Quality Risk Management Strategies for Computer Systems Validation

Héctor Sepúlveda Figueroa
Master of Engineering in Manufacturing Engineering
Edgar Torres, Ph.D.
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract *— Quality Risk Management is something that has been gaining attention in the regulated industry because it is listed as regulation in various regulatory agencies such as FDA, ICH, ISO, ISPE and other involved regulatory agencies, but all with the same goal of improving the and manufacturing quality of a product manufactured for the patient to be administered. From this part briefly assess how QRM strategy works by Good Manufacturing Practices, and regulatory requirements and associated guidance documents, making certain methodology on QRM to CSV is presented. We must take into account that there is no fixed for all situations that arise in a given time methodology. The competent professional is the best person to select which type of methodology will do the QRM to be adjusted to the problem presented in the areas related to computer systems. In this article we present how we can achieve risk reduction through QRM in CSV.*

Key Terms *— Computer Systems Validation, Quality Risk Management, Risk Reduction, Strategies.*

INTRODUCTION

The Food and Drug Administration (FDA for its acronym in English), adopted in 2002 based on strict compliance risks in manufacturing and / or manufacture of pharmaceuticals and medical devices focus when a review of its overall approach was started according to practices required in each organization known as Good Manufacturing Practices (GMP's) for the 21st century.

As part of this program was revised regulation 21 CFR Part 11 [1]. A reason for this, industries were alerted to adopt a focus on quality risk management (QRM) to be interpreted as regulation in Computer Systems Validation (CSV). Importantly, QRM is not a separate process or CSV, nor Lifecycle Development System (SDLC), but is an ongoing process and should be integrated into the overall development cycle systems.

A practical approach to QRM in CSV suggested emphasizing related questions such as:

- You need to validate the system?
- What is needed to validate?
- Why it's important?
- How should emphasize quality throughout the cycle validation?

The purpose of this paper is to elaborate on the methodology regarding the management of risks in situations in which they must demonstrate compliance with regulations and established parameters can be carried out every process and wrapped to deliver a high quality product procedures and can be marketable in the relevant market as well as display a concise summary of regulations and guides in the industry, both strategies required to implement risk management quality CSV.

DESCRIPTIVE INFORMATION

- **Computer System Validation (CSV) [2]** - Technical discipline through documentation to ensure that a computerized system (software and hardware) does exactly for which it is designed in a consistent and reproducible under strict quality requirements in industries by regulatory agencies and impose the need for controls and specific procedures to throughout the SDLC.
- **Regulations** – Action to regulate, adjust or tidying, regulate the operation of a system, determine standards. Your goal is to take control and guarantee the quality of products manufactured or manufactured.

- **GAMP** – Founded in 1991 by a group of experts in the pharmaceutical industry interested in evolutionary expectations FDA to fully comply with GMP's. In 1994 associated with ISPE to publish the first guidelines of the GAMP and provide seminars, which aims to promote understanding of the regulation and use of automated systems in the industry. His last review was in February, 2008, known as GAMP 5 [3].

Table 1
GAMP Categories for CSV

GAMP 5	
Category	Description
GAMP 1	Infrastructure Software
GAMP 2	N/A (Eliminated in last review)
GAMP 3	No Configurable Software
GAMP 4	Configurable Software
GAMP 5	Bespoke Software (0)

Note that the category GAMP 2 was eliminated because the technology has advanced and complex use of firmware is done, it related to simple firmware, which can be software.

- **Regulatory Guidelines** – Regulatory authorities require that the pharmaceutical manufacturer to maintain guidelines and procedures for all activities that could affect the quality, safety, identity and purity of a pharmaceutical product. This includes procedures for implementing lifecycle and validation and to support the operation of the process.

The pharmaceutical manufacturer will have to prepare written procedures that clearly establish that need to be documented activities, what information the documents contain, how critical information is verified, which is responsible for generating the documentation, and the review and approval are required for each document. Each procedure must give detailed for the execution of specific tasks or assignments instructions, and must be in writing in accordance with the procedure of pharmaceutical manufacturer to write and approve procedures and guidelines. For each document, the meaning and importance of each signatory must be defined.

