Applications of LIMS to Stability Testing

Managing pharmaceutical stability testing can be very demanding, especially on small- to medium-sized companies developing and producing OTC, generics and new Rx products. Some companies outsource the actual inventory management and testing requirements, but they are still required to track progress and report results as part of their QA or development process and will need to meet guidelines set by regulatory bodies such as the FDA and International Conference on Harmonization (ICH). Laboratory Information Management Systems (LIMS) provide a powerful way of managing and reporting the outcome of these studies.

LIMS can be implemented in all types of pharmaceutical laboratories from QA/QC and R&D laboratories to laboratories analysing clinical trials of novel pharmaceuticals. Stability testing, however, is a particularly interesting application of LIMS. Ensuring that approved protocols are followed precisely, with "pulls" made on schedule and the appropriate tests completed, can be time-consuming and tedious tasks. Some stability managers and supervisors use Excel™ spreadsheets to store and track this work, but this approach lacks the necessary security and audit trail to comply with FDA regulations, including 21 CFR Part 11. In addition, as the information is contained in individual spreadsheets, reporting on complete studies and batches is difficult and often must be done manually. LIMS can overcome these problems. 21CFR Part 11 requires change control, validation and audit trailing of changes to the system and the data that it holds. Yet today's laboratories must be able to offer the flexibility to adapt and change their processes and workflows when necessary, and their LIMS must stay in step with these changes. Larger organisations may opt for a fully configured LIMS for stability studies, but some companies may prefer to implement a "stand-alone" stability system rather than a full-scale LIMS.

The Stability Testing Process

A stability study measures the shelf-life of a given product by testing a series of samples stored in environmental chambers to simulate accelerated testing. Tests are conducted for samples stored under varying conditions and for varying lengths of time, since product stored in a warm, bright room might expire sooner than the same product stored in a cool, dark environment. The requirements for stability testing are described in 21CFR211.166 (Revised as of April 1, 2012):

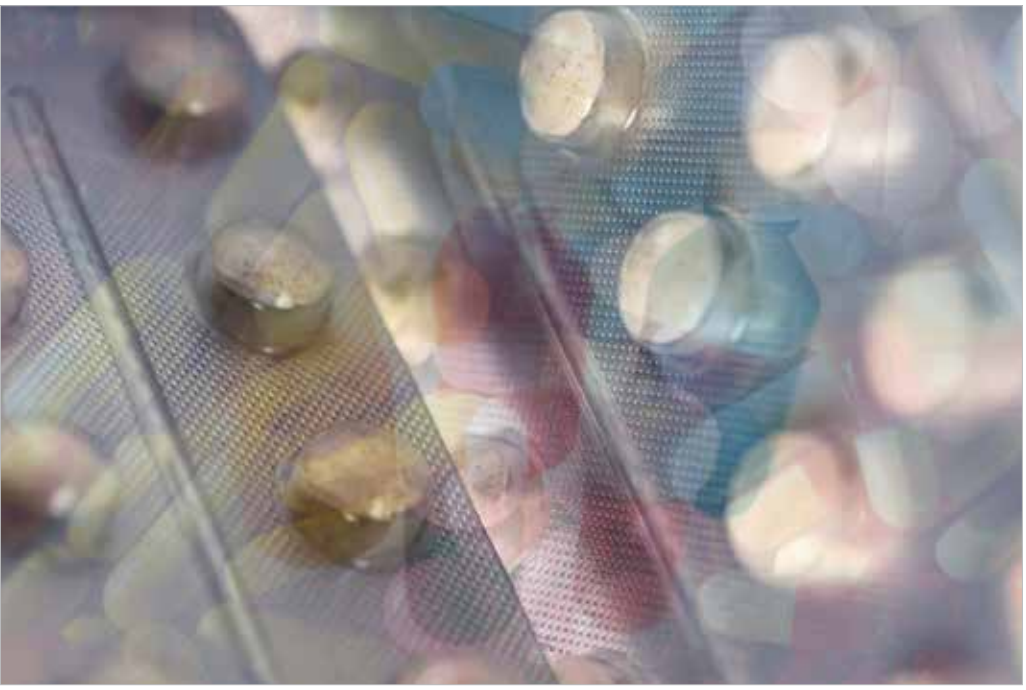
(a) There shall be a written testing programme designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written programme shall be followed and shall include:
  (1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
  (2) Storage conditions for samples retained for testing;
  (3) Reliable, meaningful, and specific test methods;
  (4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;
  (5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labelling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf-life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf-life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:
  (1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
  (2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labelled "No U.S. Standard of Potency" are exempt from the requirements of this section.

Stability studies are required at different stages of the product life-cycle. Initial stability studies are required for product registration purposes and set shelf-life, storage conditions and specifications.



Follow-up (commitment) studies occur after registration to verify the registration data, and then there are ongoing studies after registration and marketing, to prove that conditions are still valid. The latter is generally required for all licensed medicinal products on the market, and will cover each product, dosage and primary package type.

Use of LIMS in Stability Measurements

Clearly stability testing is a major undertaking, requiring the management of significant amounts of data from a variety of sources. In addition, clear, cohesive reporting of stability testing results is required, both for dossier submission and for ongoing studies. The use of an appropriately configured LIMS or stability module within a LIMS can automate and control the entire operation of the stability study, including:

- Protocol creation
- Study initiation and management
- Inventory management
- Sample login scheduling
- Future workload reporting
- Stability study reporting

This approach simplifies the whole study management process. Critical components in the study include sample actions, time points and storage locations. The three key types of action that a sample will experience in a laboratory are testing, moving and non-moving. Testing requires withdrawing the required quantity of sample to perform whatever analytical tests are required. Moving actions cover transfer of samples from one condition to another, whilst non-moving actions cover in-situ activities such as freeze/thaw or shaking. Use of a stability LIMS can optimise the number of samples to be stored for a study, thus avoiding shortages and waste, as well as saving staff time by automatically registering pulled samples with test and limits. In addition, full management of storage room locations increases efficiency.

