DIGITAL TRANSFORMATION IN QA/QC LABS

The role of an integrated LIMS solution on supporting data security, accuracy and integrity.

Within the last 15 years the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have asked the pharmaceutical industry to look afresh at its development and manufacturing processes, and establish foundations for a seamless, end-to-end quality-by-design (QbD) approach to the pharmaceutical product life cycle. Embodied in FDA's 2004 report, "Pharmaceutical cGMPs for the 21st Century – a risk-based approach," QbD is a concept that, as EMA states, "aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines."

Effectively, QbD is founded on the principles of deriving a thorough understanding of the attributes and behaviours of materials, development and manufacturing processes, and using that understanding to build quality processes into the complete product life cycle. Ultimately this should result in consistent, higher quality, safe drugs, developed and manufactured through processes that reduce the risks of failure at any stage.

Keeping QbD in mind, wind forward a dozen years and in 2016 FDA issued and invited comment on its draft guidance, "Data integrity and compliance with cGMP guidance for the industry," which was authored because the agency had been witnessing an increasing number of cGMP violations involving data integrity. The draft guidance aimed to help clarify the role of data integrity in current good manufacturing practice (cGMP) for drugs, as stipulated in 21 CFR parts 210, 211, and 212. As its introduction states, "cGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based upon their process understanding and knowledge management of technologies and business models."

A Digital Infrastructure

In today's high throughput, data-intensive laboratory environment the principles of QbD, data completeness and integrity should support the functions and operating ethos of any Quality Assurance/Quality Control (QA/QC) operation. Implement a comprehensive, intelligent informatics infrastructure and the job becomes less daunting. This laboratory-focused digital infrastructure is likely to be founded on laboratory information management system (LIMS) functionality to orchestrate test scheduling, manage samples, and automate critical processes. Today's high-end LIMS will also acquire and channel analytical data directly from measurement and testing instrumentation, offer advanced analytics to support trend identification, and highlight nonconformity and out-of-specification results.

Some software platforms provide additional day-to-day housekeeping operations, from scheduling instrument calibration and maintenance, to linking to reagent and consumables inventory, and keeping on top of operator training and permissions.

Reducing reliance on paper-based processes, log books and reports may help to improve data security, accuracy and integrity. Having a LIMS solution that offers bidirectional support for key systems means analysts do not have to transcribe results from an instrument panel onto paper or from paper to another manual medium. This helps to ensure data integrity and minimizes errors, but also eliminates data redundancy. STARLIMS solutions offer out of the box bidirectional support for chromatographic data systems (CDS) such as Empower and Chromeleon, as well as enterprise resource planning (ERP) platforms such as SAP.

Automation for Critical QA/QC Processes

STARLIMS can be configured to provide key points of automation for a majority of the QA/QC laboratory's critical processes. The software will generate calculations, reports, workflows, alerts and reminders, as well as trigger retests. Calibration, environmental and stability sample scheduling is similarly automated via STARLIMS, while the software can be configured to issue purchase requests when inventory stocks are low. STARLIMS in addition supports sample outsourcing, and provides the lab with visibility to allow fast identification of samples that need to be send out to third parties, while at the same time allowing personnel to track samples to make sure that testing is completed on time. It is not all about managing in house activities. QA/QC labs must ensure that any outsourced analytical workflows are managed with the same degree of diligence as in-house operation. Some aspects of QC testing, such as microbiology, are now commonly outsourced to specialized laboratories. From a regulatory perspective, seamless, bidirectional data traffic coming into and flowing out from the QA/QC lab removes error-prone manual data entry stages that could feasibly undo all good works afforded by accompanying digital systems. Therefore, contract partners need to have the same level of secure data management in place, and ideally connect into a conduit for two-way, fully traceable digital data input and transfer.

Supporting Data Integrity and QbD

STARLIMS supports end-to-end assurance of data integrity through traceability of associated processes related to sample or batch, combined with secure sample management capabilities, audit trail, electronic signatures, chain of custody and instrument integration. This collectively minimizes opportunities for human error and unauthorized changes to data. Effectively, all data is traceable, secure and trustworthy.

The intelligent platform supports the QbD concept from early development through to manufacturing. In a QA/QC setting, for example, lab staff can effectively get ahead and prevent changes to product consistency by reviewing process control and trending charts generated in STARLIMS, and so identify variations or anomalies that might impact on manufacturing process or testing.

