HCL

Computer System Validation– an Integral Part for Effective Laboratory Automation Service

WHITE PAPER

1. Abstract

Validation Service has now become an integral part of Lab automation Service, specially in the area of Pharmaceutical Industry. Objective of this service is to validate whether the defined purpose for which Lab Automation Project has been undertaken is met or not. In case of Pharmaceutical Industry, this service often considers general rules and guidelines as was laid down by United State's Food and Drug Administration Act (US FDA). This whitepaper intends to explore various methodologies used for this validation service, challenges faced and how HCL uses the expertise to offer state-of-the-art validation service to industries as a part of its Lab Automation Service offering.

2. How Computer System Validation (CSV) Service evolves?

The concept of validation was derived from engineering principles of validation of mechanical system that has been extended to the software industry. Software engineering comprises the core principles consistent in software construction and maintenance: fundamental software processes and life-cycles, mathematical foundations of software engineering, requirements analysis, software engineering methodologies and standard notations, principles of software architecture and reusability, software quality frameworks and validation, software development, and maintenance environments and tools.

To extend it further during mid 1970's, Ted Byers and Bud Loftus, two Food and Drug Administration (FDA) officials first proposed the concept of validation in order to improve the quality of pharmaceuticals (Agalloco 1995). The first validation activities in 1995 were focused on the processes involved in making these intended pharmaceuticals product only. However, immediately user community realized the utility of validation service and did not hesitate to spread across this concept to associated processes like environmental control, media fill, equipment sanitization and purified water production and these days it has extended to validation of Computer System in the area of Quality Assurance of desired products.

Feeling the necessity of Validation, FDA published a guide to the inspection of Computerized Systems in Pharmaceutical Processing, also known as the 'bluebook' (FDA 1983). In recent past, American FDA and the UK MHRA have added sections to this 'Bluebook' specifically to address the need of Computer System Validation. For MHRA this is Annex 11 of the EU GMP regulations (EMEA 1998), whereas for American FDA, this is 21 CFR Part 11 for rules on the use of electronic records, electronic signatures (FDA 1997).

According to both American FDA and UK MHRA, computer system validation is defined as *"Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled"*

As the demand of this service is increasing consistently, Information Technology Service Provider companies are also no exception to realize this need. This results the formation of a separate Centre of Excellence on this Validation service at these companies. Most of them are now integrating validation service as a part of software service offering specially in Life Science and Healthcare field, more preciously in Laboratory Automation area. This will be discussed in detail in the next section. Pharmaceutical Companies on the other hand finds this combined service very much cost effective. Outsourcing of this validation service to these companies adds three key benefits to Pharmaceutical Industry house, namely, neutral 3rd party authorization of implemented software, ease of availability of regulatory audit documentation and reduction in dedicated in-house manpower for regulatory compliance.

3. Lab Automation & Validation Service

Laboratories in an Enterprise today are facing lot of challenges in order to remain competitive. These challenges are a result of a combination of market forces, including cost-restraint measures from the managed care industry, and an overall move toward containment of national healthcare costs.

As pressures increase for labs to become more productive and cost-efficient, they are forced to look more closely at their internal

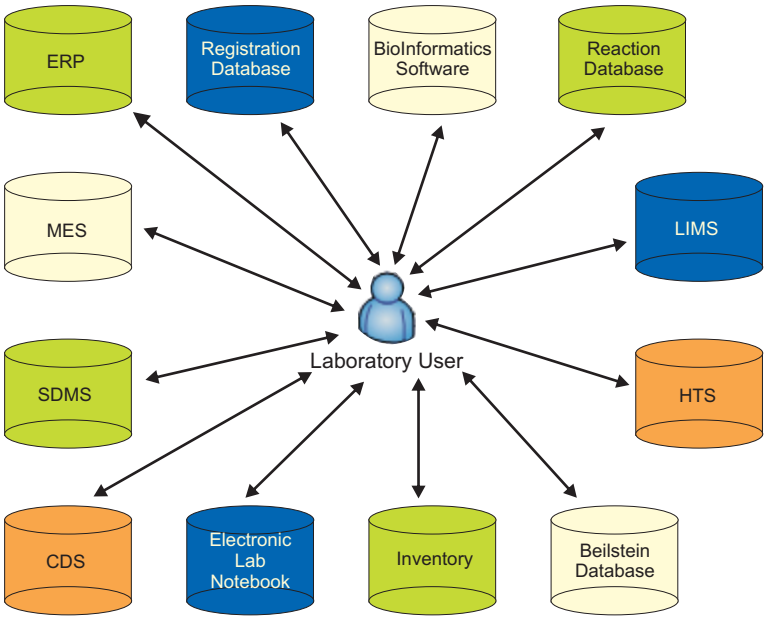
processes for ways to increase productivity with smaller budgets. In order to survive in the future, it will be necessary for labs to adopt as many of the following strategies as possible:

- Run more tests with existing infrastructure.
- Speed in data acquisition from analytical instruments with accuracy
- Retain lower operating costs.
- Use more automation in a paperless environment.

The answer to this challenge is Laboratory Automation. By definition *"Laboratory Automation is a multi-sphere algorithm to research, develop, optimize and capitalize on technologies in the laboratory which enable new and improved processes, generate higher ROI and improve end-user satisfaction."* It helps in

- Availability of data on demand for better decision making
- Enhancing time management,
- Higher ROI , Productivity and Data quality

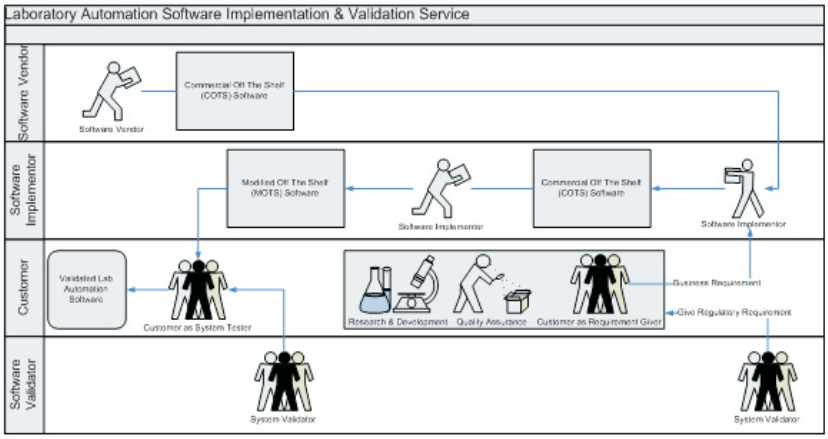
Lab Automation indicates appropriate and timely harmonization of different laboratory centric software to deliver defined service. These are like LIMS (Laboratory Information Management System), ELN (Electronic Laboratory Notebook), SDMS (Scientific Document Management System), CDS (Chromatographic Data System), ERP (Enterprise Resource Planning), MES (Manufacturing Execution System) etc.



In Pharmaceutical Industry, laboratories like Research & Development along with Quality Control & Assurance play a key role to ensure timely delivery of drug moiety to the market and production of those as per guiding specification & standards. Needless to say, software plays a key role in managing information related to these activities. Therefore, it is very important to make sure software used in Laboratory Automation are adhering to the International Rules & Regulation as like US FDA or UK MHRA before those are used for their intended purpose. Following is the list of some Validation Guiding Specification commonly used in validating Laboratory Automation System:

- Guidance for Industry: General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- GAMP (Good Automated Manufacturing Process)
- PDA Technical Report 18, Validation of Computerized Systems
- 21 CFR 11
- 21 CFR 820
- ASTM E2066-00 Standard Guide for Validation of Laboratory Information Management Systems
- NRC Regulatory Guide 1.170 in compliance to 10 CFR 50
- 1012-2004 IEEE Standard for Software Verification and Validation

Validation as per FDA allows Pharmaceutical Users (Both Direct and Indirect) to methodically establish a baseline for control of the software used in the regulated environment. Whereas as per GAMP, "In the pharmaceutical and biotechnology industry, Validation (drug manufacture) refers to establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes" (from European Union Good Manufacturing Practices Guide, Annex 15). The following diagram explains the relationship between Laboratory Automation and Validation:



Depending on situation Software Vendor and Software Implementer are the same group. Software Validator may be played by the same group or may be outsourced to Information Technology Service Provider group.

