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GMP Series

How to design a Laboratory Data Management System

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Excerpt from the GMP Compliance Adviser

Contents

1 Laboratory data management systems (LDMS)

Dr. Ulf Fuchslueger

Here you will find answers to the following questions:
- For what reasons were laboratory data management systems introduced?
- What is the proper way of introducing a data management system that meets the regulatory requirements?
- What must be observed when operating a laboratory data management system?
- What must be observed when a laboratory data management system is used as the basis for a paperless documentation system?

1.1 Principles

The term *laboratory information management system* (LIMS) was introduced in the first half of the 1970s when laboratories began to computerise and automate processes and data evaluation. If at the beginning, an attempt was made to use individual solutions to automate individual and highly repetitive tasks, things have since moved on, and a wide range of commercial and partly specialised LIMS products with a comprehensive range of functions is now available. These products support all areas including early research, development and quality control.

For a long time, the term *laboratory information management system* (LIMS) was used as a synonym for the more general term *laboratory data management system* (LDMS). In addition to the classical LIMS products, a number of other product categories that offer supplementary functions have established themselves since the beginning of the 21st century. These include, first and foremost, *electronic lab notebooks* (ELN) and *lab execution systems* (LES). ELNs are typically used in research and development with LESs more likely to be found in subsequent analytical development and quality control. Different providers offer various strategies and use different terminology, which sometimes leads to an obscuring and merging of product categories.

This chapter focuses on laboratory data management systems for quality control and analytical development in the pharmaceutical industry. The term LDMS is now used to refer to LIMS, LES and ELN. A large part of this chapter also applies to other IT systems in regulated environments.

1.1.1 Reasons for introducing an LDMS

There are many arguments in favour of the introduction of an LDMS. The more important ones include:
- Increased efficiency in the laboratory
- Improved quality in the laboratory
- Utilisation of the inherent benefits of electronic data recording and management
- Electronic systems used to achieve compliance

Increased efficiency mainly results from
- Automation of repetitive processes
- Combination with other systems (e.g. connection of analysis devices and linking up with materials management and procurement systems [ERP])
- Better utilisation of resources due to an improved overview and more predictability
- Faster decision-making due to improved availability of information (examples: information on OOS results and complaints, statistic trends for methods, devices or products)

With the introduction of an LDMS, complex stand-alone solutions such as validated Excel sheets and local databases can be eliminated.

The systematic introduction of an LDMS can also lead to a significant *increase in quality* of processes and data. On the one hand, an LDMS defines the processes, ensuring that the individual process steps are carried out in the correct sequence by authorised persons only. On the other hand, the automatic transfer of data (e.g. numeric values) from the analysis device to the LDMS and the automatic documentation of data in a certificate eliminate transfer errors and reduce the burden of control. Using an LDMS, the monitoring of calibration and maintenance intervals, the training level of the employees, the expiry dates of reagents and compliance with standards can be carried out at no extra cost, which leads to a further increase in quality. The same applies to the use of bar codes for identifying samples, reagents, devices and consumables.

The introduction of an LDMS has further positive effects due to the *inherent benefits of electronic data management*. These include the immediate availability of data regardless of location (depending on the system, this may even include raw data), the introduction of company-wide standards for quality processes, data management, data backup and data security as well as quick and partly automated sharing of information between departments, locations or companies and the subsequent reduction of barriers and acceleration of processes.

As a rule, modern LDMSs meet all the technical requirements defined in 21 CFR Part 11 and EU GMP Guidelines Annex 11. For this reason, a fully validated LDMS can also be used to help *meet the regulatory requirements* that apply to electronic data management. It can, for example, migrate data generated by systems that do not fulfil the current regulatory requirements into a regulated environment (see example in figure 1).

The software that is used to control an NMR device and evaluate the relevant data does not meet the regulatory requirements (no access control, no audit trail, no version control). Sample-specific data (e.g. the designation of the sample, sample preparation, measuring method) is transferred from the LDMS to the device software using device interfaces prior to measurement.
After measurement has been completed using these parameters and the raw data (including the meta data) has been saved on the computer used for controlling the device, the data is automatically and immediately transferred to the LDMS database.
Separate software is used for the evaluation of the data, which has direct access to the data saved in the LDMS, i.e. in a controlled environment. Processed data is stored in the LDMS or in an archiving solution, e.g. in PDF format. This ensures that raw data is handled in accordance with the regulatory requirements. It also offers optimum traceability of data generation and evaluation despite the shortcomings of the device software (with the exception of the access control for the device software)

Figure 1 Example for the migration of data into a regulated environment

1.1.2 Official requirements and industry standards

An LDMS is a quality-related computerised system which must be validated. When introducing an LDMS in a regulated environment, several regulatory requirements must be met, including the EU GMP Guidelines Annex 11 and 21 CFR Part 11.