While it is easy to get overwhelmed by acronyms, marrying a LIMS to a scientific data management system (SDMS), and to electronic laboratory notebook (ELN) capabilities – whether acquired as an add-on or embedded in the LIMS – will further reduce the likelihood of errors that manually transferred data introduces, while ensuring that all standard operating procedures (SOPs) are being adhered to and followed, step-by-step. The addition of ELN capabilities for recording and reporting experiments and data means that in principle, all workflows and processes can be electronically orchestrated at the front end, and recorded at the back end.

It sounds simple, but in reality, many commercial LIMS solutions depend on third party vendors to provide that additional, but crucial functionality. In contrast, STARLIMS offerings include a fully integrated LIMS, ELN and SDMS solution. Eliminating the need for third party vendors means configuration does not require complex interfacing or integration, and reduces the total cost of ownership.

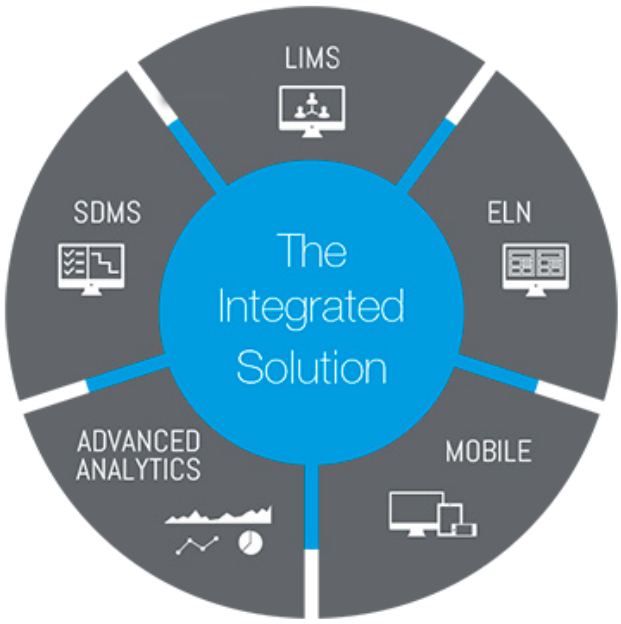

Figure 1 – Optimization of data management, accessibility and integrity with a single platform.

Advantages of a Holistic Solution

As an end-to-end solution STARLIMS negates those accountability headaches that are inevitably associated with dealing with multiple vendors for system support and issue resolution. Implementing a single, holistic solution also reduces the risk that one or more of the modules or add-ons will not operate as intended, which could impact on validation efforts and project schedules. The advantages of a fully integrated solution are multiple.

A modern LIMS will provide for electronic signatures and a secure audit trail to comply with 21 CFR Part 11, schedule equipment validation, calibration and maintenance, and verify that individual users have the necessary authority and level of training to carry out analytical procedures. Couple this functionality with an understanding of the samples, materials and processes, and with predictive analytics, and the platform can spot trends, highlight outliers and direct out of specification or results to relevant personnel for assessment and action, and/or sign-off, before batch release.

Take a holistic perspective and an ideal LIMS infrastructure – whether on premise or cloud-based – should thus be intuitive, user friendly, and configured to the laboratory's business rules. The system should offer authorized lab technicians, lab managers, and business executives easy access to key scientific and business decision-making data, in real time, and in digestible formats. The more complete the data, the more insight will be derived for directing next steps, implementing business changes, and maintaining lab operations at the top levels of efficiency.

The ALCOA Effect

Every aspect of QA/QC lab operation, data acquisition, handling and management could come under regulatory scrutiny, so the bottom line is that the lab adheres to the main principles of data integrity, i.e. that data is complete, consistent and accurate, as laid out by FDA in the 2016 data integrity draft guidance. In effect all data should be "attributable, legible, contemporaneously recorded, original or a true copy, and accurate," (ALCOA), which has become the laboratory mantra for achieving data compliance, whether through electronic or paper-based data management.

While all data created or acquired may be subjected to a regulatory inspection, meeting those ALCOA principles, whatever the data source, destination or format, is more easily achieved when data is acquired electronically. Even so, as set out in a 2017 presentation by the Office of Manufacturing Quality's Office of Compliance, and the Office of Policy for Pharmaceutical Quality's Office of Pharmaceutical Quality, at the Society of Quality Assurance Annual Meeting, "paper-based and electronic data record-keeping systems are subject to the same requirement."

Integration, and the 'What, Where and How' of Big Data

The requisite for integrating a LIMS platform directly with analytical or measuring instrumentation is a no brainer, so that data can be captured at source, at the time it was generated. Instrument integration means that the days of cutting and pasting balance printouts, or printing hundreds of pages of chromatographic runs, are well behind us. Configure adequate parallel security into the platform, and results are locked at source so that data can not be changed, deleted or added without authorized reasoning and outcomes. STARLIMS is designed to allow integration with instruments that have RS232 and TCP/IP connections. Data from standalone instruments attached to a computer can also be captured through STARLMS SDMS, as long as the output is readable to the human eye – e.g. in formats such as PDF or Word.

