



LIMS interfaces

To obtain sufficient tangible benefits from a Laboratory Information Management System (LIMS), the system must be interfaced to analytical instruments inside the laboratory and to other applications of the organization it serves. Not to interface a LIMS is a waste of time and effort. In this column we look at the interfacing of analytical instruments and systems to a LIMS and also a LIMS to other systems. As this issue of Scientific Data Management is focusing on LIMS, we will also discuss approaches to validating such systems in the pharmaceutical industry.

The role of a LIMS

A Laboratory Information Management System (LIMS) is unlike any other piece of laboratory automation equipment available to the analytical chemist. It can provide benefits both within the laboratory and outside it. Thus, a LIMS has two targets:

- the laboratory — the information generator
- the organization — the information user.

The problem is how to site and implement a system so that it hits both targets effectively.

Figure 1 shows an outline of the high-level functions that a LIMS should undertake. The diagram shows a LIMS sited at the interface between a laboratory and an organization. Samples are generated in the organization and logged into the LIMS, the samples are analysed within the laboratory and data are produced and reduced within the LIMS environment to information, which is transmitted back into the organization. Figure 1 represents the ideal siting of the LIMS: both the organization and the laboratory benefit.

The line dividing the organization and the laboratory shows that the system is of equal benefit to both parties.

However, there are two other implementations that are possible with a LIMS, which result in different positions of the interface between the laboratory and organization. Figure 2 shows the more common implementation. This is probably typical of the majority of early implementations of LIMS in the 1980s. The main functions carried out by the system are the same as in Figure 1 but the emphasis of the implementation is different. The boundary between the organization and the laboratory has been moved up and the benefit of the LIMS is almost exclusively that of the laboratory with little payback for the organization. Here the LIMS is a toy for the laboratory

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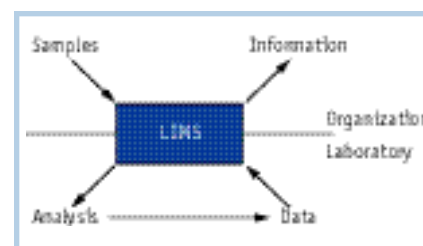


Figure 1 The ideal siting of a LIMS.

that few others are allowed to play with. The system is built from the bottom up with no consideration for anyone outside of the laboratory.

The rarest alternative LIMS implementation is presented in Figure 3. This is the top-down approach, where senior management — or worse the information technology group — has decided that a LIMS will be implemented. There has been little consideration for the laboratory, only the organization. The analysis and data gathering functions of a LIMS within the laboratory have been ignored, which allows the staff the latitude and the excuse to develop their own alternative local processing solutions. This system requires additional work by the staff to ensure its success, in addition to the normal analytical function. The likelihood of failure with such a system is much higher than with the other two forms of implementation.

As can be seen when comparing the three alternatives, there is a balance to be found between the needs of both the organization and the laboratory. The division of functions between the two must be carefully defined. However, the initial implementation should be towards

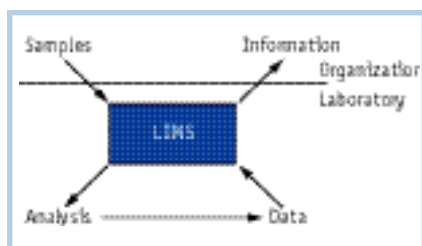


Figure 2 The bottom-up implementation of a LIMS.

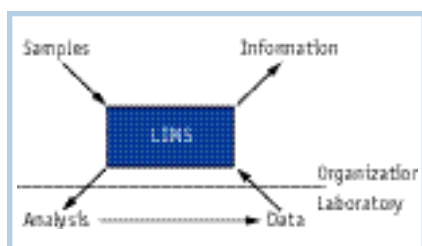


Figure 3 The top-down implementation of a LIMS.

the analytical laboratory, the information generator. Automating the information generator is the key to success for the whole LIMS.

This approach requires interfacing for rapid information and data transfer. Within the laboratory, instruments are interfaced to the LIMS to automate the data gathering process. Outside the laboratory, the LIMS is also interfaced to other systems to deliver the information rapidly to the decision-makers.

Interfacing options

There are three basic interfacing options available when you consider data input and output for a LIMS:

- No interfacing: here data are transferred manually between the instruments and the LIMS and from the LIMS to other systems outside of the laboratory. Not every instrument needs to be interfaced as this depends on use, data volumes and business need, and not every LIMS needs to be interfaced outside of the laboratory for the same reason.