4. Current Industry Scenario & Market Trend

As per IDC survey, Regulatory Validation Service will govern Information Technology spending at Pharmaceutical Industry to a significant extent. As per their survey, nearly one-third of individuals expected compliance-related IT spending to increase in 2005, while no one reported any anticipated decreases. This expectation was supported later in 2006-07 by other research studies. This trend is due in large part to the increasing number of regulations and the complexity of regulations such as HIPAA, 21 CFR Part 11, GxP and risk management expansions.

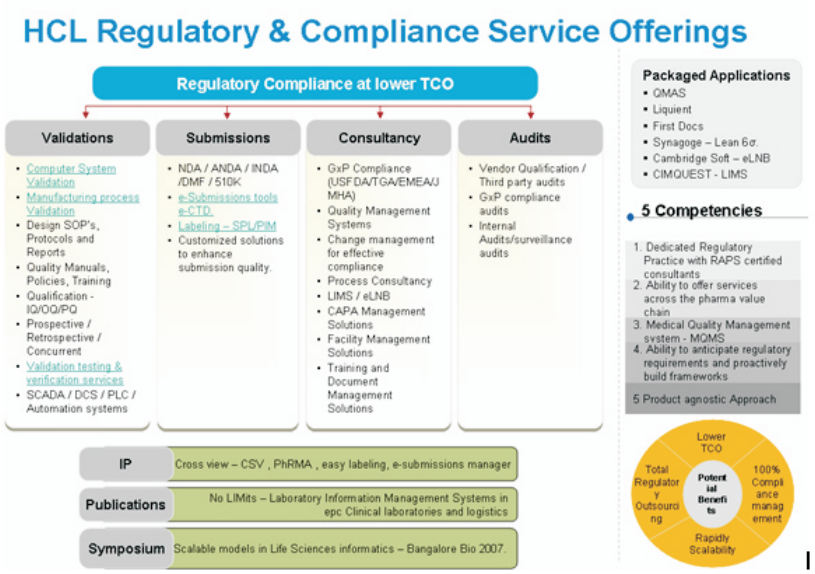
According to industry sources, Lab Automation service market is estimated to be 1 B$ by end of 2011 and Validation Service is going to contribute 10% to it. This results lab automation Validation Service to reach 100 M$ mark by 2011.

Validation Service within Laboratory Automation includes validation of Analytical Instruments as well. Now all most all Analytical Instrument makers take care of this validation service. Respective Instrument software handles Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) internally and there is a little scope of work left so far as Software Service Organization is concerned.

This leaves Software service companies to offer validation service only to package software like LIMS, ELN, SDMS and other bio-informatics software.

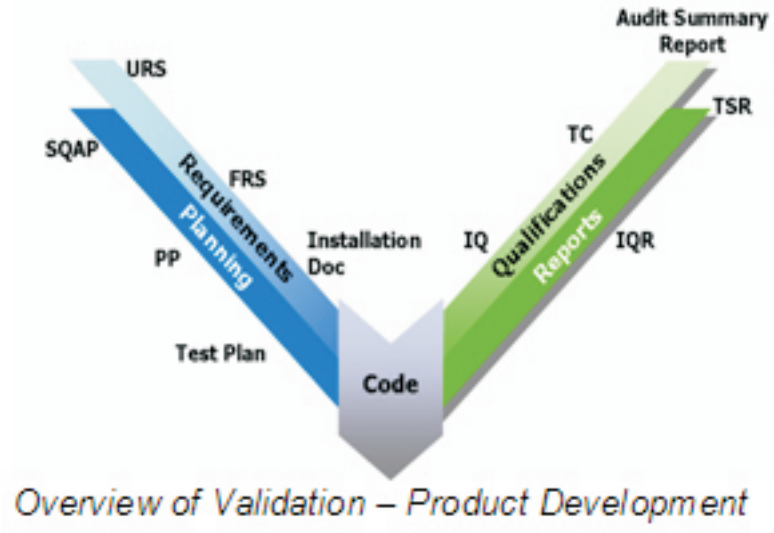
5. HCL'c Role in Lab Automation Validation Service

