Questions of Quality

Ten Steps to Heaven?

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The ten steps of a Laboratory Information Management System (LIMS) project are outlined, but are you walking the road to heaven or hell?

What is a LIMS?

In the last Questions of Quality column we discussed the boundaries and scope of a LIMS. It can be defined as a computer application that is capable of capturing, analysing, reporting, and managing data and information using a database. The key components of a LIMS are the computer hardware, the communications network, and the software (operating system, software tools, programming languages, database, and data). The problem is to fit a commercial LIMS into your laboratory and the way you work. How do you do this? The answer is to follow the systems development life cycle (SDLC).

Systems Development Life Cycle

This instalment of Questions of Quality and the next will look at the development and implementation of a system that follows the traditional computer SDLC. It is this approach that chromatographers will find unusual. Normally, equipment is purchased off-the-shelf and used with little or no modification. However, a different approach is necessary with complex laboratory automation such as a LIMS. In this instance, the users must state what tasks they want the system to undertake. This often places the chromatographer in a difficult position because he/she is not certain what the system should be, or is, capable of doing.

The ten stages of a LIMS project are:

- analyse needs
- specify user requirements
- write a validation plan
- devise a transition plan
- select a supplier
- develop functions
- pilot a system
- qualify or validate the system
- train users
- roll out the system to users.

The SDLC can be represented as a V, as shown in Figure 1. The first eight stages will be covered in this month's Questions of Quality. The training and roll out of the system to the users and their involvement in the whole of the SDLC will be discussed in the next Questions of Quality.

Will the System Operate in a Regulated Environment?

The first question you should consider before starting a LIMS project is "will the system operate in a regulated environment?" Such an environment is Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), or International Standards Organization (ISO) Guide 25; all of which have specific requirements for the validation of computer applications. Therefore, if the answer to the question is yes, then the development of the system should be documented to demonstrate the quality of development. It is my experience, and that of others, in these environments that development is evidenced through documentation. The absence of documents suggests that no activities took place.

If the system will not operate in a regulated environment, there is no

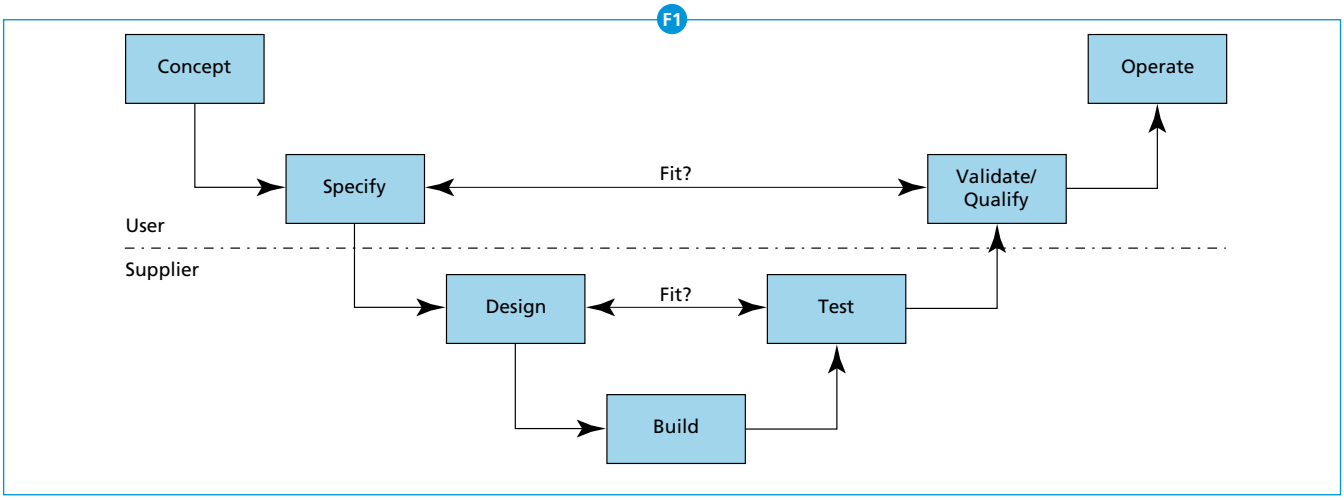

Figure 1: *Systems development life cycle. N.B. When specifying a design it is necessary to consider testing and validation/qualification before operation can proceed.*