However, to automate a laboratory with no interfacing is to create an island of automation in a sea of paper. You are merely automating the status quo with little or no business benefit and poor return on investment. Manual operations and repetitive transcription error checks must be eliminated to provide the productivity and cost savings needed to pay for the LIMS. Manual data entry should not be forgotten as it can be useful in an emergency, but for routine use it is not recommended.

- Unidirectional interfacing: this involves the transfer of data from an analytical instrument to the LIMS or transfer of data and information from an external system to or from the LIMS. This method of interfacing provides some immediate business benefit by eliminating the majority of transcription error checking and

post analysis reporting. However, the instrument is still set up manually, although with modern data systems instruments using copy and paste functions can reduce this task.

- Bidirectional interfacing: as the name suggests there is two-way communication with the instrument or system. For interfacing of analytical instruments to a LIMS, set-up information and run sequences are downloaded into the instrument from the LIMS and, after analysis, analysis information is transmitted back to the LIMS.

For applications outside of the laboratory that may interface with a LIMS, we could be looking at production information and sampling information for both clinical trial material or production batches being downloaded from an Enterprise Resource Planning (ERP) system. Once the whole analysis is complete, analytical batch release information is transferred to the ERP system for linking with the batch records for formal release.

Instrument interfacing within the laboratory

Interfacing analytical systems used within the laboratory is a major area where business benefits can be obtained with a LIMS. The benefits case is usually better (i.e., larger sums can be calculated) where the laboratory is essentially manual and there is little electronic data transfer between instruments and the LIMS.

Some typical instruments for interfacing are

- Analytical balances: these are usually interfaced unidirectionally to transmit weighing data or single discrete values to the LIMS. The operation to be automated can involve just a single weighing of the weight of material taken (after the weighing vessel has been tared off-line) or the whole process from the

taring of the weighing vessel through to the final weighing of the material. More complex interfaces can link the weight taken of analytical reference standards to stock control records and calculations based on weights, for example, loss on drying. Some bidirectional interfacing is possible to feedback results on loss on drying (i.e., within expected results or the sample must be returned to the oven for a further period).

The interface between the balance and the LIMS could also involve barcoding samples and standards as a means of rapid data entry running in parallel with the instrument interface, for example, sample identities or instructions.

- **Chromatography Data Systems (CDS):** A CDS can be interfaced either unidirectionally or bidirectionally depending on the laboratory's requirements. One issue to consider before interfacing is the nature of the CDS: are there a number of standalone PCs that would have to be interfaced individually or is there a networked data system that would require just a single interface? The simplest approach is a networked data system for speed of interfacing, control of data transfer and reduced validation cost (see Figure 4).

The download of a LIMS worklist to the CDS can be converted into a sequence file that should enable the CDS to be set up for a specific analysis. The worklist file can detail the LIMS number, sample identities, any weights of samples, order of analysis and any replicates involved. If this process were just unidirectional, then the download information would have to be input manually.

Post analysis and integration, a data file can be uploaded to the LIMS. Usually this will contain a LIMS number, sample identities and the required results information (analyte concentrations or amounts). However, more information could be transferred such as quality control results if used, standard information and results, system suitability data results and raw data file identity, but only if the laboratory requires this information to be held centrally in the LIMS.

With some systems interfacing a CDS can be taken a stage further if required. When reviewing a specific result in the LIMS it may be possible to view the corresponding chromatogram in the data system by spawning the CDS software from within the LIMS. This would certainly

help an analyst to review results more efficiently and quickly make decisions about accepting or rejecting a run.

- More complex analytical instruments, for example, spectrometers, are more difficult to interface with a LIMS as the data to be transferred are usually spectral. However, using standard file formats there are readers that can be used in conjunction with a LIMS to have read-only access to a data file as described with the CDS system above.

Interfacing to external systems outside of the laboratory

There are many systems with which it is possible to interface a LIMS. The options used will depend on the siting of the laboratory (research, research and development [R&D] or manufacturing). We will look at interfacing to other applications rather than extending the LIMS into areas outside of the laboratory, which is another story.

Let us look at the various interfacing options that are possible for virtually any laboratory.