Standard Operating Procedures (SOP) and written instructions for operating personnel on how to operate the manufacturing process is required. These will cover the operation in conjunction with the computer system and the tasks that are independent of the computer system. Where there is a requirement for Quality critics to be manually entered into the computer system data, you must have an additional check on the accuracy of the entry. If the computer system is not designed to take and record this control then the relevant SOP must include this check by a second operating [2].

Key validation procedures and system are:

- Preparación de procedimientos estándar
- Document review
- Glossary Validation
- Critical evaluation parameter
- GMP's criticality and risk analysis
- Process validation methodology
- The validation of computerized
- Development of validation plans
- Development of project plans and quality
- Specification manufacturing data

The incorporation of these procedures and the resulting documents in the quality management system will Provide a single point of monitoring and file for all procedures validation.

- **ICH Q9 Guidelines –** The ICH harmonized tripartite Guide was completed in Step 4 November 2005.

This Guide provides principles and examples of tools for quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, inspection and reporting processes / review throughout the cycle life of pharmacological and medicinal) substances (pharmaceutical, biological and biotechnological products, including the use of materials, solvents, excipients, packaging and labeling of raw materials [4].

- **Validation** - In the pharmaceutical industry, medical device, food, blood products, biological products, tissues, establishments, clinical trials conducted by institutions, validation is a process of establishing documented evidence that a process, process or activity conducted in the production or testing maintains the desired level of performance at every stage [5].

In Pharmaceutical Industry is very important, apart from the final testing and product compliance with the rule that the adaptation process to produce itself must ensure that the process will consistently produce the expected results. Here the desired results are stated in terms of specifications for the outcome of the process. Therefore, training systems and equipment is a part of the validation process.

It is a requirement of food and medicine, drug regulatory agencies such as FDA guidelines practices. From a wide variety of procedures, processes and activities should be validated. is divided into a series of sections that include the following types of validation [6]:

- Equipment
- Facilities and Amenities
- HVAC systems
- Cleaning
- Processes
- Analytical Method
- Computer Systems (CSV)
- Packaging
- Others

CSV at Qualification Process

Among the references given in the Plan Validation of the authors of the protocol should ensure that all aspects of the process or equipment qualification; that can affect the efficiency, quality and product registrations or are properly qualified. Qualification includes the following steps:

- Design qualification (DQ) - shows that the proposed design (or designs to an item off the shelf) will satisfy all the requirements that are defined and detailed in the user requirement specification (URS). The successful implementation of the DQ is a mandatory requirement before construction (or acquisition) of the new design may be authorized.
- Installation Qualification (IQ) - shows that the process or the equipment meets all specifications, is installed correctly and all required components and documentation necessary for the continued operation are installed and in place.
- Operational Qualification (OQ) - shows that all facets of the process or equipment operating properly.
- Performance Qualification (PQ) - shows that the process or equipment performs as intended in a consistent manner over time.

Quality Risk Management

Organizations of all types and sizes face internal and external factors and influences that make it uncertain whether and when they will achieve their objectives. The effect this uncertainly has on an organization's objectives is "risk" [7].

Each product or process has its risks. Risk reduction to zero is not a realistic goal. However, the protection of patients through the system QRM quality and manufacturing process and manufacturing is being given prime importance in pharmaceuticals and medical devices. It is important that product quality is maintained during its production and use.

The focus of QRM indicated by regulatory agencies with quality control tools based on collected statistics are aplicads in any regulated industry. QRM is a systematic control for the assessment, control, communication and review of risks; which begins by identifying potential risks associated with a product or process utlizados to develop, manufacture and distribute the product.

QRM process ensures a high quality product to be given to a patient. Besides that QRM improves decision-making if a problem occurs quality.

METHODOLOGY

Quality Risk Management (QRM) has general principles according with the internationally harmonized guideline (ICH Q9 Quality Risk Management) stated these principles:

Risk management should be used to evaluate how to ensure compliance and determine the prioritation resulting from the action, not by a decision regarding the need to comply with applicable law or legal requirements.