Big data has put pressure on data archiving and storage. Capacity in an SDMS is not an issue, but 'what', 'where' and 'how' to store and retrieve data makes the configuration of silos and the format of stored data critical. An SDMS should make intuitive searching and easy access a matter of course, and help to direct access to contextual information and all metadata, including relevant information on the equipment used, the analyst who carried out the test, reagents and instruments used. From a regulatory viewpoint, and particularly in QC environments, the relationships between data and metadata should also have a baseline assurance of security and traceability. It is virtually impossible to achieve that required level of data security, completeness and inherent integrity, using pen and paper records.

QA/QC labs must be able to verify during audit how they derived their data, as well as pin all metadata to key results. This is hugely time-consuming using a manual system, and accessing logs, workflows, SOPs and measurement results – from weights to pH – records on personnel and instruments is a major task. Imagine relying on paper-based records and having to gather all the data that pertain to the analysis of a lot during an investigation or an audit. That task will span gathering all laboratory notebooks in which sample and standard preparations have been documented, finding logbooks with instrument information, and finding all the forms in which the instrument calibrations and other key data were recorded.

Easy Access and Real Time Monitoring

Electronic solutions can pull up all relevant information attached to a result with just a few clicks. STARLIMS gives lab personnel complete visibility of all processes related to the testing of your sample or lot in one centralize location, from information on the analyst who carried out the task, to data on the instrument and its calibration and maintenance history, specifications of raw materials used to create the final product, and approval of results. By collating all this information in a single platform, electronic systems provide the opportunity to apply trend-based analytics, identify out of specification results and their causes. And critically, results and trends can be monitored and checked in real time, rather than retrospectively, making it possible to pre-empt issues with workflows, SOPs and test failures.

Errors are almost inevitable when manual data entry is involved. According to research published in the Journal of End User Computing's Special issue on Scaling Up End User Development, "20% to 40% of spreadsheets contain errors"[1] . The vast majority of mistakes are unintentional and accidental, but there have been cases where inspections have resulted in warning letters or even plant closures in light of evidence of intentional data mishandling. Such mishandling may include data manipulation or substituting results, sidestepping out of specification results, destroying records, failing to record activities at the time they were performed, or deleting raw data.

Authorization and Big Brother Oversight

Shared logins and inadequate access authorization steps are other areas for regulatory concern, as is the practice of testing into compliance, essentially retesting batch samples following failure or atypical/out of specification results until acceptable readings are obtained. Implement a secure informatics infrastructure with the necessary compliance-focused features and it becomes virtually impossible to manipulate results without the necessary authorization and validation.

An automated system will similarly maintain a big brother view of who is doing what in a lab. Historically, if equipment used to carry out a test run had not been calibrated the manager or technician would have to go back and justify or invalidate the data that was generated, or perform additional tests to confirm that equipment performance was within acceptable parameters. Feasibly this could require a complete batch retest, causing significant delays in batch release, and adding to physical costs associated with the use of reagents, consumables and collecting samples.

STARLIMS will not allow technicians or analysts to proceed with tasks that they are not qualified or trained to perform, nor assign samples to be tested on instruments that have not been calibrated, or are due for scheduled maintenance. Test Methods are defined within the system and certification requirements are defined for these methods or procedures. The system intelligently supports the prevention of errors that later could be costly and could lead to in lengthy investigations.

Becoming more proactive

Using STARLIMS laboratory managers can be proactive, rather than reactive, and focus their time on value added tasks, while minimizing or completely negating reliance on manual and paper-based processes and systems. Advanced analytics offered by STARLIMS allow managers to oversee the health of their lab, and drill down into operational data to gain greater insights, spot trends, and identify the root cause of negative trends, which supports impact assessment and aids faster decision making.

Exploiting an informatics platform to manage staff, equipment and reagents and consumables can dramatically improve resource management, and optimize the use of existing systems and laboratory resources. The most valuable asset of any lab is its personnel, from technicians, to managers and executives. Allowing people to get on with their primary roles, rather than spend time manually entering, handling and managing data to ensure compliance, further helps to maximize efficiency and make the most of human expertise.

Reference:

1. “What We Know About Spreadsheet Errors”, Raymond R. Panko, University of Hawai’I, College of Business Administration. http://panko.shidler.hawaii.edu/SSR/Mypapers/whatknow.htm

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