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LIMS – The Risk-Based validation option

An Assessment

WHITE PAPER

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Abstract

Risk-based validation requires that risks posed by software systems that may be detrimental to patient safety, product quality or data integrity, be managed. Conservative validation has been based on a generalized and simple but often over-cautious approach to human health risk assessment. Complete end-to-end validation of a software system may not be the most cost effective way forward.

The move by the pharmaceutical industry towards a risk-based approach of validation has been facilitated by FDA's significant initiative towards a scientifically-driven risk-based approach to validation.

Introduction

In times of increased competitiveness, ever-increasing regulatory mandates and global turmoil, pharmaceutical companies are striving to continually improve their operational efficiency. As such, almost all companies are looking to information technology to provide reductions in operating costs and increased efficiency by automating existing business processes. Laboratory Information Management Systems (LIMS) plays a key role in the pharmaceutical industry's efforts towards automation. In August 2002, the Food and Drug Administration announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. The new initiative was taken up with the following guiding principles in mind

- Risk-based orientation
- Life-cycle approach with the organization QMS
- Cooperation with International regulatory partners for harmonization
- Strong public health protection and safety considerations
- Enable FDA resources to focus on the most critical areas which are prone to health risks

In pursuing this new initiative, the US health agency has actively collaborated with other regulatory authorities, in multilateral, international forums, such as the International Conference on Harmonization There has been several key guidance documents from The International Conference on Harmonization (ICH), like the ICH Q9 (Quality Risk Management) and others. Together these form the foundation for a new methodology aligning drug development and quality.

While the risk based approach is applicable to all areas of compliance (systems, processes and people) this paper focuses primarily on software systems validation.

Business Challenge/Problem

Emphasis on regulatory compliance, full traceability, precise sample identification and tracking, documented corrective actions, established and controlled methodology (SOP document management), reproducibility and tamper proof information, are all challenges that are unique to the pharmaceutical industry that have required these companies to undertake lengthy and costly customization projects on the various software system used by their laboratories. One such example would be - the customization efforts on generic or off-the shelf laboratory information management systems (LIMS). Since these systems capture certain personal or sensitive information, it is crucial to test the strength of security of the application. Sufficient controls must be put in place to ensure that the security of the data is not compromised. Since most available LIMs application are web-based, accessibility and security can

be important issues to consider. On one hand organizations are required to give system access to their users around the world on the other hand there is a possibility of exposing their secured and sensitive data.

It has become extremely crucial to provide management with comprehensive information generated out of these systems and at the same time provide the assurance of security of their data. Considering the time it takes to bring a drug from discovery to market, data is perhaps one of the most important assets a pharmaceutical company has. As such, to ensure that these web applications works reliably and correctly under different situations these factors need to be accounted for and tested. Hence considerable effort needs to put for test planning and scripting. Test Cases are written to cover the different scenarios not only of functional usage but also technical considerations. Thorough and accurate validation of such systems is critical and is a regulatory mandate.

The approach that in order to satisfy regulatory expectations, everything should be validated all of the time, cannot be a justifiable case; in most instances validating everything, all the time may just be a waste of effort and hence time and money. The time required in validating software systems and validation's potential drain on resources is often seen as disincentives by organizations towards their validation efforts. Validation, as many would like to believe, is work which is not necessary and that it does not add value; it is an exercise in futility required to satisfy the FDA. Also there isn't a single method of validating the many software systems used by companies whose products are subject to regulatory requirements. Hence validation evolves as a costly and time-consuming exercise.

This is apart from the other typical challenge that would be common for all software applications that is - in most cases, by the time the application goes for testing, it has been in the development process for a considerably long period of time and the organization is eager to send it to the end-users. In these circumstances, finding "adequate" testing time remains a perpetual problem. Hence exhaustive testing is most often a rare possibility. This, in spite that testing could be the last step in the implementation/development life-cycle to ensure safety of the data and the organization before a software system is brought on-line and is considered usable in a cGMP environment

Determining how much testing is 'enough' and how "efficiently" that testing effort is to be allocated with respect to a software system has been facilitated by this shift towards risk-based validation.

Current Industry Scenario

FDA's definition of 'Validation' is broader than the way the term validation is commonly used in the IT industry. In the IT scenario, validation usually refers to performing tests of software systems against its requirements.

One reason why companies operating in the regulated environment resist from introducing software systems is the cost of installing and maintaining such systems. Apart from the initial cost of installing the system, there is cost involved in validating and revalidating the software system in order to make it fit-for-use in a cGMP environment. However, despite these challenges there is an increasing trend toward the use of software systems by the pharmaceutical companies for reasons of practicality and efficiency. FDA has facilitated this trend by promoting a risk-based approach to validation which if implemented efficiently can give considerable cost reductions in introducing software systems.

