

PAT INITIATIVES FOR QC/QA OPERATIONS:

Enabling Paperless Processes for Manufacturing Batch Records and QC Laboratories

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With the current Food and Drug Administration (FDA) focus on modernizing the regulation of pharmaceutical manufacturing and product quality, companies are being forced to reexamine and adjust their traditional development and commercialization processes. The industry's current Good Manufacturing Practice (cGMP) initiatives along with Six Sigma, Lean Manufacturing, and Process Analytical Technologies (PAT) encourage the adoption of new technological advances to enable high quality and efficient manufacturing. Key adoption goals include assured compliance with current regulations, reduction of overall cycle times for production and release of final product, and improved productivity measures for operational cost reductions.

Late stage pharmaceutical development and manufacturing has not changed its historical paper-based, manual data-capture infrastructure. The principle reason is that highly regulated environments resist change due to validation costs associated with change. Recently, industry and the FDA have become increasingly aligned with respect to utilizing innovative technology to bring manufacturing processes up to 21st century requirements for lean operations and assured product quality and efficacy.

Leading companies are implementing a new approach to "automating compliance" by utilizing modern technologies for building quality into the compliance infrastructure by including: Standard Operating Procedures (SOPs), work instructions, analytical methods, data sheets, batch records, and more. Many of these programs are often called "Right-First-Time" or "Operational Excellence" programs. Their key conclusion is that compliance activities can be automated creating a new, more productive paradigm, reducing compliance risks, and providing higher productivity and improved quality.

Automation enables companies to institutionalize these new initiatives and build cost effective "best-practices" into their operations. Recently published results demonstrate the point.³

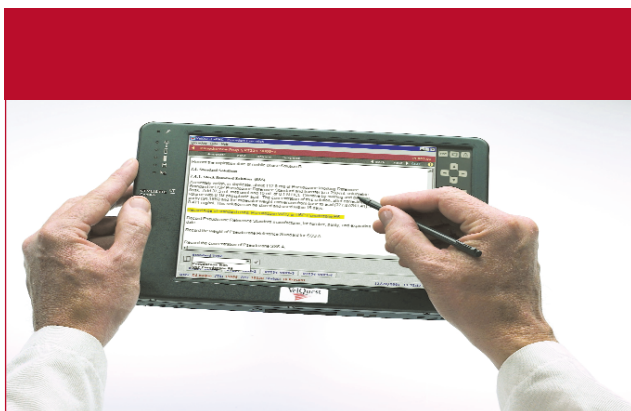


Figure 1: A digital version of a standard operating procedure (or method) is presented to the QC lab analyst or production floor operators with automatic capture of critical method-based data. This process eliminates transcription errors associated with paper-based notebooks.

Significant liberation of resources from leaders in the field demonstrate more than 20% elimination of labor from documenting, reviewing, and approving tests, translating into faster cycle times, more predictable release times, and assured product quality.³ In addition, the workforce enjoys a better work environment and can invest new-found time in higher quality activities or satisfy increasing capacity demands within the bounds of existing operations.

This paper outlines the current situation in manufacturing and quality operations relative to industry compliance initiatives and manufacturing challenges. It profiles an innovative “method-centric” software platform, designed for the analyst or operator, to electronically execute and manage Quality Control (QC) testing protocols and production batch records, yielding significant reductions in overall product release times. This technology platform is in alignment with the principles of PAT (process analytical technologies) for QC and manufacturing processes.

The Paper-Based Process Situation in Pharmaceutical Manufacturing

Today, the U.S. Pharmaceutical Industry spends approximately \$100 billion on manufacturing. By improving manufacturing efficiency by only 5%, the industry could yield over \$5 billion¹ annually. Many pharmaceutical companies have

prioritized initiatives to eliminate the routine, non value-added tasks that often impact overall cycle times and cause system errors. A recent research study confirmed that in most regulated companies, approximately 70% of laboratory-based resources are participating in compliance-related functions.² One such non value-added task is the common practice of using paper within documentation and quality operations. Use of lab notebooks and data binders, and their significant peer review and management review, add complexity, time, and space challenges for the pharma industry. Within the quality operations, initiatives to “go paperless” are expected to create operational benefits yielding millions of dollars in efficiency gains.

An “e-manufacturing” environment enables immediate communication between the many disparate data sources ranging from product and process development, pilot operations, incoming raw materials inspection, in-process monitoring, and final quality control lab results. Interfacing these data sources and higher-order information management technologies, such as Laboratory Information Management Systems (LIMS) and Enterprise Resource Planning systems (ERP) provides a platform for critical-path decision making to radically improve product release cycle times. Going paperless can allow real-time

management of the quality data across the entire enterprise.

