Regulatory Compliance – How LIMS Can Support the 10 Principles of GMP

Laboratory information management systems (LIMS) are used extensively in pharmaceutical laboratories to manage, track and report on samples, tests, test results and more. Laboratory testing can be involved at every step from raw material analysis through to the finished product. Since the pharmaceutical industry is highly regulated to ensure the safety of products for consumers, the use of LIMS must also conform to the requirements of the appropriate regulatory body. For example, the Good Manufacturing Practice (GMP) principles of the US Food and Drug Agency (FDA) help ensure quality of manufactured product throughout the manufacturing, processing and packaging stages. The FDA deems a drug to be adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice..." GMP is used to create a quality framework for manufacturers to make sure that the products are safe, pure, and effective. There are 10 key principles of GMP and it is important to understand how a LIMS can satisfy each of these requirements.

Good Manufacturing Practice

GMP principles (often designated 'cGMP' – *current* Good Manufacturing Practice) address a wide range of issues such as record-keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling. However they offer individual manufacturers the flexibility to decide how to implement the necessary controls in the most appropriate way for their particular business. This flexibility allows a laboratory to configure a LIMS to meet its individual needs and workflows, providing in doing so it fulfills the 10 key principles of GMP. Once a company has been authorised to manufacture and sell pharmaceuticals and pharmaceutical ingredients, it is subject to ongoing audits and inspections. The LIMS must, therefore, support functionality to address this. These include audit trails, time- and date-stamping of all actions, version control of all reference data such as test definitions, data entry authentication and comprehensive user and password management capability.

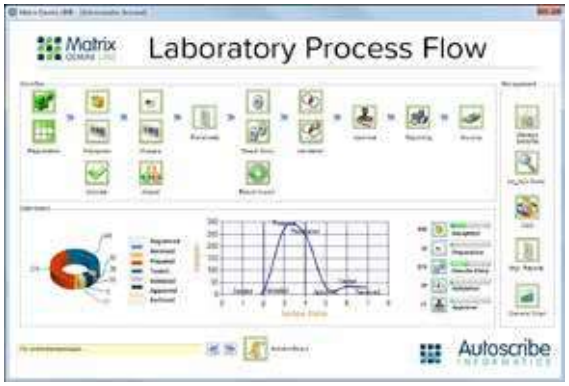

Figure 1 – Typical QC laboratory process flow

Figure 2. Management of documents, competency records, etc.

LIMS in the Pharmaceutical QC Laboratory

Pharmaceutical quality control laboratories have an important function in both raw material evaluation and production, and can significantly impact overall manufacturing performance. Enhancing laboratory productivity leads to improved manufacturing efficiency, and information management in laboratory operations is essential to improving laboratory efficiencies. Using a LIMS to control, manage, organise, document, analyse and report information leads to improved efficiency and functionality of data storage and manipulation. The system is likely to be required to manage data for a wide range of analytical techniques for both the raw materials and finished products. Raw materials and finished products have to conform to pharmacopoeia and relevant product licences. However, individual laboratories have their own workflows and processes. Ideally the LIMS should be capable of being configured to reflect this. This could cover the definition of screen and menu designs and customer-specific tables/modules, and support multiple specific screens designed to minimise possible user error (e.g. different login screens for different product classes, such as raw materials and finished products). Unique user interfaces can graphically represent workflows and the progress of samples through the laboratory.

The 10 Principles of cGMP

Any compliant LIMS will be able to satisfy the requirements of the 10 principles of cGMP.

1. Defined operating procedures and work instructions to establish controlled and consistent performance

Standard operating procedures (SOPs) and work instructions can be stored and maintained within an integrated document management system in the LIMS. They are then available for users to reference directly from the LIMS.

2. Adherence to written procedures and instructions

If SOPs and work instructions are available for users to reference directly from the LIMS, then relevant SOPs can be presented based on the current user task, and visual workflows created to guide users through the laboratory process. By defining access rights and managing competency records within the LIMS, users are only able to carry out tasks relevant to their function and which they have been trained to carry out.

3. Prompt and accurate documentation of work for compliance and traceability
As users complete workflow tasks or actions within the LIMS, an electronic signature can be created that records who completed the action and when. A reason for the action can also be recorded if necessary. Data entered should be recorded directly in the database at the time of entry. Analytical results, and the ID of the instrument used, should be captured automatically, removing the possibility of transcription errors and a record of media and reagents used can be maintained. If users are allowed to modify data within the system, an audit trail should be in place to provide access to a complete history of the changes made, including who, when, why, and the changes made.

