

A Practical and Cost-Effective Risk Assessment for the Validation of Commercial Laboratory Computerized Systems

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Risk management and risk assessment for computerized systems validation are now key regulatory issues since the FDA’s reassessment of the 21 CFR 11 regulations (1). There are several risk analysis methodologies available that could be used for computerized system validation. In a recent publication, however, the conclusion is that one methodology does not fit all situations and the prudent professional should select the best methodology applicable for the problem at hand (2).

Risk assessment for commercial laboratory computerized systems needs to be carefully understood as the regulations make it clear that the laboratory is responsible for scientific sound work (3). The GAMP Forum has published *Good Practice Guide for Laboratory Computerized Systems* (4), which contains a risk assessment methodology based upon failure mode effect analysis (FMEA), but this is a relatively complex methodology for most of the commercial systems used in the laboratory today as noted in a recent column in *Spectroscopy* (5).

The practical risk management approach outlined in this article is based upon taking advantage and leveraging what a vendor already has undertaken during development of the whole system (for example, design and testing) and will do during its operational lifetime (for example, regular calibration and maintenance). The essence of the approach is based on two questions:

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- Do I need to validate the system?
- If I do need to validate, how much validation is required?

The second question is more tactfully phrased than the usual one, which is, What is the minimum I can get away with? The overall process is presented in Figure 1.

Define system use and records generated

The first thing to do is to define what the system does—What is its intended purpose and what is the system used for? This is an important stage because if this is not done correctly, the rest of the work fails. When starting this process, you will need a good technical understanding of how the system works and the records created by a system. The intended use of the system must be documented and approved by laboratory management and quality assurance. Some areas where a spectrometer or a chromatograph could be used are identification or testing of raw materials, intermediates or finished products or development of methods.

Then, the records generated by the system when used as defined by its intended use need to be documented. This is important because the computer validation world is undergoing a complete revision of approach: moving from a system to a record-based approach (1, 6). Once the records have been identified, their impact can be assessed, depending upon the intended use of the system, the records generated can be high-, medium-, or low-impact ones (6). Note that high-impact records (for example, electronic signatures) can be found with medium-impact ones (for example, validation records). As befits a regulated industry, there are more high-impact records than medium and low ones combined.

Do I need to validate?

The first question of the risk assessment is relatively easy as the Computer Validation Initiative Committee (CVIC) of the Society of Quality Assurance (SQA) has written a simple questionnaire designed to answer this question (7). This was produced circa 1996–1997, but the laboratory-based questions still hold

today, and some of these are presented in Table I.

If all responses to the previous questions are “No,” then validation of the system is not required and the system can be documented as such. It is important to understand that assessments do not remain static as reorganizations and mergers can impact and new software releases can all affect the way that a system is used after an initial assessment has been made. Therefore, the prudent will always recheck the assessments at key stages of a system’s life cycle. However, if the answer to any of the questions is “Yes,” then the system needs to be validated and we can move to the second stage of the risk assessment.

What is the extent of validation?

This is always the difficult question, as the answer is always prefaced “it depends;” however, here is where the regulations come to help us in defining an approach to risk assessment as shown in the following list:

- European Union GMP Annex 11 (8) states that the extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated.
- ICH Q7A—GMP for Active Pharmaceutical Ingredients (9) states in §5.40: Good manufacturing practices (GMP)-related computerized systems should be validated. The depth and scope of validation depends upon the diversity, complexity, and criticality of the computerized application. Furthermore, in §5.42: Commercially available software that has been qualified does not require the same level of testing.
- FDA General Principles of Software Validation (10): Section 6.1: How much validation is needed? The extent of validation evidence needed for such software depends upon the device manufacturer’s documented intended use of that software. For example, a device manu-

