill all or part of the needed requirements for your Environmental Monitoring program?

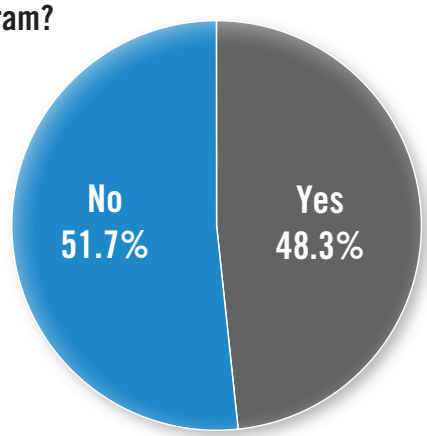


Figure 3. Which Areas of Your Environmental Monitoring Program are Most Challenging

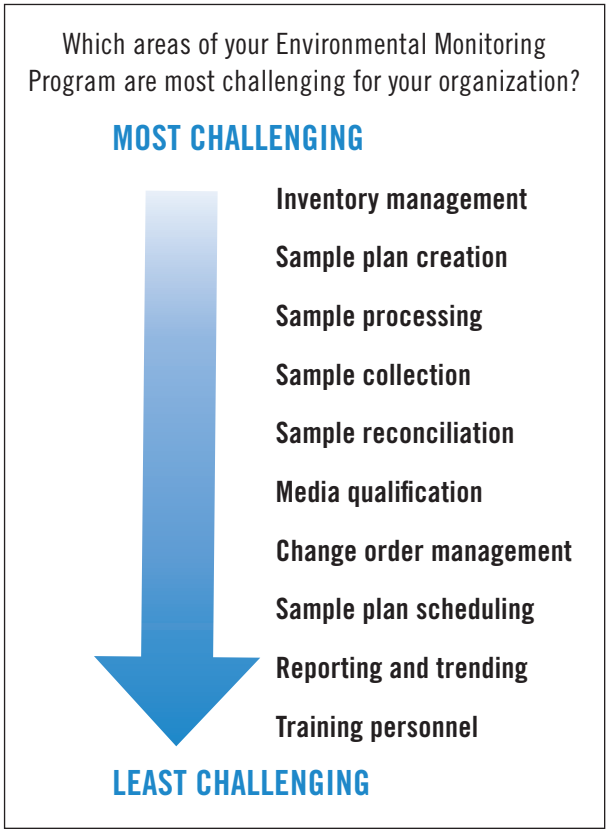
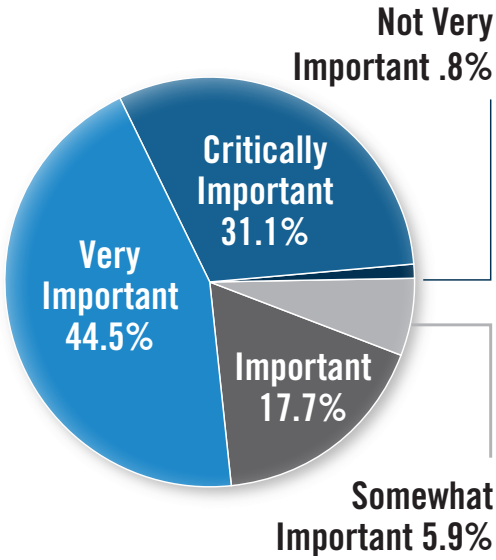
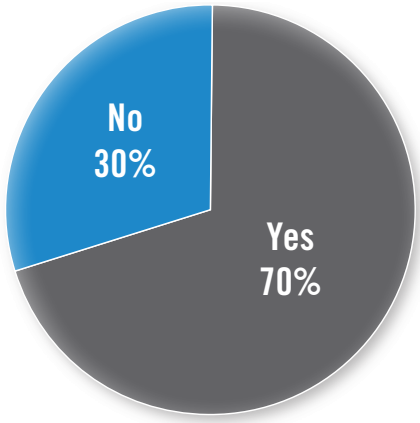


Figure 4. How important is it to your organization to access trending data within your Environmental Monitoring program?



For the majority of respondents, access to trending data ranges from "Important" to "Critically Important" as shown in Figure 4. The reason why trending data is so important is that operational managers can identify a location or locations that could become a problem and implement a mitigation process to reduce the CFU count accordingly. Most electronic environmental monitoring systems provide trending reports as part of the software application.

Figure 5. Is your organization managing Environmental Monitoring equipment calibration via an information technology solution?



Environmental Monitoring Equipment Calibration Monitoring

The Pharmaceutical Manufacturing/BIOVIA study asked, "Is your organization managing environmental monitoring equipment calibration via an information technology solution?" Problematically, some 30 percent responded that they do not use an IT tool to manage environmental monitoring equipment calibration, identifying yet another area for the introduction of human error.

