WHITEPAPER

SIX ESSENTIAL WORKFLOW STEPS FOR PAPERLESS, AUTOMATED, END-TO-END ENVIRONMENTAL MONITORING

The consequences of microbiological contamination of drug products run the gamut from FDA warning letters through product quarantines and recalls all the way to plant shutdowns. Actions like these can cost drug manufacturers significant time and money, as well as resulting in manufacturing delays, product shortages and negative public opinion. For these reasons, effective and efficient microbiological and environmental monitoring (EM) is a mission-critical priority for pharmaceutical and biotechnology drug manufacturing and packaging operations.

This white paper discusses six critical workflow steps required for EM monitoring under aseptic manufacturing conditions. Of course, best practices for non-sterile products can, and often do, include environmental monitoring for production facilities and process water. This paper also touches on hardware considerations related to mobile EM workflows in the lab.

To begin, we should first address a couple of questions. What are the consequences of not monitoring manufacturing operations to ensure that products meet all necessary safety and efficacy standards? And how do today's industry-wide EM challenges trickle down into specific, day-to-day EM workflow inefficiencies in the microbiology lab, especially when the workflows rely on a dis-harmonized mix of paper-based, manual and semi-automated processes?

AVOIDING THE FDA WARNING LETTER

Recent warning letters from the U.S. Food and Drug Administration highlight the regulatory challenges for organizations that lack EM compliance as follows:

> *"Your firm does not have appropriate laboratory testing to determine if each batch of drug products, purporting to be sterile, conform to such requirements [21 C.F.R. 211.167(a)]."*

> *"Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity [21 C.F.R. 211.160(b)]."*

> *"Your firm does not have written procedures for environmental monitoring during aseptic processing, including sampling frequency, sampling locations, or procedures for alert and action levels."*

In these three cases, the companies have not documented adequate microbiological and environmental monitoring processes to establish compliance with current Good Manufacturing Practices (cGMP), or they could not ensure that written procedures were followed. These are the kinds of immediate problems that drive drug manufacturers to implement a more comprehensive, best-practice EM solution.

Broader industry initiatives also impact the decision to better integrate and automate critical development processes. This is especially true for global organizations that are changing the way they work to achieve operational excellence and improve productivity enterprise-wide. For example, manufacturing organizations are often encumbered by systems that still require manual data input or rely on hybrid automation processes coupled with paper-based systems. With a view to creating more value with fewer resources, the "Lean Transformation" approach is requiring organizations to identify and eliminate non-value-added activities. Driven by today's "lean" requirements to reduce waste and implement right-first-time procedures while still maintaining compliance, many organizations are investigating the use of cutting-edge automation technology to improve business competitiveness. Microbiological environmental monitoring offers numerous opportunities to improve operational excellence in an area critical to business success.

ADDRESSING INDUSTRY-WIDE EM CHALLENGES

A best-practice EM software solution for the 21st century needs to meet compliance requirements in real-world production environments while also addressing the following EM challenges:

- The number of samples requiring management can fall into the millions on a global scale for a single company with site volumes often exceeding 300,000 per year.
- The vast majority of companies utilize well established, paper-based systems but these can be error-prone and resource intensive, further increasing cost structures for operations.
- Many multi-site organizations have disparate, paper-based and semi-automated systems with no global harmonization strategy for the mission-critical cGMP requirement.
- Required flexibility of existing EM systems to deal dynamically with routine/random/on-demand batch scheduling often compromises existing automation software systems.
- Existing IT/IS systems are stretched to customize some level of automation, but fail to achieve fully comprehensive paperless data capture and workflow management.
- Full integration of the microbiological EM system with laboratory execution, inventory management and trending/reporting capabilities is highly desirable, especially when combined with a mobile lab informatics interface.

CONFRONTING EM CHALLENGES IN THE LAB

The industry-wide EM challenges listed above filter into the daily operations of the microbiology lab. Here scientists and technicians often struggle with home-grown, paper-based or semi-automated EM systems that are error-prone, wasteful and resource hungry. For example, operators collect samples in clean areas and record details such as name of operator, location, time, activity and batch number either on the media plates themselves or in paperwork. When the samples go to the lab, these details are transcribed again, either into electronic systems or different paperwork. After the plates are incubated, lab technicians go through them again to route those with colony counts to ID teams for analysis and identification. Each of these stages in the EM process introduces new opportunities for incorrect transcriptions, missing data and other errors that can trigger batch rejections and product delays.