There are three practical interests behind the drive toward a risk-based approach to validation:

- Enables organizations to focus more closely on the areas of the software system that pose the greatest threat to product quality and patient safety, in the event of failure.
- Results in opportunities of financial-saving since cost of validation is reduced within the organization, and as a result throughout the industry
- The result of an industry-wide shift toward risk-based validation approach as compared to traditional validation gives the opportunity to introduce innovation, without adversely affecting product quality or patient safety.

It is common understanding that Risk-based validation is a method that will reduce the time and effort expended in validation, and therefore will positively impact productivity and profitability. Thus for industry, Risk-Based Validation represents the most efficient and effective combination of quality assurance and business sense. Also, this new approach has far-reaching implications for validation, which has always been considered as a regulatory compliance exercise with its major emphasis upon documentation. Regulated companies have discovered that compliance and Validation are not options – it's the law.

The Risk-Based Validation Approach

In the pharmaceutical industries context, risk can be defined as the resultant of the probability of occurrence of harm and the severity of that harm to the company and its shareholders and employees, regulatory bodies and the population at large, that is to say all stakeholders in the drug development process.

In "Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach" a Final Report in 2004, FDA had identified a risk-based orientation as one of the driving principles of the cGMP initiative and predicted that this approach will help focus where its inspections are likely to achieve the greatest public health impact.

The FDA guidance for industry for risk assessment recommends that software validation should be focused on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity.

The GAMP method advocates categorizing software systems and performing validation based on the extent of validation recommended for the category in which the software is placed - System-level assessment. As per GAMP, at a minimum a LIMS, could be software with standard interfaces and functions (Category 4 - relative low risk category). However, typically these systems are not used as-is, rather they are configured/customized to meet the requirements of the implementing organization, in which case it is to be handled as custom components (Category 5- high inherent risk)

Risks could also be assessed at the functional requirement level so as to focus validation efforts on those system functions that are at high risk with respect to data security and patient safety. Risk Assessment is done to determine the Risk Level of the Requirements in the system, in the case of adverse events related to the requirements. Risk Levels will help determine the scale of testing that is needed to be performed on that function. This requires the ability to approach the requirements at a system-level, in order to identify the generic risks as well as at a micro-level to identify the specific risks pertaining to that function. It is also important to ensure that involvement of individuals from various cross-functional disciplines within an organization is there, so that risks are assessed from the business, technical, regulatory and other aspects. However this may be an acceptable investment in view of the validation efforts saved thereafter.

Risk assessment exercise would essentially consist of the following steps:

- **Risk Identification –** what components/functions might fail within the system.
- **Risk Analysis** – components of the risk associated with failure can be Business, technical or regulatory
- **Risk Evaluation** – calculated on the basis of severity of impact, probability of occurrence and detect ability associated with the risk
- **Risk Prioritization** – Based on evaluation, the various risk elements can be prioritized as ‘High’, ‘Medium’ or ‘Low’
- **Risk Mitigation Strategy** – Decide on the precautions to counter the risk.
- **Monitor & Review Risk Assessment** – Review the risk assessment exercise on an ongoing basis and update, as appropriate.

The output of the Risk Assessment exercise may be a quantitative estimate of risk (Risk Score), depending on the risk evaluation methodology used, or a qualitative description of a range of risk (using qualitative descriptors, such as “High”, “Medium”, or “Low”).

SCALING TESTING STRATEGY AS PER RISK LEVEL OF THE FUNCTION WITHIN THE SYSTEM

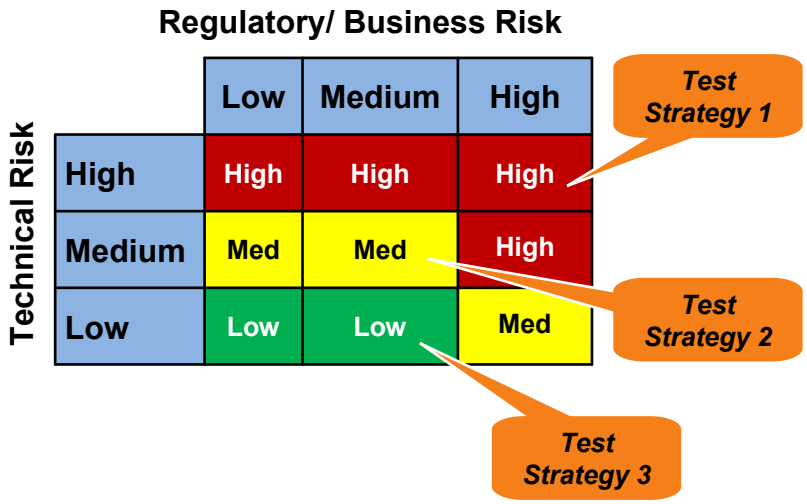

FIGURE-1

Example: if there is Requirement that has a high Impact if it fails, high Probability that it will fail (mainly if it is a configured or customized part of the application) and Data Integrity could be impacted if the Requirement fails, then the range of test activities on the function could include cross-functional testing with negative and boundary testing, in multiple test scenarios and/or datasets, along with performance testing, which may be part of Test Strategy 1.