HCL has a strong validation practice as a part of its Life Science and Healthcare division. Funded by industry experts in the area of validation, HCL offers the following services:

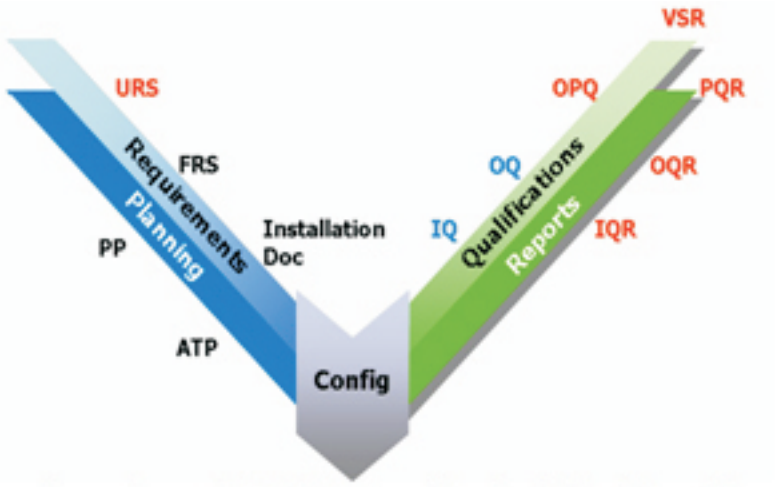


HCL offers Validations, Submission, Consultancy and Audit services as a part of its Regulatory Compliance Service Offering.

HCL uses traditional "V" model while offering Validation service to packaged laboratory automation software. This model can be used for both Software Development Validation and Software Configuration Validation. HCL, through its Validation Centre of Excellence, offers services to both these area. For both these cases, HCL performs Requirement Study and generate certain planning documents, whereas during validation exercise, some documentary evidences are generated. The following figures explain activities and output of both the phases.



Overview of Validation – Product Development



Overview of Validation – Product Configuration

As an example, for any COTS LIMS systems validation, HCL performs the following activities and generate the following outputs:

- Requirements Specification Review and GAP Analysis: We review the requirement specification as is laid down by the user community or LIMS Implementation Vendor. We also perform an AS-IS study to understand if there is any GAP with respect to requirement at present and which has been documented previously. If a GAP is identified, we document the same and validate it with respect to regulatory framework. Under some cases, these GAPs are also assessed based on merit and submitted in the form of Change Request to customer.
- System/software specifications: We also review the System/Software Specification to understand and document if there is any GAP with respect to Requirement Specification and System Design Document (SDD). This creates a Traceability Matrix to establish the link between the requirement specification and SDD
- Risk Assessment: This is a crucial stage as during this phase, we analyze process and procedure vis-à-vis COTS LIMS application to identify RISKs. While identifying, we also consider different guiding FDA / GAMP4 specification. This Risk Assessment document will later generate different Change Requests to the product Vendor or to internal Quality Assurance Team.
- Validation Plans (VP) : This often refers as Master Validation Plan and it documents Requirement / Plan under the following heads
  - Purpose
  - Concept of Operation

- Risk Analysis
- Environment
- Functional Requirement
- Software Design/Configuration
- Test Plan / Scope with indication of Exclusion Criteria
- Test Specification and Cases
  - Test Result Recording
  - Test Exception Handling
  - Test
  - Test Data
  - Test Result Analysis & Reporting
- Resources
  - Personnel
  - Facility
  - Schedule
- Version Description Information
- Operations/Maintenance/Training/User Instructions

- Installation Verification/Qualification (IQ) : This step also has further sub activities like
  - Development of Installation Qualification Protocol
  - Development of Installation Qualification Test Cases
  - Execution of Installation Qualification
  - Reporting Installation Qualification (IQR)
- Operational Verification/Qualification (OQ) & Performance Verification/Qualification (PQ) : Like Installation Qualification, these two steps also follow the similar process like creation of Protocol, Validation Test Cases, Execution of Validation and Reporting of Validation Results (OQR and PQR). However, in case of Performance Qualification, HCL prefers to have a Operational LIMS systems for a length of minimum 15 days.
- Validation Summary Reports (VSR): This report is a summary of finding of all individual qualification reports like IQR, OQR and PQR. This is considered as final deliverable to the requesting organization.
- Maintenance logs and change control requests: As was pointed out earlier, HCL validation engineer adds value to the validation exercise by not limiting themselves to submission of Validation Summary Report. They always try to find the deviation from regulatory perspective and maintain an Issue Log. This issue log generates Change Control Requests if requesting organization desires so.