- **E-mail:** linking a LIMS to an organization's e-mail system can allow the delivery of interim and final results to clients. E-mail is essentially a transport mechanism that could be used as an alternative to, or as well as, paper for reporting.
- **Intranet:** a laboratory could use a browser interface either standalone or attached to a corporate intranet to allow all clients within the organization to look at final results and download them for further work (e.g., statistical analysis if required within their departments).
- **Internet:** contract laboratories carrying out work for external organizations could use the Internet to communicate results from the LIMS. Alternatively, pharmaceutical companies could liaise with the contract laboratory in a number of

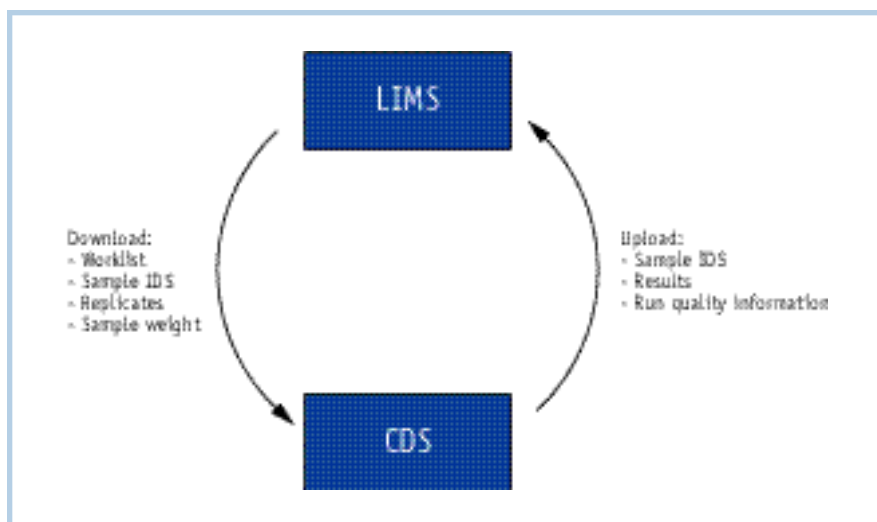


Figure 4 Chromatography data system interfaced with a LIMS.

ways such as submitting and requesting analyses and receiving updates. Care needs to be taken in this area as security is a major issue, especially after the publication of the final rule on electronic signatures and electronic records (Federal Register, 21CFR11, March 1997). Here we need to consider digital signatures and encryption to ensure that changes are not made to documents and results etc.

Laboratories operating within manufacturing may want to interface with a number of applications. The major question with these large systems will be how would the interfaces work: which application is the master and which is the slave or subordinate? In general, the master application will be the one that is external to the laboratory, as this usually has a greater business impact (see Figure 5).

Typical examples in this area could be

- Enterprise Resource Planning (ERP) systems: as typified by SAP R/3, these systems are intended to automate the whole of an organization from production planning, manufacturing, logistics, materials management, human resources and quality. Many LIMS are now being interfaced to ERP systems in a bidirectional manner.

Information about production schedules and sampling activities is passed to the LIMS and logged in. Samples are taken and received in the laboratory, analysed and compared against the analytical specification. The certificate of analysis is then transmitted to the ERP system for collating with the batch records from the Manufacturing Execution System (MES) and a decision taken on final release of the manufactured batch.

- Manufacturing Execution Systems: an MES is used for executing the manufacture of batches of material (instrument control), recording the materials used and recording the

conditions and yields etc. In-process samples may be taken at important stages of a reaction or at the end of specific stages and analysed.

Therefore, interfacing between the MES and a LIMS would enable the go/no-go decision from the results of an in-process sample to be set in motion sooner than with paper or manual systems.

- Document management systems: these could be used for collating material throughout manufacturing (and also R&D) to make manufacturing summaries easier. Reports from a LIMS that concern method validation or analysis could be exported to a document management system for collation and incorporation in higher level reports.

When a LIMS is sited in an R&D environment, there tends to be a more diverse range of systems and applications that it could be interfaced with. Some of these systems could be

- Pharmacokinetics analysis software for further analysis of bioanalytical data.
- Clinical Data Management Systems (CDMS) for transfer of data concerning human clinical trials.
- Toxicology Data Systems as above but for animal studies.
- Clinical trial supplies and logistics software for formulation and drug development.

- Molecular modelling and chemical diversity software for combinatorial chemistry.

- Statistical analysis packages.

The key item to consider in all of the external systems and applications that could be interfaced with a LIMS is the business needs for the linkage. What are the problems that must be solved and how will the organization benefit?

Validation of LIMS interfaces

Why validate?: The rationale for validating the interface and indeed the whole LIMS installation is driven from a regulatory perspective: you must validate to stay in business. My view is that you should think of validation as investment protection — you want to validate the system to ensure that it meets your business needs. If you take this approach, the additional time and effort — best practice is about 10% additional cost — is investment protection, as approximately 50% of LIMS installations fail to meet initial expectations.