If risk is in the medium category, that is failure of the function may indirectly affect patient safety or product quality or failure to demonstrate compliance may results in not so significant health hazard, or financial loss, then the functionality may be tested as part of Test Strategy 2, wherein it may be necessary to test for all positive paths but negative paths for only security tests related to the function, without using multiple scenarios.

If a requirement is considered less of Risk to fail, for example, a core part of the LIMS application that satisfies the requirement, testing may not even be necessary if the organization implementing the system is satisfied with the level and extent of testing the product organization performs on their product. Thus with necessary supplier involvement, independent validation of off-the-shelf functions and procedures may not be necessary depending on the accuracy and completeness of supplier documentation and the overall risk tolerance of the organization. In this case, even if validation is required, it may be as simple as a review activity, and not as complicated as designing a series of test cases with known input data and expected output that will verify that the function executes correctly within the system. That is to say, minimal testing/review on that said requirement could be conducted. That is to say, Test Strategy 3 could be adopted.

Once the risks are identified and evaluated, the Risk mitigation actions are determined, documented and followed through in the validation planning phase. The Validation Plan uses the risk assessment results to define and monitor the scope and rigor of validation enabling the organization to scale their validation efforts appropriately.

It is not only important to scale down testing efforts, but equally important to scale down the effort spent on the assessment process itself, according to the risks categories within the system, so that the time gained on reduced testing is not lost on doing unnecessarily exaggerated risk assessments exercise.