requirement to document the development. However, this is contrary to the principles of Good Computing Practice, in which each stage of development should be documented. By not documenting the development of the LIMS, you will considerably increase the risk of failure. Therefore, even if there is no requirement for documenting the development, I strongly suggest that you do so. If you don't want to formalize development in this way, may I suggest that you just send a cheque for the time and money that you would have spent on the system, made payable to my eldest daughter, Jennie, to me, care of *LC·GC International*? She will waste the money just as quickly, but the difference is she will enjoy herself far more than you will during the failure of your LIMS project. An additional benefit is that my wallet will rest easy.

Quality development will usually add a further overhead to the project of up to 10%. However, this is effort well spent because approximately 50% of LIMS projects fail, or fail to meet initial expectations; the additional effort will help ensure that the system will meet business and user requirements. A rather novel idea really.

Step 1: Analyse Needs

The work in this stage establishes the reason for the system. During this process, a needs analysis is undertaken which defines the nature of the LIMS to be acquired and describes its goals and risks within business and technical constraints. This can result in some documents.

- *Needs Analysis Report*: This describes the basic problems that the proposed system should solve, such as replacement of an older system or expansion of existing facilities to overcome a bottleneck that is rate-limiting for the laboratory.
- *Project Proposal*
- *Preliminary Budget Proposal*
- *Initial Project Plan*: The project plan should be updated as the project progresses. Planning in the early stages of a project is not detailed enough and as the project unfolds this is corrected.

The size and significance of the system to be acquired will determine how much documentation is needed. For a small LIMS, a preliminary budget proposal may be sufficient to document this phase. For the acquisition of a larger system (e.g., for a site or an international multi-site system), a project proposal with an outline project plan and an extensive needs-analysis report will probably be required.

A decision should be made at this point — whether the project should be approved with money and resources made available.

Step 2: Specify User Requirements

When budgetary approval is given, the acquisition phase can start. The first stage is to write a *Requirements Specification*, which describes the functions that the system needs to perform. This fixes the baseline against which prospective systems will be assessed and the installed system will be validated. The LIMS matrix, described in the last Questions of Quality column, can be used as the basis for drawing up the user requirements. The requirements may be phased (Table 1, step 4) provided there is a core working system.

If the LIMS is to be validated, the requirements specification is mandatory: A system cannot be validated without an up-to-date requirements specification. When the requirements change, the system requirements specification must be updated to reflect these changes. Why all the fuss about this document? Validation is currently defined as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes" (1). Note the phrase "predetermined specification" — this is the requirements specification.

When the requirements specification is complete, a Request for Proposal (RFP) is written, detailing the information that the department requires to make a selection. The RFP also helps the supplier format its tender or proposal. The requirements specification and RFP should be separate documents, because if there are changes in the user requirements, only one document needs to be updated. As well as defining the user functions, the requirements specification should identify the preliminary configuration of the system. See Table 1 for an outline RFP.

Step 3: Write a Validation Plan

As soon as the user requirements are defined, the validation plan should be written. Validation is not the last stage of the life cycle — it should be an integral part of the project. The old saying that you cannot test quality into a system is very true; only by designing quality into the LIMS from day one of the project will you succeed. If the validation is considered from the start of the project (prospective validation) rather than as an afterthought (retrospective evaluation), this will save you considerable work.

The validation plan will outline the aims of the system and, most importantly, the deliverables that should be produced from each stage of the life cycle to demonstrate that the work was actually done. Producing the documentation may sound like hard work, but with a little thought, the documents can be produced within a standard and structured format relatively quickly. This is in contrast to retrospective evaluation, in which these documents or statements have to be constructed some time after the events. Memories can often be bad.

Step 4: Devise a Transition Plan

It is important early in the project to plan the transition from the current way of working to the new LIMS. This is a crucial part of any LIMS project and is often neglected, resulting in problems later.

If you have a manual system in your laboratory, the transition should not be too complex or involved. Sometimes, the new LIMS may replace an existing system. Therefore, planning should start early for the retirement of the old system and deciding what to do with any existing data that is stored on the system. Regardless of the current working practices, the new LIMS should deliver some immediate benefit to its users to encourage them to learn the system. For the first roll-out of the LIMS, do not attempt to deliver a complete system. Aim instead for a core system that meets the major needs of the user community. Note that the user community, as shown by the LIMS matrix, is inside and outside the laboratory.