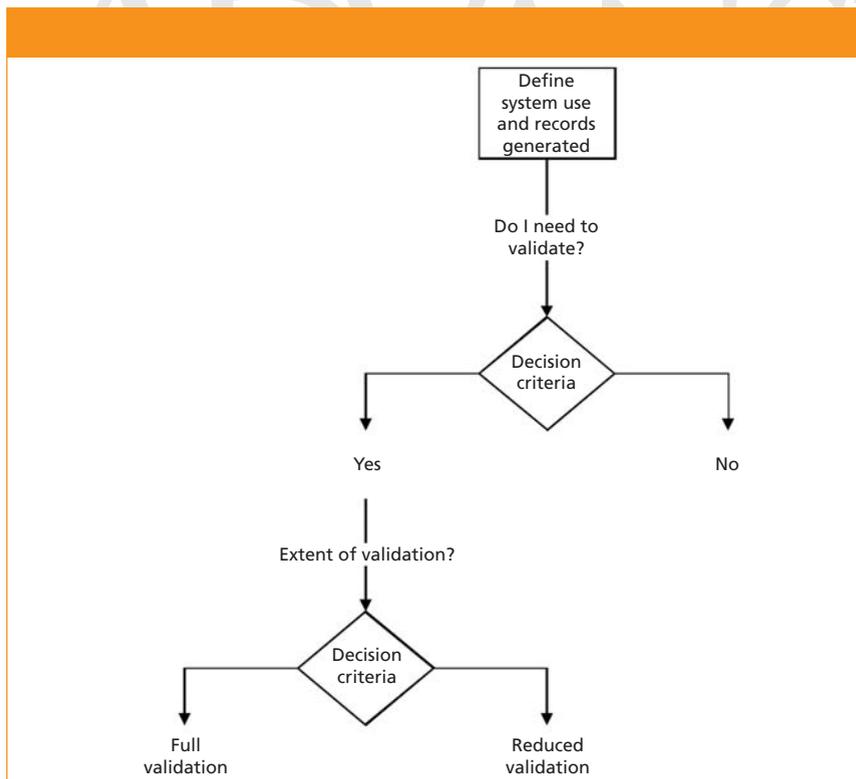


Figure 1: Flowchart of validation risk assessment for a laboratory system.

Some questions to determine if a laboratory system requires computer validation

- Is the computerized system used to support any of the following activities?
 - 1) Manufacture, storage, distribution, return, salvage, or reprocessing of a drug product?
 - 2) Manufacture or storage of active pharmaceutical ingredient (API), starting materials or intermediates?
 - 3) Testing of drug product or API for formal release?
 - 4) Generation of, submissions to, or withdrawal of an Investigational New Drug Application (IND)?
 - 5) Generation of, submissions to, or withdrawal of a New Drug Application (NDA)?

facturer that chooses not to use all of the vendor-supplied capabilities of the software only needs to validate those functions that will be used and for which the device manufacturer is dependent upon the software results as part of production or the quality system.

From the statements in the regulations and guidance, the two main factors that determine the extent of validation are:

- What does the system do? This is based upon the documented intended purpose of the system and, thus, the impact of the records created by a system
- What is nature of the system software? For example, commercial off-the-shelf (COTS), configurable COTS software or custom coded (good automated manufacturing practices [GAMP] software categories 3, 4, or 5, respectively) (11)?

Therefore, it is the combination of the records created by the system coupled with the software that created the records that should determine the overall validation approach. Quad erat demonstrandum?

Based upon this approach, we need to consider a simple approach that takes the combination of the impact of the records generated by the system and the software used to generate them to produce a simple tool to decide on the approach to validate a computerized system used in the laboratory. This is shown in Figure 2.

Here the record impact is plotted versus software GAMP category as flows.

- *Record impact:* The records generat-

ed by the system are classified as either high or low. This is based upon the *GAMP Good Practice Guide for Part 11 Compliant Records and Signatures* (6), where the high records are those that are submitted directly to FDA or are included in regulatory submission, stability data or used to for batch release of drug product. Low records are use used for in-process monitoring of drug product, active pharmaceutical ingredient (API) support data, validation records, and other material not directly submitted to FDA.

- *Software used to generate the records:* High classification is either an application that is a custom or a configurable COTS software application (GAMP categories 5 or 4). A low classification is a COTS software package providing an off-the-

shelf solution to a regulated process (GAMP category 3).

Plotting both as shown in Figure 2 allows an overall classification of either high (that is, full validation) or low (reduced validation) to be applied to a laboratory system.

So what validation do we do?

The validation work that results can be divided into two approaches:

Full validation. This would take the computer application and apply a system implementation life cycle (SILC) as outlined in the *GAMP Good Practice Guide for Laboratory Computerized Systems* (4) and modified in a recent "Focus on Quality" column (5). Note that further modification of the validation can be undertaken both in the overall validation plan for the system and in the risk assessment of the individual requirements (12). This latter topic will be the subject of a future "Focus on Quality" column in *Spectroscopy* (13).