Lab personnel must also contend with an ever increasing number of samples and the need to handle complex monitoring schedules with limited resources. Unfortunately, all too often, current IT systems are over-extended when it comes to customizing automated, paperless, mobile data capture and workflow management for EM. There is little wonder that global organizations with geographically disparate sites using a variety of solutions are keen to explore leaner, more efficient and harmonized end-to-end EM programs.

THE SOLUTION: AUTOMATING END-TO-END WORKFLOWS FOR ALL EM TASKS

A best-practices software solution for 21st century microbiological monitoring should ideally begin with front-end workflow tasks (i.e., sample plan creation/scheduling) and flow through to back-end microbiology lab tasks (i.e., incubation, ID and analytical test-method automation), as well as reporting. These workflow book-end tasks, coupled with easy-to-set-up mobile procedure execution functions (planning/scheduling/assigning/labeling combined with bar coding capabilities) complete the best-practices EM solution for controlled environments. For optimum flexibility and timeliness, the system should also enable non-IT system administrators to create and update required EM procedures.

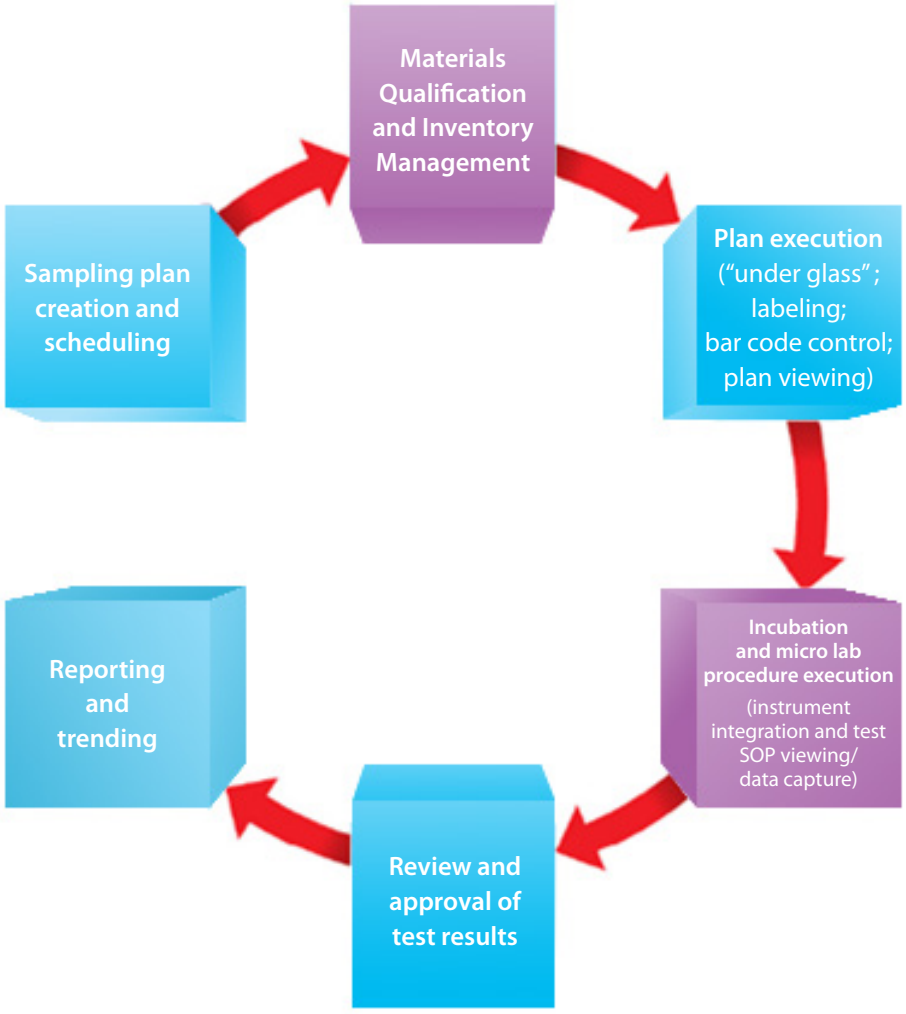

Figure 1: *Comprehensive workflow automation for all EM tasks*

An improved benchmark approach to automated, paperless, end-to-end environmental monitoring and reporting should incorporate and harmonize the following six essential EM activities.