The overall plan for the implementation of, or changeover to, the new system should be planned at this stage to manage user expectations. This is essential to forewarn the chromatographers who will be affected by the implementation of the LIMS. For instance, who among the user community will be the first group of users? The credibility of any LIMS can be easily lost during the roll-out to users and it is vital that the first users are sympathetic to the system. Poor planning and management of the user expectations from the start will cause a problem that will take much effort to overcome. We will discuss this in more detail in the next instalment.

Step 5: Select a Supplier

The first stage in this process is to prioritize the functions in the requirements specification. The detailed listing of the functional requirements will enable the laboratory to define its criteria for selecting the new system. Each requirement should be listed as either mandatory or optional.

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Table 1: Selected Sections in a Request for Proposal (RFP). The Twelve Sections of the RFP for a LIMS are Described as Follows:

Description of the laboratory and the work undertaken:
This should start with a brief description of the organization and the industry sector it is in, followed by the function of the laboratory and how it helps the organization meet its aims.

Staff numbers and organization:
The number of staff, levels of qualification (technician, academic, etc.), and how they are organized. It may be appropriate to insert an organizational structure to help the description. What are the roles of the functional elements of the laboratory?

Analytical instrumentation:
Describe the main analytical instruments used in the laboratory: makes and models and overall numbers. Will instruments be connected directly to the system or interfaced using a network? Do you have sufficient volumes going through the instrumentation to justify on-line connection to the LIMS?

Level of automation:
How automated is the laboratory: autosamplers for instrumental automation? Are other types of automation used, such as robotics or sample processor apparatus?

Sources and volumes of work:
Who are the main customers of the laboratory? What types of samples are submitted and the total numbers involved? The type and number of tests applied to each sample should be described.

Speed of turnaround:
The turnaround time required by the laboratory may influence the nature of the hardware and its configuration or the integration with other computer systems.

Further processing of results:
How is the final report compiled? Will this be part of the LIMS or is the system to be interfaced to another system that is responsible for the further processing?

Past, present, and projected workload:
Historical numbers of the workload for the past three or more years and a projection based on today's knowledge is important to help size the LIMS hardware, including the disks, with a degree of confidence.

Corporate computing policy:
Software, hardware, and communications at local and corporate levels. This is an area of varying design constraints that have an impact on the tools and hardware to implement the system.

Data input from other systems:
If the LIMS is to be connected to another system, describe it, and also what data, in which format, will be transferred. Estimate the data volumes to establish the bandwidth required.

Data output to other systems:
The same applies to the output from the system.

Integration with networks and communications:
Details of acceptable network protocols are essential. What is the e-mail system if integration is a requirement to transmit results to clients?

- A mandatory function is one that must be present for the system to operate properly and meet regulatory requirements.
- An optional function is desirable if it is a standard operation on a system but the basic functioning of the data system is not affected if the function is not present.

The list of mandatory requirements establishes the base for selecting a particular system and supplier, and this is a key document. The selection tests can be devised from the prioritized mandatory functions. In addition, they can be used in the acceptance and qualification test plan and test scripts.

Training is a key component of successful implementation of the new system and must be considered as early as possible in this step. Training requirements need to be discussed with the suppliers and modified to the specific circumstances and type of system. Training should not just cover the use of the system but also the development of functions using the programming language and how to manage and maintain the system.

During the process of preparing the RFP, a number of LIMS suppliers should be selected based on any previous experience, discussion with other system users, or on information from trade adverts. For practical reasons, the

number of suppliers should be kept relatively low (approximately six to eight initially). The RFP is sent to the selected vendors and a tender should be received within a defined timescale (usually, approximately six weeks after receipt). Tender responses are reviewed against the selection criteria and those systems that meet all, or the majority of, mandatory requirements should be selected for actual testing.

Testing two systems allows you a degree of choice in selecting the final LIMS. If more systems are tested, this will increase the choice, but also the time and effort involved. This is particularly important when a small laboratory is considering a LIMS; you will not have the time and resources that are available to a medium-sized or large laboratory and may only be able to test one system. However, it is vital that you spend time on this phase to get the decision right, otherwise you won't know whether you have made the correct choice of system until 6–12 months, and a lot of time and effort, later.