Reduced validation. This uses a single, integrated validation document to record the intended purpose of the system and the associated testing. Systems falling in this category are typically standalone systems within the laboratory. The approach is linked closely with other mechanisms such as the pre-analysis system suitability test or calibra-

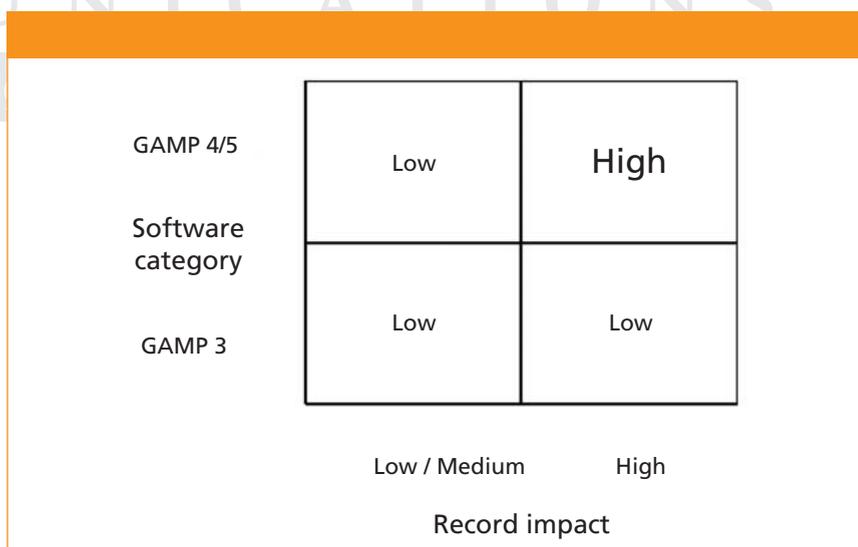


Figure 2: Plot of the record impact and software category to determine a validation approach.

tion check to demonstrate that a system is under control. Requirements are individually numbered but are only focused on the intended purpose of the system, security, and electronic record integrity, preservation, and protection. The integrated document also contains the test scripts and the document is preapproved before test execution and contains the summary report for review and approval after testing is completed.

The overall process is simple and easily understood and is coupled with normal controls used in laboratories and vendor maintenance, calibration, and qualification activities.

Validation planning is provided by a validation master plan using the format described in EU GMP Annex 15 (14), which also is used as an inventory of systems and their validation status with regular updates.

System risk assessment in practice

Two examples of laboratory systems will be discussed that have been assessed using this overall approach.

Time of flight mass spectrometer. The single user instrument is used for elemental analysis (high resolution for molecular formula confirmation) on APIs for IND and NDA submissions, impurity identification to support process chemistry and support to discovery chemistry for the identification of unknown and known compounds. Therefore, the records generated by the system are high impact. However, the software used is commercial off the shelf (GAMP category 3). Therefore, the overall risk assessment of the system is low as shown in

Figure 2 and this would be validated using an integrated document. Furthermore, the software was qualified by the vendor upon installation, there are regular preanalysis calibration checks carried out before using the system and the system is regularly maintained by the vendor.

The assessment of a system that submits records to a regulatory agency as a low risk might seem strange but why

not? Look at the work that the instrument does and the overall control elements in addition to validation. It is the holistic approach that integrates computer validation, instrument-system calibration and the overall maintenance program that provides the control and risk mitigation for many laboratory systems.

Nuclear magnetic resonance spectrometer

This instrument is used as both a research tool and for proof of structure determination the latter records are used for submission for investigational new drug (IND) and new drug applications for active pharmaceutical ingredients. Therefore, the records generated are high impact. The software was configurable and also contained many vendor supplied and custom macros for operation of the software making it GAMP category 4/5. Therefore, the overall approach here was a full validation of the system. Although there are similar control mechanisms such as calibration checks and regular maintenance with the

previous example, it is the nature of the software that determines the different approach due to the custom macros.

Summary

An easy-to-understand risk assessment process for computerized systems used in the laboratory is presented and discussed. After documenting the intended use and the impact of the records generated by a system, two questions are asked:

- Do I need to validate the system?
- How much do I need to do?

The overall process is simple and easily understood and is coupled with normal controls used in laboratories and vendor maintenance, calibration, and qualification activities.

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