Risk can only be managed effectively when identified, evaluated, considering to implement mitigation measures and communicated. Here the four stages of a process are incorporated QRM effective as defined by the ICH Q9 [4]:

- Quality Risk Identification
- Quality Risk Assessment
- Detectability
- Definition Quality Risk

Table 2
Risk Chart Indicating their Level of Risk Acceptance

Impact (Consequence)	Probability (Likelihood)		
	Low	Medium	High
High	0	2	1
Medium	3	1	1
Low	4	2	2

ISO 73 and ISO 14971 Guidelines: Risk Management Definitions [8]

- Risk Management: The systematic application of policies, procedures and practices to the tasks of analyzing, evaluating and controlling risks. From Figure 1, this is the general process that is the subject of this paper.

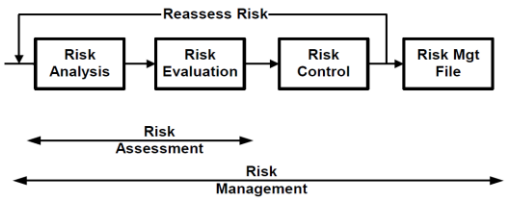

Figure 1
Risk Management Process Adapted by ISO 14971

- Risk Assessment: The overall process of risk analysis and risk assessment. It is the main sub-process and consists of two elements: risk analysis and risk assessment as shown in Figure 3. This is the FDA stated requirement.
- Risk analysis: Systematic use of available information to identify hazards and assess risk.
- Risk Assessment: Judgment on the basis of risk analysis, that the risk is acceptable that has been achieved in a given context.
- Risk: combination of the probability of occurrence of harm and the severity of that harm.
- Damage: injuries or damage to the health of persons or damage to property or the environment. Note that this is for a medical device; this should be interpreted as the consequences of a software error or malfunction of the system.
- Severity: measurement of the possible consequences of a hazard.
- Hazard: potential source of harm.
- Risk Control: The process by which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within acceptable levels. Note that all risks can not be eliminated, but is mitigated within acceptable levels. What is acceptable is determined by the operating environment and functions that automates the computer system.

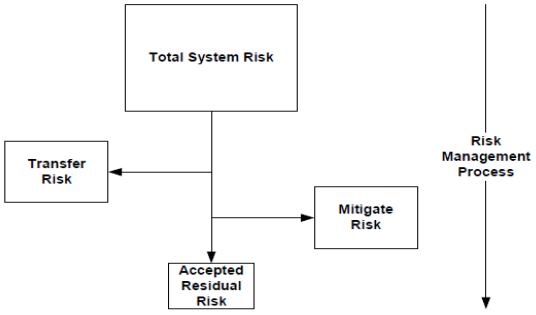

Figure 2
Example from a Risk Management Process

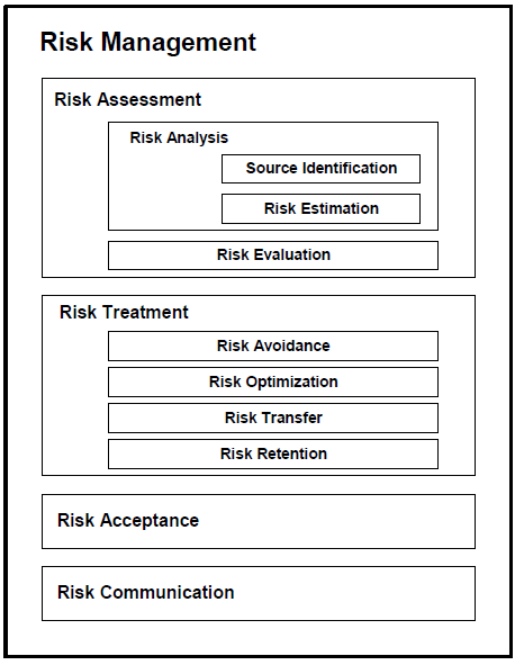

Figure 3
Terminology and Relation to Risk Management taken from ISO Guide 73

Risk Management Goals

The overall objective of the risk management process is shown in Figure 3. It has to take all the risk identified in a computer system, and reduced by mitigation activities using different approaches or design so that the residual risk is manageable within acceptable limits. There are a number of options that can be used [9]:

- Assumption of Risk: Accept the potential risk and continue the operation of the IT system without further action.
- Risk prevention: avoid risk by eliminating the cause of risk and / or consequences such as adding design features or procedural controls that prevent the risk occurring.
- Limiting the risk: Limiting risk by implementing controls that minimize the adverse effects of a hazard is the exercise of a vulnerability (eg, use of support, prevention, detection controls) or by authorizing the operation for a limited time during which the additional risk mitigation by other means is putting in place while.
- Risk transfer: Transfer of risk by using other options to compensate for the loss, for example, buying insurance against the threat of carefully defined circumstances.

It is important to understand that not all risks are the same level. That's why most risk analysis methodologies classify the risk and deal with the highest priority / severity first and often can leaving lower risk as they are within an acceptable level.

There are additional definitions of IEEE 1540 (Software Lifecycle - Risk management processes) that should include consideration here:

- Acceptability: Exposure to loss (financial or otherwise) that an organization is willing to tolerate risk.
- Probability: A quantitative or qualitative expression of the probability that an event will occur.

It is important that the acceptability be included in these definitions as succinctly summarizes the residual risk of a computerized system. Typically, the negative side may be misinformation or regulatory citations bad validated system.

STRATEGIES FOR QRM IN CSV

The Validation Master Plan in QRM serves as a summary of overall strategies for the validation of an installation. This Validation Master Plan provides an overview of each process and describes the validation approach along with supporting rationale validation.

This VMP addresses all activities related to equipment, services, processes, systems and procedures that may affect product quality. Specific systems, equipment, utilities, and procedures to qualify and processes to be validated be determined on the basis of documented risk assessment [10].

The purpose of validation plan is to demonstrate that critical equipment, systems and processes of how they are designed and intended for certain functions. All validation will be conducted prospectively following written and

approved protocols. Change control and qualification of equipment and systems will be conducted in a manner consistent with the policies and procedures of the company. Specific equipment, systems and processes to be validated be determined on the basis of a documented risk assessment. VMP may include:

- Systems, equipment, methods, facilities, etc., that are in the scope of the plan
- Current validation status for the systems within the project scope
- Compliance requirements for validation, including how the validated state will be maintained
- Schedule of validation activities

Validation Master Plans can also include:

- Required validation deliverables
- Validation documentation format
- Current validation procedures and policies
- General validation risk mitigation strategy

Validation Master Plans should be approved by the head of Site Quality, plus other senior department heads as appropriate. Senior management approval is necessary for Validation Master Plans because their support is essential for the success of the plan.

QRM is also used for validation of Computer Systems and Computer Controlled Equipment. To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);

To determine the extent of validation, e.g.,

- Identification of critical performance parameters.
- Selection of the requirements and design.
- Code review.
- The extent of testing and test methods.
- Reliability of electronic records and signatures.

System Development Life Cycle [11]

The SDLC is the period of a system from its conception to retirement. It is a model used for the planning, implementation and control in the management of automation projects computer, through a systematic and structural approach. This method, if understood and accepted by all participants in question, improves communication and enhances flexibility of project, resource allocation, cost control, and overall quality of project.

Most important advantages of the SDLC approach to project management: Visibility development system. The system becomes explicit, tangible and accessible through ENERATION of intermediate products of labor as supporting documents) or SDLC The method also makes meet that supporting documents are developed in an orderly manner (as a natural product the development process), allowing the opportunity to conduct inspections and reviews appropriate at key points along the process facilitates the validation process, one resulting in more effective and less costly

What is the importance of implementing the Development Lifecycle of a computer system? Software Quality Assurance. The quality cannot be tested in the "post" system; to be built during the development process itself. The measurement and controls adequate quality assurance must be present throughout the process development for ensure a final product with the expected quality. THE SDLC gives birth to the Life Cycle Validation SVLC) System Validation System Life Cycle ", which has become the foundation of each program validations computers to the regulated industry.