1. Sample Plan Creation and Scheduling

The EM system should enable eligible in-house system administrators to build and edit EM workflows for sample scheduling, collection, incubation/inspection and approval, as well as recording data using drop-down lists to select specific operations (locations, sampling types, frequencies, etc.). The application should display sample plans and collections on a system calendar with color-codes indicating priority and current status of sampling operations. Staff with access privileges should be able to create and revise schedules easily using drag-and-drop functionality. The application should also provide printed bar-code labels containing all metadata needed for each sample type or batch to speed plan execution by operators.

2. Materials qualification and inventory management

The EM process should include the ability to qualify and manage all materials and equipment required for use during monthly, weekly and daily sampling. A built-in inventory management system should provide assurance that all needed media, plates, filters, swabs, instruments, etc. are qualified and ready for use with all qualification data and metadata automatically captured in case they are needed for tracking/tracing or investigational purposes.

3. Compliant Plan Execution

Operators should be able to execute sampling plans "under glass" using an EM-qualified handheld tablet with each step highlighted and required documents linked. All media plates should have unique bar codes; every location within the sterile area should also be bar-coded. With this type of system, after taking the sample, the operator scans both the media plate and the location. The system then links the two bar codes and puts all the information together (e.g., name of operator, location, time, activity, batch number, etc.). The bar code model helps ensure that all samples are evaluated; it also eliminates transcription errors and paperwork and enables real-time electronic tracking/tracing of samples and their disposition (ID testing, results or waste). EM data are captured direct to database through wireless technology, assuring complete, accurate data with a real-time electronic audit trail.

4. Microbiology Lab Procedures with Instrument Integration

All post-sampling lab procedures should also be displayed "under glass," with negative findings scanned for effective data management closure and "hits" flagged for identification or further testing (i.e., second incubation). The system should display specific test methods so analysts can easily perform step-by-step procedures with all data, metadata, instrument reports and parsing captured by the system. Any lab inventory items (e.g. reagents, filters, etc.) should also be tracked and traced in real time. The system should continuously monitor sample status and provide operators/analysts with visual indications of timing limits to ensure compliant analytical results. All instruments and devices used in the process including particle counters, microbial testing systems and automated ID instruments—whether RS-232 or PC-based—should integrate directly into the EM system database for automated and compliant electronic data capture. This data capture/integration should also extend to the qualification procedures and instrument data pertaining to inventory items and supplies consumed by EM processes.

5. Review/Approval of Test Results

The EM procedure execution system should automatically organize result data and metadata in a dashboard view for peer and supervisory review and approval. The system should also link all instrument results to the appropriate lab instrument or room device reports for ease of viewing and approval. Compliance flags should highlight any out-of-specification/out-of-limit (OOS/OOL) or audit trail conditions for immediate action, if necessary. The review dashboard should contain all equipment identification numbers and time/date stamps for each step in the analysis process, all of which can be used for management reporting purposes (e.g., instrument utilization reports, maintenance schedules, etc.).