Typical Stability LIMS Components

A well-configured stability LIMS will address all the key functionality of stability testing:

a) Protocol Design

Protocol design allows information concerning the study such as the purpose of the study, the identity of the study director, location, product, etc to be stored. Typical requirements may include each study having multiple batches with multiple conditions upon each batch. Batches may need to be initiated on a different date from a different production batch, with different raw material suppliers, or may be required because of packaging or dose changes. Batches in development may be caused by formulation or packaging changes. Good protocol design accommodates FDA and ICH guidelines, including matrixed protocols and standard room temperature, accelerated and intermediate conditions.

b) Storage Room Operations

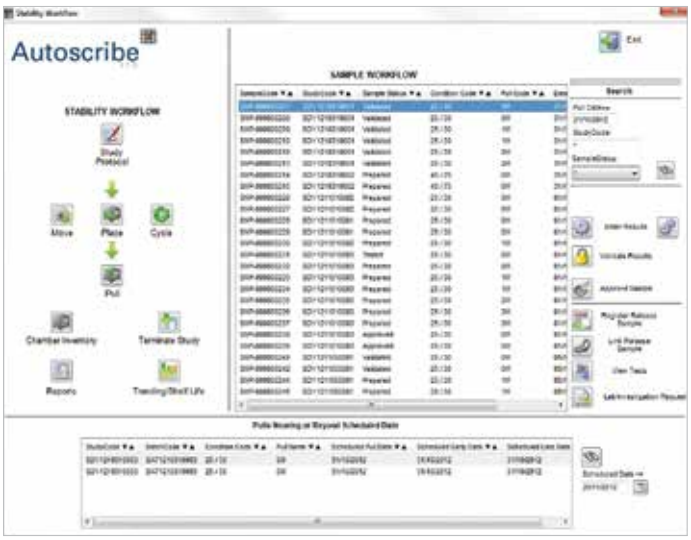
Stability storage room operations should be appropriately managed to include planned start dates for each batch as well as the placement date and any cycles or moves required. A typical “cycle” might be to invert the container every three months or to turn the light in the chamber on and off at preset intervals. A move is defined as when the containers are moved from one condition to another. Unplanned or emergency moves required by chamber failures should be recorded. The exact location of each batch (room, chamber, rack, shelf, box) should be stored for every condition. All actions such as placements, pulls, moves, cycles, relocations and scrapping should be recorded with the actual time and date, and

the ID of the person completing the action. These values may be compared to the planned dates to identify any problems or changes. Work lists may be generated for storage room staff, showing what tasks are required during the period.

c) Inventory Management
Good inventory management will ensure that there is enough material in storage to complete the study, without generating large amounts of waste. This can be done by calculating the number of sample containers of each batch that must be placed at each condition in order to execute the protocol, taking into account factors such as the number of pulls, the amount of sample in each container, the amount required for each test, and whether replicates can be performed on the same sample.

d) Recording Test Results
By storing test results for each batch, condition and time point in a results database, limits can be set up for each test at each condition/time if required. The results database can provide a full audit trail so that if any value is changed once it is stored, the original value is not lost, but stored before the new value is accepted. The identity of the person making the change, the time/date and reason for the change should be recorded along with the new value. Historical versions of all results can be readily made available for investigation.

e) Reporting
Standard reports include the protocol and batch status, placement and pull lists, tests required, summary reports that include test results to date and an OOS report. Typically reports may be exported in many different formats including Excel™, Word™, HTML and more for inclusion into other documents. Statistical analysis is also extremely useful, which may include shelf-life projections or accelerated shelf-life calculations using the Arrhenius equation. The results to be analysed can be selected from study, batch, condition, date range, test and component, with the resulting plots and graphs stored and integrated into final reports.



LIMS workflow for stability testing

f) Regulatory Compliance
The system should assist in compliance with 21 CFR Part 11, for example to accommodate the implementation of an electronic signature, whenever it is deemed necessary (such as when editing a specification, amending a test or changing a test result). User authorities should be individually defined, controlled by a unique user ID and password combination. Password rules should include, for example, the minimum number of characters in a password and an agreed expiry date to ensure regular re-allocation of passwords to all users.

Configurability

It is clear that LIMS can make a considerable contribution to managing stability studies, but given the sheer range of studies that may be required, the system needs to be configured to the particular application. Most LIMS are configurable to some degree, however, depending on the particular system, a programmer or other IT person would need to write scripts or new custom programs to design new screens or link menus in different ways to support different workflows. Some LIMS, however, use exactly the same core program suite but feature a configurable 'layer', or set of configuration tools that allows each system to be set up to exactly match user requirements. This makes the process of configuration much simpler for the supplier, and less time-consuming for the user. In fact, this approach even offers the user the possibility to be involved in the configuration process.

Validation

Computer systems, software and instruments regulated by authorities such as the FDA require "validation". Each company must decide how to carry out the validation of the LIMS. One approach is to carry out the validation internally, providing there is a qualified person available. An alternative way is to utilise the services of a qualified validation specialist (often organised by the LIMS supplier) who will make on-site visits to both gather the necessary information and carry out the validation before producing a report.

John Boother Managing Director at Autoscribe Ltd, has had involvement in around 5000 LIMS projects. Autoscribe is a UK-based global supplier of LIMS to both the laboratory and the wider business markets, with distributors in every continent offering localised technical support. Visit www.autoscribe.co.uk for more information.
E-mail:john.boother@autoscribe.co.uk.