Tests should be devised and performed for each selected LIMS. The results of these tests, together with the comments of users on subjective elements of the system, should be used to select a final supplier.

When a final supplier has been selected, or if you have the time concurrently with the testing of the systems, the quality procedures of each vendor should be investigated. This involves assessing how the system was developed and tested, and how problems are recorded, tracked, and resolved (including the help desk). Alternatively, a vendor audit can be undertaken.

A vendor audit is becoming increasingly important to regulatory agencies. The Organisation for Economic Cooperation and Development (OECD) GLP guidelines for computerized systems (2), specifically mention that users should ensure that a vendor has produced the system under a quality procedure. These state that "computerized systems should be designed to satisfy GLP principles and introduced in a pre-planned manner. There should be adequate documentation to recognized quality and technical standards… For vendor-supplied systems it is likely that much of the documentation created during the development is retained at the vendor's site. In this case, evidence of formal assessment and/or vendor audits should be available at the test facility."

The United Kingdom Pharmaceutical Industry Computer Validation Forum (UKPICVF) has produced the Good Automated Manufacturing Practice (GAMP) guidelines (3) which outline the steps to be taken in the acquisition of a computer system from a vendor, including an emphasis on auditing the vendor's quality procedures.

Before the purchase order is issued, contract negotiations should take place to cover items such as price, payment schedule, and what the supplier will do about missing items or how to handle requests for enhancements or extensions. Negotiations will continue until both parties agree on the initial configuration of the system. Thus, any specific points will be included in a contract between the LIMS vendor and the laboratory. We discussed the contract in a previous Questions of Quality column (4).

Step 8, Part I: Qualify or Validate the LIMS

Yes, I *can* count and the sequence of numbering *is* deliberate; but you can't develop a system until it has first been installed at your site. Therefore, the system has to be installed properly, not just thrown off a truck at your front door. So, this part of the qualification or validation of the system is concerned with the installation.

The initial system configuration, the RFP, and an outline of where the system components are to be sited and connected are used to write an installation plan for the new LIMS. The installation of the major system components is usually undertaken by the vendor's staff and the job completed and tested by them. However, when components are connected to the organization's infrastructure (such as a network or other computer applications), the roles and responsibilities should be discussed and agreed between all parties (again this might be an area for inclusion under contract discussions). The tests to be performed on each module of the system as it is installed are described in the *Installation Plan*. These tests may often be the standard ones that the vendor uses in all installations; occasionally they may include some specific ones from your laboratory or organization. The output of this process is an *Installation Plan* for the installation qualification stage.

The *Installation Plan* is used by the appropriate personnel to install the purchased hardware and software. When a module of the system has been tested correctly, it is signed off and the next module is installed and checked. As components are installed, a configuration log is completed to establish the components that comprise the initial configuration of the system. The outputs of the process are an *Installation Report* and a *Configuration Log*.

The second part of the qualification occurs after you have developed the system to your requirements.

Step 6: Develop Functions

It is unlikely that you will find a LIMS that matches your requirements fully. There will be some basic functions that every LIMS will perform, but some you will have to make or develop yourself. LIMS vendors provide tools to help you achieve these functions and these come in two main types: specific laboratory-oriented programming languages that allow you to develop laboratory-based functions; and programming tools that are available with the database used in the LIMS.

When additional functions are required they need to be specified in writing, then written and tested by laboratory staff, in-house computer staff, or the LIMS vendor. If you do this in-house, by whatever means, it should be done in a quality way and you should have documented procedures. An alternative approach to the traditional specification of the functions is to use prototyping. This starts with the specification; however, the user funtions are developed in an iterative manner with the programmer working in close collaboration to develop the functions.

Prototyping is an effective approach but it must be managed effectively, otherwise, functions can be developed and modified because "the screen does not look right". Equally important with prototyping is that the requirements specification is updated to reflect the latest version of the prototype.

You have two approaches with prototyping, either hacking code to achieve the functions or structured programming. The former is fast but when the desired system is reached, the operational system must be programmed from the start for a robust and maintainable system. Of course, when the management hears that the system is ready, there is pressure to roll out a prototype that is not intended for operational use. The latter approach is slightly slower but allows the programming effort to be maximized and the operational system to be ready to go when you have written the user documentation. You were going to write down how to use the system, weren't you?