4. Prove that the systems do what they should through validation
The LIMS should be able to manage data and information that supports system validation. For example, instrument calibration and sensitivity measurements and records can be managed through LIMS and are easily accessible for validation purposes. QA/QC information has always been a fundamental component of LIMS and can be used to validate the accuracy of in-line analysers and process analytical technology (PAT) processes.

5. Properly defined and designed system and equipment
An appropriately configured LIMS should help validate and ensure facility, system and equipment suitability. As an example, facilities must be designed to prevent contamination (microbial, particulate or cross-contamination). An environmental monitoring facility within a LIMS will allow the setup of sampling points within a sample location, e.g. within a sterile filling facility, the air vents, bench tops and the filling machines themselves need to be monitored for contamination. The tests (and associated limits) and testing frequencies required for each sampling can be defined. After results are recorded, alerts can be triggered by 'out of specification' results, with previous results being reviewed to identify possible trends.

6. Properly maintain facility and equipment
It is possible for a LIMS to support instrument and equipment maintenance and calibration schedules. This means that instruments and equipment can be flagged as unavailable if they are out of maintenance or calibration. It is also possible to prevent tests being assigned to specific instruments if they are flagged as unavailable.

7. Define, develop and prove job competency
Competency and training records can be maintained within LIMS. This makes it possible to prevent individuals carrying out specific tasks if they do not have a valid training record.

8. Protect products from contamination
A LIMS configuration will support QA/QC testing regimes that help ensure ongoing product quality. Environmental monitoring functionality is specifically designed to monitor possible contamination at specific location and sampling points on an ongoing basis.

9. Build quality into products
A LIMS can support the standard QA/QC processes used in manufacturing. Raw materials and finished products can be tested against master record specifications and release mechanisms

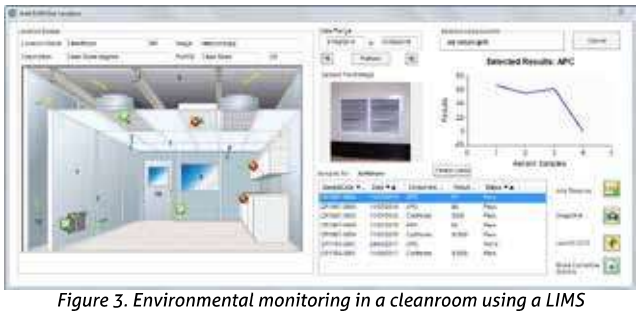

Figure 3. Environmental monitoring in a cleanroom using a LIMS

implemented for batches and lots. Defined workflows help ensure adherence to quality processes and full traceability of any actions carried out can be provided.

10. Perform regular audits to ensure compliance
A LIMS can support the audit process (internal and external) by providing access to required information from a single integrated source. Training records, instrument calibration and maintenance records, the results of QA/QC testing and other relevant information can be recorded in, and retrieved from, the LIMS database, together with required electronic signatures and audit trail.

Penalties for Non-compliance
GMP is designed for the prevention of: adulteration, falsification of data, inadequate traceability, mislabelling, counterfeiting and ultimately the release of potentially dangerous products. While the actual method of implementation is the responsibility of the manufacturers and suppliers, the use of a LIMS can improve laboratory efficiency and help ensure compliance. The failure of an organisation to comply with GMP regulations in any context, including the LIMS, can result in very serious consequences. Regulatory bodies have wide ranging powers, including:

- Withdrawal of authorisation/ licenses
- Closure of facilities
- Debarring of companies
- Debarring of named individuals from the industry
- Substantial fines ($3 billion)

Significant costs can arise as a result of regulatory action, including the cost of product recall and discontinuation. There can be internal direct costs related to scrap material, remediation costs and suspended operations. Finally, non-compliance can seriously damage a company's reputation and brand, with potential knock-on effect on shareholder value. A LIMS that supports the principals of GMP and which is configurable to your needs can help manage these risks.

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Simon Wood PhD, Product Manager at Autoscribe Informatics, has 30 years' experience in the commercial LIMS environment. He is an acknowledged expert in the field of scientific and laboratory informatics. With a degree in Plant Biology from Newcastle University and a PhD in Mycology from the University of Sheffield, Simon successfully moved into the field of laboratory informatics.

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