With regard to GLP, the OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, No 10 (The Application of the Principles of GLP to Computerised Systems) must also be observed[1].

Along with various, sometimes older standards, GAMP – currently version 5, also referred to as **GAMP 5** – has established itself as the leading industry standard for the validation of computerised systems. At this stage, the FDA also refers to GAMP for the validation of computerised systems (Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application). For this reason, GAMP should be taken into account when an LDMS is introduced.

1. GLP Consensus Document `The Application of the Principles of GLP to Computerised Systems', 1995, OECD/ OECD/GD (95) 115 (Environment Monograph No.116)

1.2 Specification phase

The first step in any project is detailed and thorough planning. Although not formally specified in the regulations, this principle also applies to the introduction of an LDMS and is a key factor in the success of the project. Figure 2 shows that investment in the planning phase pays off. Errors that are only discovered at a later stage of the project or changes carried out at a later stage cause an exponential increase in the cost of the project.

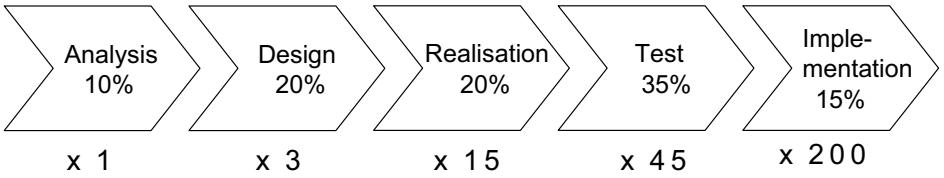

Figure 2 *Costs of IT projects in the pharmaceutical industry (%) and cost factors resulting from planning phase errors after discovery in the respective phase*

GAMP recommends the so-called **V model** (see figure 3) as a reference phase model for the implementation of validated computerised systems. GAMP 5 introduces the term **verification** which is also used in the traditional qualification phases. The left side of the "V" contains the different specifications and is generally referred to as the design or specification phase. Implementation (creation) is followed by the respective test phases (right side of the "V"). The system is tested and released during this verification phase.