Regulations and Cost Controls

The pharmaceutical and biotech industries are challenged to improve product quality, productivity, and compliance, while at the same time, generating an annual double-digit growth for their stakeholders. This is becoming difficult due to the large number of branded products coming off patent over the next three years and questionable new product pipelines. The entire “product lifecycle” (research, development, and manufacturing) must be streamlined and optimized for efficiency. Within this environment, large amounts of data are being generated across the entire enterprise with most of the information documented in paper-based systems (notebooks, forms, logbooks, and binders). Today, many manufacturing and laboratory operations rely on the ubiquitous use of paper-based “systems” that can generate errors and can require constant “checking” and manual peer-review verification procedures. These processes add no value to the operations and contribute to costs.

In the late 1990’s, the Code of Federal Regulations (CFR) 21, Part 11 emerged as a demanding regulation for the pharmaceutical industry. Regulations that affect the overall scope of electronic

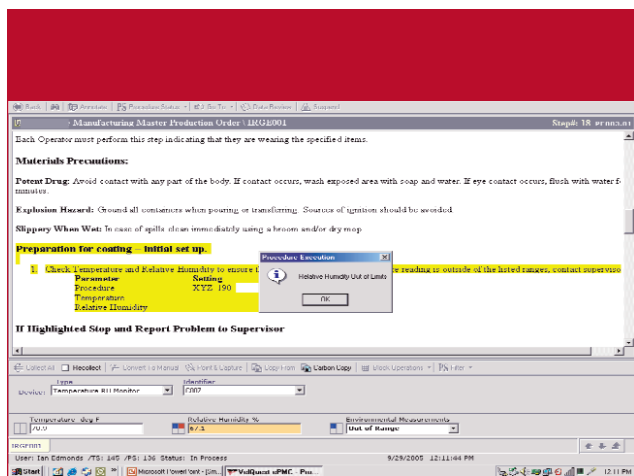


Figure 2: A digital version of an SOP (method or batch record) is presented to the lab analyst or production floor operator with automatic capture of critical method-based data. Any out of norm entry is immediately “flagged” to the operator.

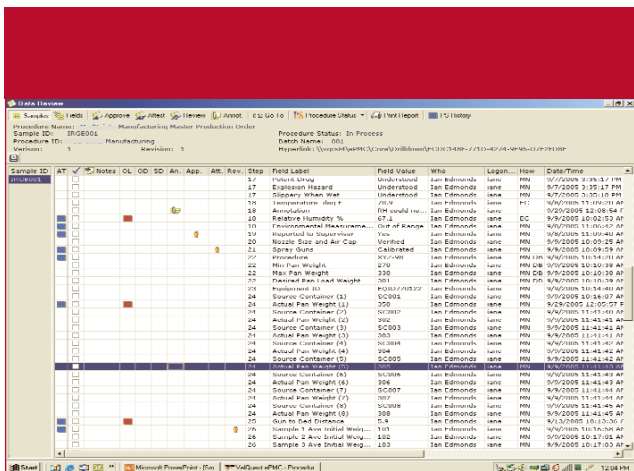


Figure 3: After a batch is completed, all data is presented to reviewers with visual “flags” for all specifications or expected process norms and materials expiration requirements along with instrument calibration dates, audit trails, annotations, e-signatures, and direct “drill-down” links to the data sources at the click of a mouse button.

records have added new priorities for compliance management. Part 11 has recently been modified to provide a more rational framework for implementation; however, the rule still applies if the electronic record is in a “high risk” area as defined by the data’s potential impact on human health. The manufacturing and Quality Assurance (QA)/QC functions fall into this “high risk” definition.

Good Manufacturing Practice (GMP) Electronic Notebooks Open the Door to the Compliant, Paperless Quality Operation

A unique PAT lab paradigm process was developed in the late 1990’s that allows a lab or production batch process to embed an automated data capture software application within a company’s existing SOPs, batch records, or test methods. In doing this, the technology presents only the current revision of a test method or production step to the approved and trained operator and, in real-time, captures all the critical data and metadata created during the process of implementing a method on the lab or process floor.

The software application takes the existing written protocols (methods, batch records, or SOPs) and presents it via wireless tablet Personal Computer (PC) to the analyst or operator as an electronic version with embedded, real-

time data-capture technology that forces data entry either manually or automatically (direct from instruments and equipment). The technology can be thought of as a “QA/QC PAT e-Notebook.” At the end of the process, all the data is aggregated in a reviewer dashboard (see Figures 1, 2 and 3)

with data flagged for specifications or expected process norms and a direct link to the original data source. Review times are typically reduced by a factor of 50–75%.³ Instrument report files are captured and organized in a secure repository for future needs using off-the-shelf electronic printing technologies such as Adobe Acrobat® print drivers. Access to the application platform is controlled via a secure and granular privilege grid with audit trail, time and date stamping, and electronic signature capability as required by 21 CFR Part 11 regulations. The resulting data is accessible to only authorized members of the QA review or management team. Departmental reports, including certificates of analysis or batch release documents (see Figure 4), can be automatically created and approved.