This process may be different in case any GxP COTS system is intended for validation. However, before we discuss this aspect, let us understand what the core principle behind this validation

exercise is. A frequently overlooked element for COTS use is the end user validation requirements. We will now discuss the validation requirements for COTS software, provide points to consider during the product selection phase, some of the common pitfalls and misconceptions associated with COTS applications, and how to define the documentation and quality systems necessary to achieve and maintain an adequate validation status for a COTS system.

As we have discussed earlier, Validation of computerized systems used in producing, managing, and reporting data for pharmaceutical activities is required by the US Code of Federal Regulations, Title 21, parts 210 and 211, as well as in other related pharmaceutical areas. A recognized problem area in this software validation includes the end user validation requirements for COTS applications.

Two widely recognized references for computerized system validation, the PDA Technical Report No.18, Validation of Computer-Related Systems and the GAMP (Good Automated Manufacturing Practice) Guide for Validation of Automated Systems in Pharmaceutical Manufacture, present widely accepted and recognized validation concepts and procedures. These reports draw from the essential steps in the life-cycle validation approach, all of which should be evaluated and interpreted in any computerized-system qualification project. Much of the development, design, and test requirements are completed by the vendor; however, it is the end user's responsibility to verify that the vendor has provided the application in accordance with these defined procedures.

That is the reason while we carry out one such exercise; we put our primary focus to validation of End Users. HCL, with the help of Industry Expert take care this part with ease. As per GAMP4, approach to be followed during such as assignment will be

"The user should define validation procedures and requirements prior to performing qualification activities. These documents are the cornerstone documents in any validation effort, and they should be developed in clear, concise terms. Establishment of these documents will result in the development of concise qualification tests and verifications to demonstrate the proper functionality of all defined user requirements, business practices, and functional requirements for the computerized system.

Establishing policies and procedures to define responsibilities and requirements for any type of computerized systems implementation and ongoing support are essential. COTS applications range in complexity from the basic "one person" development/test/management systems to integration/implementation teams involving multiple departments, locations, third-party system integrators, and

defined cross-functional implementation teams. Implementing adequate quality systems and procedures for all levels of computerized system validation efforts should be completed to maintain the validation status of the computerized system."

For this reason, we take a facilitator approach during GxP Validation assignment. We look for documentation, evidence of Internal Audit system, evidence of appropriate certification of Internal Auditor from the performing organization etc.

6. Conclusion

Validation Exercise in the area of Laboratory Automation is an important step before the COTS software are used in the laboratory. Computer-related system validation, as defined in the PDA Technical Report No. 18, is "establishing documented evidence which provides a high degree of assurance that a specific computer-related system will consistently operate in accordance with pre-determined specifications." To accurately assess the validation status of a system, the validation requirements must be clearly defined and documented. Therefore, appropriate documentation of end-user requirement is a must for Implementation Vendor. Currently it has been noticed, vendors are not paying adequate attention to this step and this causes failure of COTS or MOTS (Modified off the Shelf) software implementation in the laboratory. Performing Validation is a retrospective analysis only, and we recommended this exercise to be performed during the period of Implementation only. In case, Validation is performed much after the implementation, robust Change Management System is a must to bring back operational system to normalcy, which is according to International guideline like FDA, GAMP etc.

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8. About the Author

Somnath Mukherjee is head of LIMS Practice at HCL Technologies Ltd. He has over 18 years of experience in the development of LIMS, its implementation and support services. Somnath has worked in almost all areas of LIMS, and he specializes in the area of interfacing LIMS with other software in an enterprise. Prior to joining HCL Technologies, he worked with LabVantage Solutions. Somnath has a post graduation degree in Chemical Technology and has written in multiple research publications on system automation