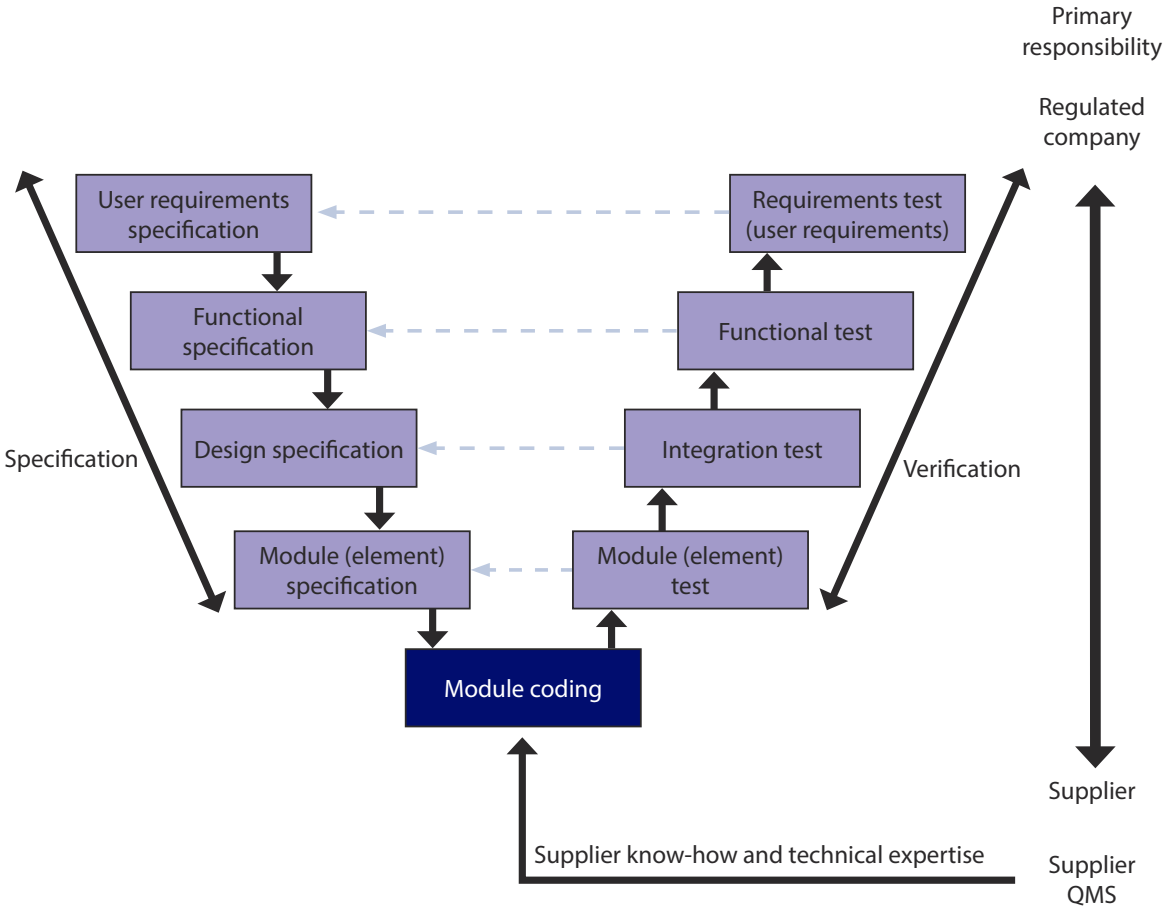

Figure 3 *V model: Specification and verification, example of category 5 software /(Source 4.4, GAMP 5 – A risk-based approach to compliant GxP computerised systems. Copyright ISP 2008. All rights reserved)*