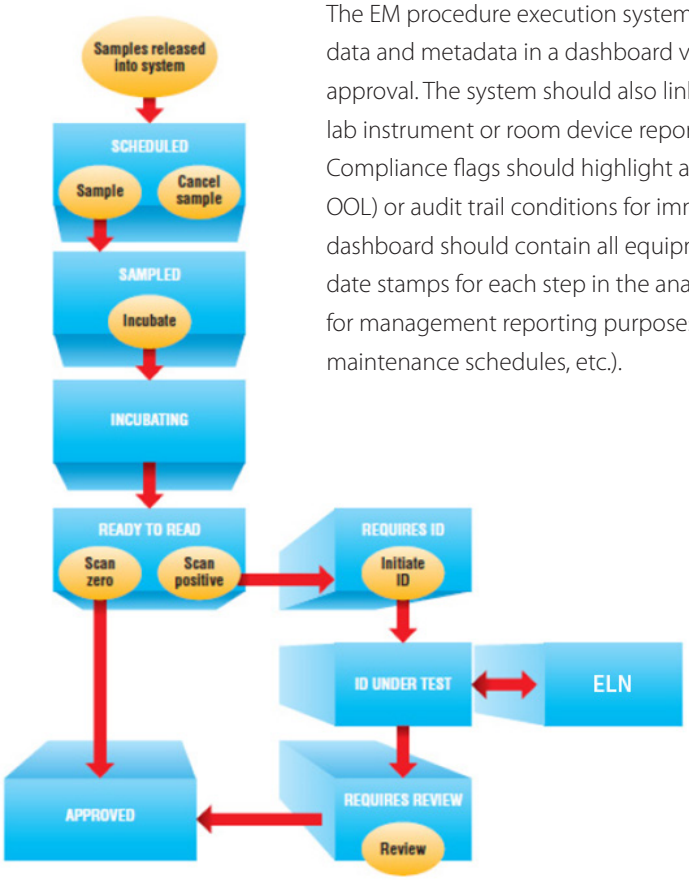

Figure 2: *EM workflow states for contact plates*

6. Reporting and Trending

To ensure compliance with good manufacturing practices, all EM sampling data and metadata should reside in an Oracle database enabling rapid extraction and reporting. Operators should be able to use existing report templates or custom graphical or tabular reports created within the EM application to show ID by location, trending by location, heat maps, excursions by room, positives by operator and other operating factors.

EM HARDWARE CONSIDERATIONS

The mobile nature of the end-to-end EM process, coupled with the need to maintain aseptic conditions and ergonomic efficiency, warrants careful consideration of equipment used in microbiology labs. Today, lightweight mobile PCs with integral bar code scanners that meet EM aseptic requirements include the Panasonic Toughbook H1 (meets IP65 certification design requirements). This unit enables direct-link-to-database through wireless technology.

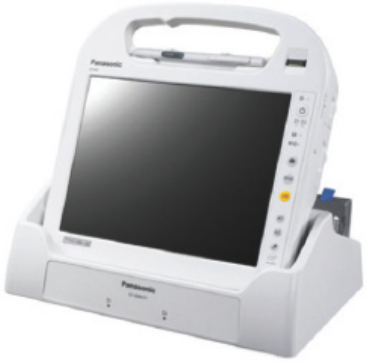

Figure 3: *Mobile IP65-certified tablet with integral bar code scanner for mobile EM workflow execution. Workflows are presented to the operator with compliance checks for media/materials, devices and instruments supporting "right-first-time" execution.*

A device such as that shown in Figure 3 enables the operator to place any plate in the inventory at the proper location and scan both the location and the plate. The software keeps track of all the metadata pertaining to the sample, eliminating the need for cumbersome, error-prone manual record keeping. The operator simply scans and moves on. The system handles all documentation and data transfer. The same bar code system can also track timing and metadata during sample incubation, capturing information such as incubator, timing, shelf location, etc.

BENEFITS OF PAPERLESS, AUTOMATED ENVIRONMENTAL MONITORING

Many pharma/biotech companies have tried to automate the microbiological monitoring of controlled environments using spreadsheets, customized LIMS software and automation software products that perform only parts of the process. Instead of patching together point solutions, the life sciences industry would be better served by a paperless, automated environmental monitoring system that is integrated with other critical ancillary systems providing laboratory execution, inventory management and reporting/trending capabilities. A comprehensive, unified EM system such as this offers organizations the ability to:

- Improve EM efficiency, reduce EM workloads
- Facilitate simpler, more flexible EM scheduling
- Eliminate EM paperwork and manual transcription
- Reduce costly errors and deviations in EM process
- Ensure right-first-time execution
- Introduce real-time data recording, tracking and tracing
- Provide electronic interface with EM methods, devices, instruments and other systems

A paperless, automated, end-to-end EM solution can reduce compliance deviations, shorten cycle times, lower costs and improve business competitiveness. Such a system can accelerate and harmonize all aspects of environmental monitoring from creating sample plans through scheduling, collecting and processing samples to recording, analyzing and reporting results.

Not unexpectedly, a 21st century EM solution offering these capabilities can also significantly reduce the incidence of FDA Warning Letters and required corrective actions that can be so disruptive to a business' operations and its reputation.

To learn more about Accelrys Environmental Monitoring, go to **accelrys.com/em.**