When you have written and tested the additional LIMS functions, you can give it to the users. Or can you?

Step 7: Pilot the System

Rather than roll the system out to the whole laboratory and watch it fall flat on its face, I would suggest that you first pilot the system with a group of sympathetic and computer-literate users. The rationale with this approach is that any problems can be recognized and resolved before credibility is lost. For instance, new ways of working that look attractive on paper can be tried out on a small scale to see if they are effective. It is unlikely that a system designed on paper will work well at the first attempt. Something is usually forgotten and it is these details, sometimes large and sometimes small, that make or break the system.

I WOULD SUGGEST THAT YOU FIRST PILOT THE SYSTEM WITH A GROUP OF SYMPATHETIC AND COMPUTER-LITERATE USERS.

Another facet of a pilot system is to size the operational computer correctly. Vendors will size the computer hardware based upon an "average" laboratory (this is the well-known laboratory in Outer Mongolia, analysing yak's milk). This approach may be a start, but I would advise that performance requirements are written into the contract with the vendor, providing an upgrade path if they are wrong. Alternatively, you purchase the smallest computer you can run the LIMS on to develop the system and test its performance to size an operational computer accurately. This second approach has a number of advantages: hardware prices are falling and performance is rising, therefore you should save some money going along this route. You will also have two computer systems at the end of the project; the smaller system can be a development, evaluation, and training system. This can be used effectively before transfer of programs and trained users to the operational computer. A modification of the LIMS licence may be required to operate in this manner.

Step 8 Part II: Qualify or Validate the LIMS

This column is starting to look like a title from a Shakespeare play. The second phase of qualification is the operational qualification or validation of the completed system. This requires a test plan and test scripts written under the validation plan for the system. The test plan will investigate the critical areas of the system, such as data acquisition, manipulation, and calculation, and also reporting of results. A number of test scripts should be written, based on the current requirements specification, the prioritized functions, and the tests used to evaluate prospective systems. The number of test scripts will depend on the complexity of the LIMS, the number and type of instruments linked to it, and the number of other computer applications interfaced with the system. The test scripts should cover the way the system will normally be used and how to resolve common problems encountered during the laboratory operation. You should look at testing with normal, boundary, and out-of-limits data.

It is important to realize that the validation must be performed in the same way that you use the system. As you have purchased a configurable system, you may have developed a LIMS that is unique. For this reason, you can never purchase a validated LIMS, or any system for that matter. If you use the LIMS without any custom programming, you will have to populate the database with your own methods and analytical approaches;

again this may be unique.

You should be able to rely on the work done by the vendor in developing a system (subject to an audit), but never rely on a validation certificate from a vendor. It is, in my opinion, misleading and wrong to sell software in this way. Systems can be certified or verified by a vendor but never validated. That is the end-users' responsibility.

When the testing has been completed, a summary report is written about the qualification testing and the whole life cycle, summarizing all the validation activities performed during the project. Inputs are all the documents produced during the projects, such as the requirements specification, the RFP, the review of the vendor's quality procedures, and the test scripts and reports produced during the qualification process. Note that I use the phrase summary report; this is deliberate. Too often validation is used as an excuse to fell large areas of forest; a summary report should be exactly that — a summary of the validation or qualification effort.

The summary report is authorized by management and should contain a statement that a system is released for use in a GXP (a summation of GMP, GLP, and GCP) environment.

That's all there is to a LIMS project really, except for the users. The next instalment will look at reasons why "user" is more that just a four-letter word.

References

(1) *Guideline on General Principles of Process Validation*, Food and Drug Administration, May 1987.

(2) Good Laboratory Practice Consensus Document: *The Application of the Principles of GLP to Computerised Systems, Environment Monograph Number 116,* Organisation for Economic Co-operation and Development (OECD) Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 10, Paris, France, 1995.

(3) *GAMP, Good Automated Manufacturing Practice, Pharmaceutical Industry Supplier Guidance for Validation of Computer Related Systems in Pharmaceutical Manufacture*, UK Pharmaceutical Industry Computer Systems Validation Forum, 1995.

(4) R.D. McDowall *LC·GC Int.* **7**(7) 386–388 (1994).