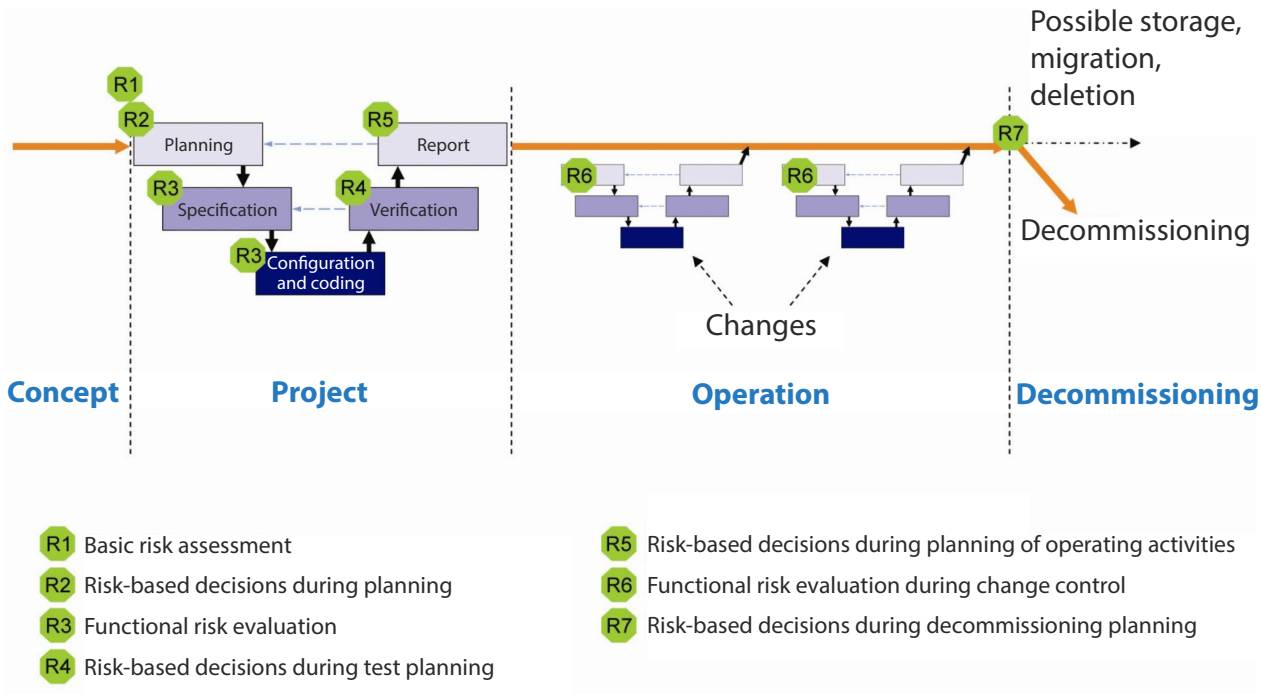

Figure 6 Use of risk evaluation when implementing and operating an LDMS (Source M3.3, GAMP 5 – A risk-based approach to compliant GxP computerised systems. Copyright ISPE 2008. All rights reserved)

As shown in figure 6, risk evaluation is not a single step in a project but a recurring process that must also be carried out when changes occur during operation.

As a rule, an LDMS has to be validated; therefore, the *basic risk evaluation* (R1) is generally brief. However, if no validation is carried out, detailed documentation of the reason and risk evaluation is required.

In the case of an order or supplier evaluation and classification of the selected system, a *risk evaluation* (R2) is carried out to justify the validation effort. This means that a reduction in the work required for certain parts of the software is acceptable, e.g. those that fall under GAMP Category 1 or 3.

The most comprehensive risk evaluation from the user's perspective is probably carried out during the *definition of test plans* and especially during performance verification (R3 and R4). The risk evaluation of the business processes in the LDMS shows the aspects that need to be looked at closely and which processes justify a less involved validation. As a result, this evaluation has an impact on the effort required for the verification and can be carried out not only from a regulatory, but also from a business point of view (*business risk*).

A further risk evaluation (R6) carried out during the *definition of change control procedures* can support a productive system and define different approaches to change control.

1.4 Verification phase

From the user's perspective, verification can be divided into three phases in accordance with the V model (cf. figure 3): integration test, functional test and user requirement test. As previously described in chapter 1.2.2 *Validation plan*, certain parts of the verification can be summarised or even left out depending on the software category.

In practice, there are different ways of structuring the application for the implementation and validation. The regulations provide no guidance on this matter and leave it up to the system owner as long as the process is controlled and described in detail.

If applicable, guidelines must also be put in place for archiving (Archive & Restore). The system owner and responsible person in QA define the content of the respective guidelines. The "O" (Operation) appendices in GAMP provide detailed instructions for the creation of documents relevant for operation.

1.6 Periodic review

Despite change control and the use of a logbook, the LDMS and all related documentation must undergo a periodic review. This is rather similar to the periodic maintenance and calibration of analysis devices.

The periodic review should, on the one hand, ensure and document that the LDMS-specific regulations are being met. It is, therefore, to be understood as the functional equivalent of the validation and productive instance. On the other hand, the periodic review is also a continuation of the traceability matrix and offers a clear overview of new requirements, additional functions and their verification. During the periodic review, it should be checked whether documents such as the system description are still up to date.

1.7 Paperless documentation and LDMS

As mentioned in the chapter 1.1.1 *Reasons for introducing an LDMS*, LDMS has several advantages over a paper-based system. Many of these arise from the automation of processes and the electronic availability of results and data. It makes sense to use an electronic system for data recording and the actual documentation in the laboratory. This eliminates inefficient paper-based documentation and avoids duplication of work.

Modern LDMSs offer the required functions and serve as a consolidation layer for the large volume of data created in a QC laboratory. At the same time, they facilitate controlled and standardised communication with higher-level systems such as enterprise resource planning systems.

The basic design of a modern architecture for LDMS in Quality Control is shown in figure 9. The graphic shows the individual components of the LDMS (blue) and the integrated analysis devices and chromatography data system (CDS). Depending on the supplier, the components shown (LES, ELN, LIMS, raw data storage) can be supplied as a single system or as components of an overall solution.