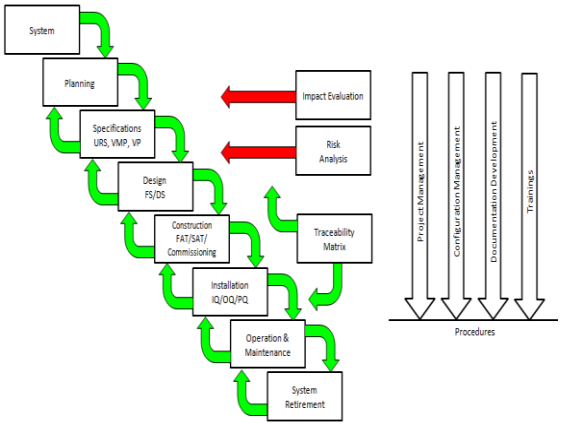

Figure 3
Systems Development Life Cycle Diagram for Methodology Phases [11]

SIPOC

To create an efficient validation, a SIPOC (Suppliers, Input, Process, Output, Customers) process can be used to define the processes involved in validation. The SIPOC provides a high level definition of the processes. Details of the processes must be defined in Standard Operating Procedures (SOP) and Work Instructions (WI).

In this section the steps of the Project Phase of the Validation process is shown in a SIPOC diagram. The diagram is created from the view of a Pharmaceutical Company that executes a project for a process control system together with the supplier of that system [12].

Figure 2: General IPO Diagram for Compression Process and Output Detectability

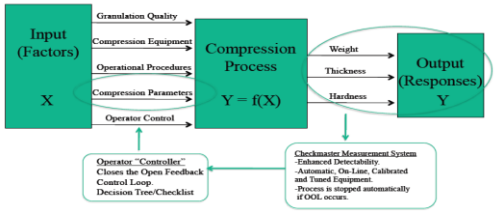

Figure 4

General IPO Diagram for Compression Process and Output Detectability

Critical To Quality [13]

CTQs are the internal critical quality parameters that relate to the wants and needs of the customer. They are not the same as CTCs (Critical to Customer), and the two are often confused.

CTCs are what is important to the customer; CTQs are what's important to the quality of the process or service to ensure the things that are important to the customer.

Figure 1: CTQ Diagram for Compression In-Process Results Detectability

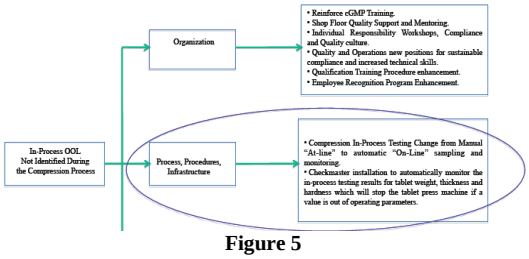

Figure 5

CTQ Diagram for Compression In-Process Results Detectability

A quality function deployment (QFD) or CTQ tree relates the CTQs to the CTCs. For instance, car door sound when closing might be a CTC, while the dimensional tolerances and cushioning needed to produce those conditions are CTQs for the auto maker.

Risk Priority Number (RPN)

Is a measure used when assessing risk to help identify critical failure modes associated with your design or process? The RPN values range from 1 (absolute best) to 1000 (absolute worst). The graphic below shows the factors that make up the RPN and how it is calculated for each failure mode [14].

Table 3

Illustration of the Factors to Calculate the RPN for each Failure

■ Severity (S)
■ Severity X Occurrence (S X O)
– Criticality
■ Severity X Occurrence X Detection (S X O X D) = RPN

- **Severity (S)** - Severity is a numerical subjective estimate of how severe the customer (next user) or end user will perceive the effect of a failure.
- **Occurrence (O)** - Occurrence or sometimes termed likelihood is a numerical subjective estimate of the likelihood that the cause of a failure mode will occur during the design life, or during production.
- **Detection (D)** - Detection is sometimes termed effectiveness. It is a numerical subjective estimate of the effectiveness of the controls to prevent or detect the cause or failure mode before the failure reaches the customer.