Therefore, the benefits of validation far outweigh the costs.

Specific regulations for validation:

This will be a very selective look at the regulations surrounding the pharmaceutical industry and their need for validation. The overall definition of validation is usually taken as: "Establishing documented evidence which provides a high degree of

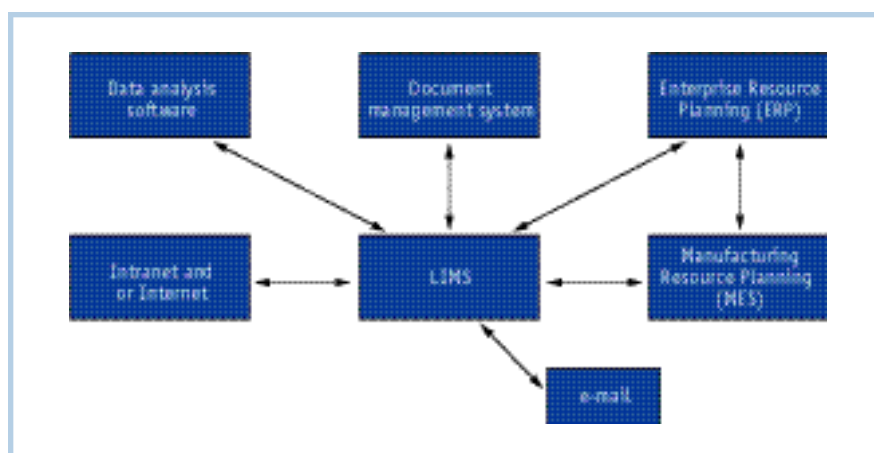


Figure 5 External interfacing options.

assurance that a specific process will consistently produce a product meeting predetermined specifications and quality attributes" (FDA Process Validation Guidelines, May 1987).

The key phrases in the definition are "documented evidence" and "predetermined specifications". Therefore you will need a User Requirements Specification (URS) that describes the interface in sufficient detail to construct the tests to confirm that it works correctly throughout the specified operating ranges.

Other regulations can be helpful in determining an approach:

- "The degree of validation depends on the use to which the system is put and if it incorporates novel elements" (EU GMP Annex 11). Therefore you can start to construct an argument that is based upon whether you use a commercially available product or have made your own interface that is unique.
- "Hardware must be properly specified to meet requirements for which it is intended and the amount of data it must handle" (Good Manufacturing Practice guidelines, 21 CFR 211.163). Here you will need to know your working practices and the associated metrics: how often, how much, maximum numbers.

Scope of validation: It is important to realize that you cannot validate every function of a system, and therefore you should be concentrating on the critical functions based around your working practices. Knowing your working practices is critical to defining the user requirements, which in turn is critical to designing the test cases to validate and hence key to the success of the validation effort. In short, if you don't know how your laboratory and company works, there is little point in starting the project.

To define the URS for any interface, you will need to know the data to be transferred from one system or

instrument to the LIMS, the volumes of data, frequency and the format of the files to be transferred etc. Will you want the transfer to be in real time or in batch mode? These requirements must be formalized and written down.

Prototyping is a good way to visualize and develop these requirements further.

When written and approved, the URS is the basis for developing the interface testing approaches. Some typical areas to consider are

- Have the data been correctly extracted?
- Have the numbers changed during the transfer?
- Are there any rounding errors between the original system and the LIMS?
- Have the data been put into the correct place in the LIMS database?
- What is the impact of network traffic and availability?
- What happens with replicate analysis or repeat analysis?
- Is the sequence of analysis correct and has no transposition occurred?
- Has the system been tested to fail with common problems?

White-box or black-box testing?:

The testing approaches that can be used in validating an interface are classified as either white box or black box.

White-box testing refers to the situation where the design for the code and the coding itself are known (i.e., transparent) and the testing can be explicitly designed to test specific algorithms and functions. Individual code units can be tested, the same can apply to modules and the whole system. Normally the developer of the interface would undertake this if we were dealing with a commercial interface package. White-box testing is essential if you have developed your own interface design.

Black-box testing refers to the situation where the specific design, coding and algorithms used by the system are unknown and only the inputs and expected outputs are known.

This is the only feasible approach when dealing with a commercial product.

Summary

Interfacing a LIMS to analytical instruments inside the laboratory and, where appropriate, to systems and applications in the organization is essential to make the LIMS cost-effective. Moreover, interfacing ensures that the laboratory is effective within the organization and ensures that the LIMS is capable of delivering the required analytical information in a timely manner to make decisions.

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