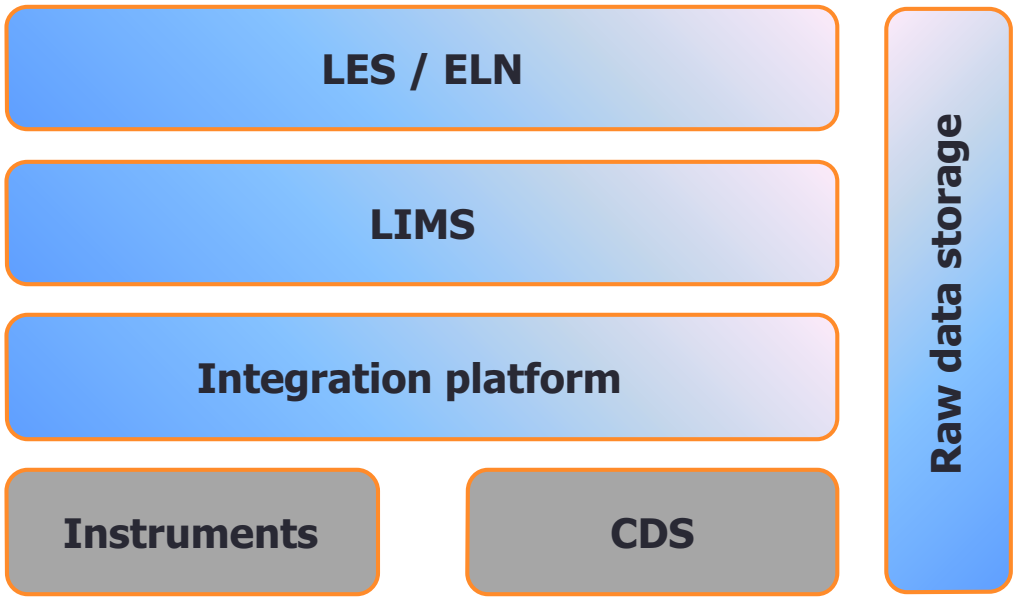

Figure 9 Example of a modern architecture for LDMS in Quality Control

To ensure the successful introduction of a paperless laboratory environment that is accepted by the users, it is important to keep the level of manual data recording to an absolute minimum. This can be achieved, on the one hand, by extensive use of device interfaces for the automatic and bidirectional transfer of data between the LDMS and the analysis device, and, on the other hand, by using bar codes to clearly identify samples, reagents, devices and consumables. Free text entries and electronic forms (LES) for data that is not automatically recorded and activities at different levels of the LDMS (e.g. sample preparation or deviations) complete the collection of data in the laboratory.

The handling of the different types of raw data created in the laboratory should be given special attention when paper-free methods are used and requires clear guidelines. It is important to differentiate between data sources that already meet the statutory requirements (e.g. modern chromatography data systems), and solutions that do not meet the statutory requirements. When a paperless system is introduced, an SOP must be created that defines the different types of raw data, describes how to deal with this raw data and provides clear guidelines on the regulatory requirements that must be met during storage (see also the chapter 1.1.1 *Reasons for introducing an LDMS*).

Summary
The introduction of an LDMS, when implemented correctly, has an extremely positive impact on the efficiency and quality of the work in and around the analytical laboratory. Many of these advantages result from the automation and automatic control of processes, and the electronic availability of data.
To ensure that the introduction of a validated system meets the regulatory requirements, the specification and verification should be based on the guidelines, classification and V-model (phase model) in GAMP 5. This includes all of the processes, from the creation of the user requirements specification to the release of the system after a successful performance verification, and transfer to the operative phase.
The operation of an LDMS requires numerous guidelines, which must be in place before commissioning at the latest. A periodic review of the system and underlying documentation should also be carried out.
An LDMS can serve as the basis and central interface for a paperless operation in Analysis and Quality Assurance and as an interface to other company departments. The aim is to keep the manual data collection to a minimum and simplify the entry and identification process with the aid of bar codes.

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1992–1998	Head of Mass Spectrometry & Gas Chromatography in the PO-Analytics department of Ciba Spezialitätenchemie AG (formerly Ciba-Geigy AG) in Basel (GLP testing facility)
1998–2003	Analytical Services Group Manager at CarboGen AG, project manager for the introduction of the global chromatography data system and LIMS; responsible for introduction of paperless laboratory environment
2003–2013	CEO of Vialis GmbH, Senior Consultant, consultancy and implementation of laboratory data management, laboratory process optimisation, LIMS, electronic lab notebooks (ELN) and system integration in a regulated environment
2013–2014	Senior Director at Accelrys Inc. and Consultant at Accelrys Management Consulting for laboratory data management, laboratory process optimisation, LIMS, electronic lab notebooks (ELN) and system integration in a regulated environment
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Special activities

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