SCALING RISK ASSESSMENT EFFORT BASED ON IMPACT OF FUNCTION

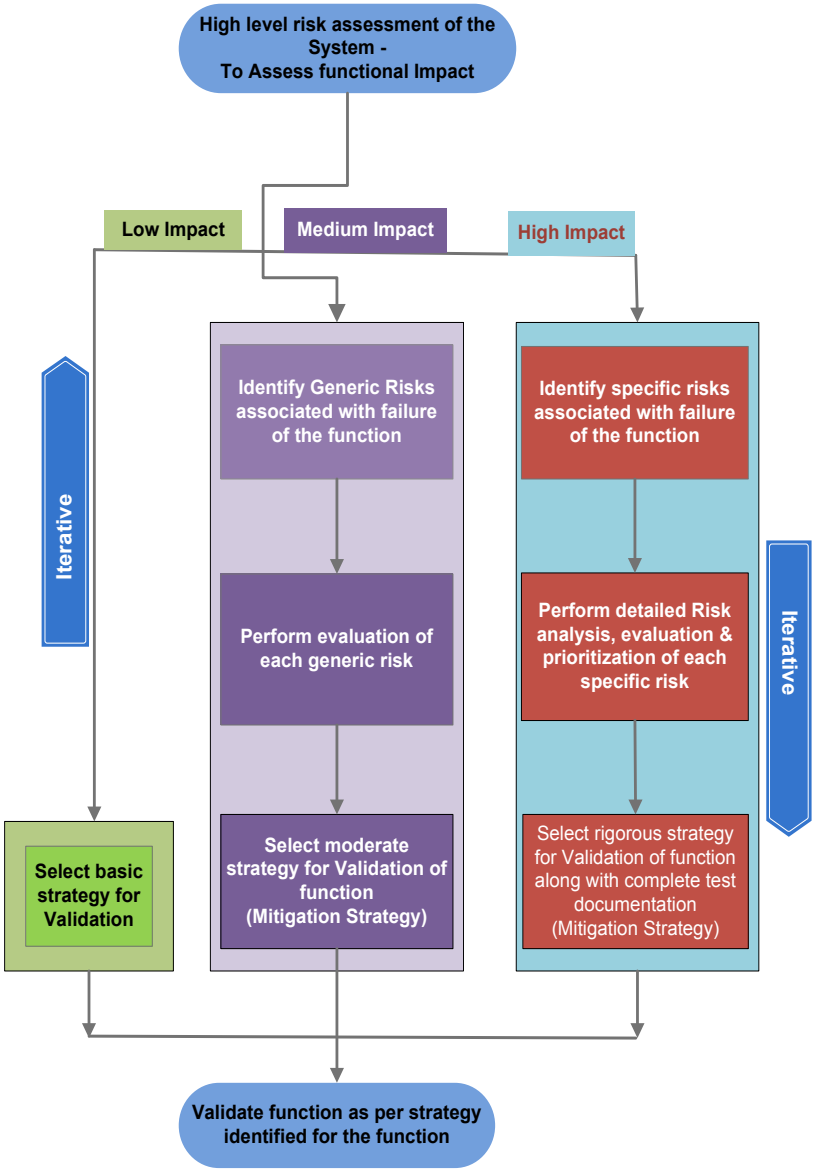

FIGURE-2

The importance of a well-documented process for assessing the risk cannot be undermined in risk based validation approach. A validation approach that is based on an undocumented analysis would be difficult to defend in an audit. It is important to write down the results of the risk assessment exercise. The methodology to be followed, the approach implemented, the mitigations taken, along with the justification for those mitigations must be documented and available for inspection during an audit. Nevertheless, from the organization's standpoint, it is just as important to focus on the actual risks and how to mitigate them, through validation, rather than the process used to assess them.

Benefits of the Risk-based Approach

A risk-based approach to Validation brings forth the following key benefits:

INCREASED VALIDATION EFFICIENCY

The risk based exercise brings out a validation profile of the software system in which critical (to patient safety and product quality) aspects of the system are identified and evaluated at levels that are commensurate with their criticality. The risk assessment process provides a justification for prioritization of activities performed by both development and testing resources Based on risk assessment at the module level or at the Requirements level, the extent of validation can be tailored as per the risk profile, resulting in an optimal Quality-Effort ratio

COST SAVINGS

The risk-based approach allows organizations to focus testing on the critical areas of the system and reduce testing efforts on scenarios that are less likely to occur or whose impact on overall quality is minimal.

Hence, Risk based validation presents the opportunity for significant cost savings since comprehensive validation testing may be performed only on the high risk areas of the application, thus improving the quality of the system and reducing the cost of potential re-work and/or regulatory action.

UNIFIED APPROACH

The risk assessment process would bring together a cross-functional team of the organization. The team's assessment exercise would result in a unified approach towards not only validation, but also quality assurance and overall risk management activities of the organization.

BUSINESS CONTINUITY

The risk assessment process affords an opportunity to review the business impact of proposed new software systems or changes to existing systems. An identification of the business risks and mitigation approaches for these risks would contribute towards business continuity planning by minimizing the impact of systems failure.

SUPPLIER INVOLVEMENT

Since most software systems now are based on configurable packages, promoting an efficient and effective way to perform validation would be to leverage the product organization's involvement, with documentation and test results wherever appropriate, especially for off-the shelf features and functionalities.

BUILD ORGANIZATION KNOWLEDGE BASE

A well-documented risk assessment conducted by a cross-functional team is a valuable source of knowledge about the system and its potential weaknesses. The assessment may also provide feedback which may lead to the identification of newer requirements or changes to the existing requirements within the system, based on selected risk mitigations

Drawbacks in following the Risk-based approach

Some of the major pitfalls to be avoided in implementing a risk-based approach towards Validation are as follows:

DETERMINING THE LEVEL OF DETAIL

It is important to conduct the risk assessment at the correct level of detail. While an analysis conducted at a very high level will yield some validation savings, all the above named benefits would essentially remain unrealized.

On the other hand, if the analysis is conducted at an excessively detailed level, the analysis itself could become an expensive and time-consuming exercise, especially when the team consists of stakeholders from various functional areas of the organization.

SELECTION OF THE ASSESSMENT TEAM

Inclusion of the important stakeholders for a given software system is important to the success of the risk assessment effort. However, an excessively large or heterogeneous team will result in inefficiencies and over-engineering of the assessment exercise leading to contributing in compliance costs, but do not help with compliance.

SELECTION OF RISK ASSESSMENT METHODOLOGY

A range of risk assessment methodologies and models exist varying in their level of sophistication from highly complex to simplistic. Apart from the advantages and disadvantages of each, the company's risk tolerance level would be an additional input in selecting the assessment methodology.

Conclusion

Risk based validation appears to be the least burdensome approach towards validation of a LIMS systems which operates in a regulated environment. The risk-based validation approach offers a pragmatic approach towards avoidance of either excessive or inadequate testing of software systems. However to gain the advantages of a risk-based validation approach, which is sustainable by the implementing organization and acceptable to the regulatory agencies, it is important that more time is spent planning and documenting the validation activities.

By adopting a well-documented, risk based approach to compliance and validation, companies can correctly allocate compliance efforts in areas that are most likely to improve patient safety and satisfaction.

A common indication of a successful risk-based validation exercise would be that the organization is able to focus more of its validation efforts on performance testing of the system rather than on testing the functional aspects of the system. Thus a Risk-based approach to validation not only gives a least cost compliance solution over green field validation efforts, but also substantially reduces project duration. Nevertheless, while this is true of a well-planned and executed risk-based approach, if the knowledge of how to implement such an approach is lacking, chances are that the real benefits of this approach will not be seen and validation costs may be as much or more than the price of the software system itself.

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