Risk Factors

In this paper, we present major risk factors in a project that can be seen as relevant or ignored, but

everything that represents risk if of their relevance must be addressed as early as possible once identified.

The strategy should always handle continuous because it may be necessary to resort to contingency plans if a risk is compounded by promoting the project to a possible failure.

Risk factors based on Van Vliet [2] [5]:

- Lack of competent staff
- Unrealistic timetable as unrealistic budget
- Malfunction
- This user interface
- Gold plating
- Volatility requirements
- Poor development tasks
- Deficiencies in real time
- Deficiencies in performance capacity

DISCUSSION OF RESULTS

In this paper, we present an example of a case study related to be discussed in the classroom under the theme of QRM on a Automatic In-Process Tablet Testing for tablets after compression (for see the differences between At line vs On-line), consisting of weight, hardness and thickness. These tests were done manually by an operator or technician, who had to be constantly making adjustments to the system because performing the entire process of testing, but when were reviewed in the area of Quality Assurance, these detected errors in consistency said tablets.

A QRM was conducted to reduce errors in compressed tablets changing the test system from manual to automatic mode. With RM conducted and implemented in such testing system could see that there was in the process increased detectability and reduced occurrence (see example in Table 4), things that the operator could not perform. At that, the RPN (Risk Priority Number) low and this means that the implemented system builds confidence for future testing in reducing errors or failures in developing the product. Otherwise, if such errors or failures are detected, the system stops immediately given until the situation is corrected.

It is Critical of this in Relation to CSV?

Regarding CSV, equipment is automated, which is a big advantage in speed and efficiency in compression tests of the tablets. To accomplish this, we must evaluate the calibration system to meet your requirements and specifications through validation and maintenance of that system to not sacrifice quality product.

In the case study we saw the difference in numbers given in the RPM before and after implementation of the automated system with 392 and 24 respectively, resulting in reduced to at 368 RPM of difference.

Table 4
Risk Assessment Evaluation (Before and after the Automated System implementation)

Detection:

Based on measurement system differences, "at line" vs. "on-line".

Table 7: Risk Assessment Evaluation (Before vs. After Implementation)

Risk Scenario	Risk Factor			Risk Priori Number (RPN)
	Severity	Occurrence	Detection	
Before Implementation: "In-Process OOS not identified during the compression process"	8 Marginal	7 High	7 Very Low	392
After Implementation: "In-Process OOS not identified during the compression process"	8 Marginal	1 Remote	3 High	24

Table 5
Before vs After Risk Acceptability Scenario Results

Table 8: Before vs. After Scencario for risk acceptability

RPN	Severity			
	Negligible	Marginal	Critical	Catastrophic
501-1000	Cannot achieve this rating	Intolerable	Intolerable	Intolerable
100-500	ALARP	ALARP	Intolerable	Intolerable
51-99	Broadly Acceptable	ALARP	ALARP	ALARP
1-50	Broadly Acceptable	Broadly Acceptable	ALARP	ALARP

CONCLUSION

In this paper some strategies for their applications regarding QRM in CSV reviewed. We analyzed some of the practical options available to carry out a good validation of computerized systems.

After manual changes made automated system according to the case study, the RPN was reduced by 368, achieving Broadly Acceptance Level at 24,

resulting in substantial increase detectability and reduced occurrence in Process Tablet Testing.

We reiterate that the risk assessment validation must be set in the situation that arises because there is no standard strategy that applies to all systems, so it is ideal to select the appropriate strategy to integrate the VMP.

The strategy or methodology to be applied, a practical approach is suggested, which should answer basic but key questions such as; It is necessary to validate the system? If so, the next question should be: How necessary is to validate the system? In a simple answer I say this: validation to safeguard product quality and comply with regulatory agencies involved in the industry to ensure the quality of life of patients by product warranties is necessary and essential.

Therefore, QRM is a systematic process for the assessment, control, communication and review of risks to the quality of a drug and / or medical device through its lifecycle for benefit and assurance for the patient, customer and everybody involved in the industry.

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