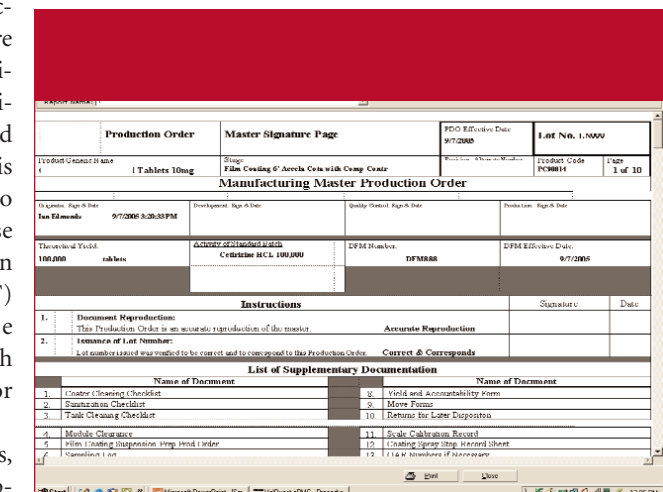


Figure 4: After a QC test method or production batch has been completed and approved, the data can be parsed automatically into departmental reports.

Time data-capture technology that forces data entry either manually or automatically (direct from instruments and equipment). The technology can be thought of as a “QA/QC PAT e-Notebook.” At the end of the process, all the data is aggregated in a reviewer dashboard (see Figures 1, 2 and 3) with data flagged for specifications or expected process norms and a direct link to the original data source. Review times are typically reduced by a factor of 50–75%.³ Instrument report files are captured and organized in a secure repository for future needs using off-the-shelf electronic printing technologies such as Adobe Acrobat® print drivers. Access to the application platform is controlled via a secure and granular privilege grid with audit trail, time and date stamping, and electronic signature capability as required by 21 CFR Part 11 regulations. The resulting data is accessible to only authorized members of the QA review or management team. Departmental reports, including certificates of analysis or batch release documents (see Figure 4), can be automatically created and approved. Data is then exported to other in-house Information Technology (IT) infrastructure requirements such as LIMS or ERP/MRP systems.

In many respects, this technology represents a tool-set for operators and analysts that supports

“process analytical technologies” (PAT) applied to the QC laboratory and manufacturing processes. Just as in physical manufacturing operations, the lab and process floor environment utilizes “method processes” conducted by the work force and through embedded “method or procedure-centric” software, the PAT philosophy can be applied to the lab and production floor with equivalent productivity improvements and significant operational cost reductions.

Conclusions

The highly regulated Pharmaceutical Industry must control costs as a result of questionable new product pipelines and the margin erosion due to the large number of products coming off patent over the next decade. Historically, the data management processes in QA/QC and the production floor have been “paper-based” requiring numerous manual checks to insure data integrity and product quality standards have been maintained. This process exists because it is impossible to fully validate human data documentation tasks. In today’s modern computer-based environments, technology can be adapted to totally eliminate these paper systems and replace them with a fully electronic method execution, data capture, review, and reporting system.

Platform software technologies designed to present approved SOPs in a digital form and embed software to

Article Acronym Listing

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| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| ERP | Enterprise Resource Planning |
| FDA | Food and Drug Administration |
| GMP | Good Manufacturing Practice |
| IT | Information Technology |
| LIMS | Laboratory Information Management System |
| MRP | Management Resource Planning |
| PAT | Process Analytical Technology |
| PC | Personal Computer |
| QA | Quality Assurance |
| QC | Quality Control |
| SDMS | Scientific Data Management Software |
| SOP | Standard Operating Procedure |

automatically prompt analysts and operators to follow the procedure as written, and automatically in real-time, capture and catalog all the data and outcomes in a secure repository, will help in the efforts to control costs and improve productivity while being compliant. This process eliminates operator method error or transcription issues in working with a paper-based notebook process. The data is automatically grouped and presented to a QA reviewer with color-coded flags for specification verification, e-signatures, and a full audit trail of activity. This process has been shown to reduce review times by over 50% and virtually eliminate rework and internal investigation processes, yielding overall operational QA/QC cost improvements of over 25%. PAT for the QC/QA and production batch processes has become a reality.

References

1. Pharmaceutical Processing, Reed Business Publications, December 2003, page 20.
2. Laboratory IT – Enabled Solutions Research Report, VelQuest Corporation, November, 2002.
3. Summary Report on International Meeting on Automated Compliance Systems (IMACS) 2005, www.imacs-world.com.