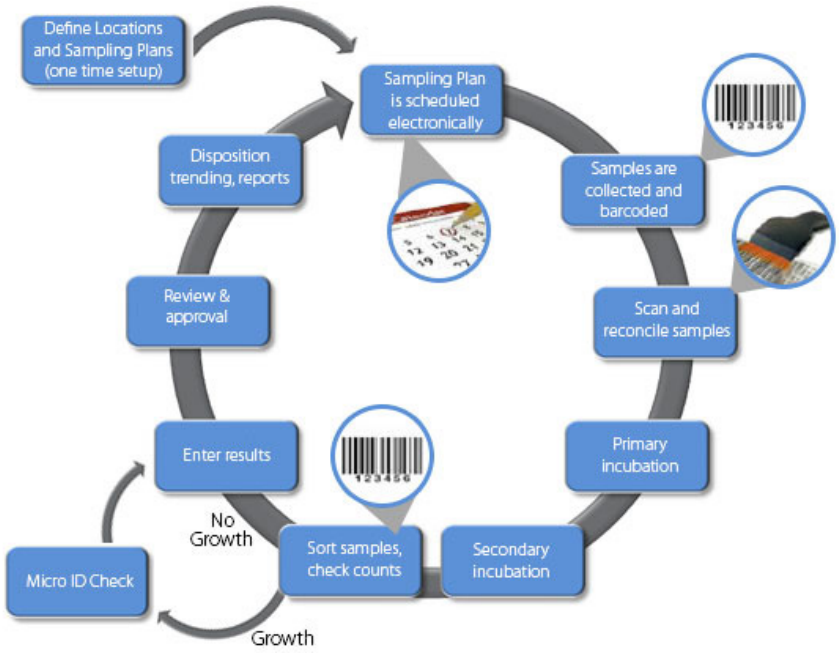
As discussed at length, error-prone paper-based procedures are detrimental to any environmental monitoring program. The use of air samplers, for example, within the manufacturing suite to test the air being discharged into the suite, is an important part of the sampling process and sampling plan. Airborne particulates can introduce contamination into the manufacturing process. As sensitive as this equipment is and needs to be, if the unit is out of calibration the resulting data could appear as acceptable when in fact, it may not be. Obviously, the use of a paper-based equipment calibration log can introduce human error into an environmental monitoring program, and that could be alleviated if a metrology system was employed.

An active notification of an out-of-calibration air sampler is much more effective in mitigating an issue versus one having to find a paper-based logbook for the particular piece of equipment that's intended for use; then looking at the last calibration date; then finally determining that, based on the last calibration, whether or not the unit needs to be calibrated. Such maneuvering will always add a lot of extra work that does not create value to the organization.

Better Living Through Environmental Monitoring IT Technology

The best way to determine if an EM application has the capability to increase productivity, improve data capture, provide necessary reporting tools like trending and, ultimately, reduce the compliant risks inherent in a paper-based environmental monitoring system may be by letting the application speak for itself. Perhaps the best way to accomplish that is to conduct a proof of concept (POC) study, where the application is installed and locations, sample plans and sample types are created per the potential users' SOP and include workflows that allow EM managers to work with the application for a set period of time, gathering metrics and noting procedural efficiencies as compared to the existing paper-based system. That will likely provide the

Figure 6. Routine Environmental Monitoring Workflow



Here is a simplified example workflow using the BIOVIA environmental monitoring application.

best evidence that the application will add value, reduce error and mitigate resource sapping manual procedures. This approach also provides confidence that the EM application meets the needs of users responsible for managing and executing the EM program including the application's ability to adapt precisely to the specified workflow.

The BIOVIA EM application uses barcodes to manage the samples within a sampling plan (which provides the ability to reconcile the samples once collected and brought back to the microbiology lab) to ensure the proper number of samples were collected, and those that were collected are in fact part of the sampling plan being executed. It also serves to rapidly eliminate the use of zero growth plates, putting the focus on those plates displaying growth by issuing an automatic determination if an alert or action level has been reached. Finally, it provides a seamless ability to connect to BIOVIA's lab execution system to identify the growth and then passing the result data back to the application's environmental monitoring application for further disposition and final approval.

The value of using an environmental monitoring application such as BIOVIA's to execute a routine environmental monitoring workflow can be summarized by the following four points:

Improved productivity. Users are not spending time transcribing data to a paper-based system.

Enhanced data capture. As the users execute the environmental monitoring workflow, the application will prompt the user to provide the data required for that step within the workflow.

Ease of reporting. Since all of the data is being aggregated in the EM database, the reporting tool provided can easily create a trending report across sampling locations and for specific time durations.

Reduced overall compliance risk. The elimination of human error and the overall environmental monitoring program will dramatically reduce, if not eliminate, investigations, thus reducing your overall compliance risk.

Anyone responsible for managing EM across a complex operational landscape knows that well understood SOPs, combined with the automated efficiencies delivered by a fit-for-purpose IT-based solution, will mitigate risk and trump a paper-based system every time. Advocating for a better system, realized by implementing advanced methodologies with cost-effective technologies that reduce risk and cost, requires fewer resources and time, and serves to demonstrate unequivocal, proactive compliance should be a welcome proposal in any risk-management discussion.

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This whitepaper, as well as the previously released recorded presentation and industry survey conducted by Pharmaceutical Manufacturing were sponsored by BIOVIA (formerly Accelrys). To learn more about Environmental Monitoring from BIOVIA, see the following links:

- Click here to view the full results of the Pharmaceutical Manufacturing/BIOVIA research survey

http://www.putmanmedia.com/assets/PhM_State_of_Environmental_Monitoring_Survey_Results.pdf

- Click here to view "State of Pharmaceutical Environmental Monitoring: Pathways to Reducing Risk and Improving Product Quality" presentation

http://www.brainshark.com/pharmamanufacturing/vu?pi=zHQz7Dklcz9Qtsz0

- Click here for the BIOVIA Environmental Monitoring Datasheet

http://accelrys.com/products/process-management-and-compliance/accelrys-lims/pdf/accelrys-environmental-monitoring.pdf

- Click here for the BIOVIA Environmental Monitoring Introductory Webinar and Demonstration

http://accelrys.com/events/webinars/pmc/how-accl-em-software-improves-productivity-request.html