CSV Program Implementation using a Risk Based Approach to align ICH with GAMP5

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Abstract *— it has been 29 years when Process Validation was created. Since then there has been a lot of creations of different types of validations. During the years there have been a lot of improvements in every validation process. Different kind of process has been created to support validations. Quality is an important factor in any process nowadays. In this project we want to align a Quality Risk Management process like ICH Q9 with GAMP5 Computerized Systems Validation process. A DMAIC problem solving method was used to identify gaps between processes and provide a clear view to resolve the problems.in conclusion the best way to align these processes is to begin with a full risk assessment, risk control and continue with the GAMP5 process.*

Key Terms *— Computer Systems Validation, GAMP5, ICH Q9, Quality Risk Management, Risk Assessment.*

INTRODUCTION

In 1987 the FDA published a document entitled [1] "FDA Guidelines on General Principles of Process Validation" that it states: "Process validation is stablishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes". The main purpose of the validation process is to provide a high degree of assurance that a specific process will consistently produce a product which meets predetermined specifications and quality attributes. FDA regulations mandate the need to perform Computer System Validation (CSV) and these regulations have the impact of law. When failing an FDA audit, the result can be in FDA inspectional observation (483s) and warning letters. By failing to corrective action in a timely manner can result in consent decrees, stiff financial penalties or shutting down manufacturing facilities.

Validation is applied to many aspects of the healthcare and other regulated industries and business. The objective of validation is to produce documented evidence, which provides a high degree of assurance that all parts of the facility will consistently work correctly when brought into use. Computer Systems Validation includes validation of both new and existing computer systems.

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries [2]. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

The ICH guidance for industry, (Q9) Quality Risk Management, offers a systematic approach to quality risk management and suggests a methodical process for the assessment, control, communication, and review of risks.

GAMP stands for Good Automated Manufacturing Practice [3]. Usually when one hears the terms GAMP®5, it is in reference to a guidance document entitled GAMP®5: A Risk-Based Approach to Compliant GxP Computerized

Systems. This document is published by an industry trade group called the International Society for Pharmaceutical Engineering (ISPE) based on input from pharmaceutical industry professionals.

In a nutshell, GAMP®5: A Risk-Based Approach to Compliant GxP Computerized Systems provides a framework for the risk-based approach to computer system validation where a system is evaluated and assigned to a predefined category based on its intended use and complexity.

RESEARCH OBJECTIVES

The main objective of this design project is an alignment of ICH Q9 with GAMP®5 process in which it is used to find gaps in the CSV process for any type of industry and apply the process to improve the CSV assessments.

RESEARCH CONTRIBUTIONS

This project supports the industries goal of operational excellence by reducing the gaps in the CSV process. This process will benefit plant sites Computer System Validation process by focusing strongly in risk assessment and improving the process globally in an industry. Some industries have trouble with their process of Computer System Validation; this process will capture all the gaps of the plant site to assure that the process is accurate and it will not have any trouble with audits or FDA regulations. This should also be a model to other plant sites experiencing problem with Computer System Validation, as well as to other companies.

RESEARCH BACKGROUND

This design project was conducted to improve the Computer System Validation gaps found in different industries such as for example: Medical Devices, Pharmaceutical, etc.

Some manufacturing plants in all over the world have had problems with the process of Computer System Validation. This process of CSV is the same for every industry but not every company use it like the other companies. Some industries use a Risk Assessments with their Computer System Validation process and there are some that do not follow the process of Risk Assessment.

ICH Q9 quality Risk Management is a great method to apply to all industries for Risk Assessment process. ICH Q9 establishes the clear priority for patient protection through the effective evaluation and management of the risks that threaten patient safety. Since ICH Q9 was published, some acronyms are familiar now to us, such as FMEA, QRM, FTA or HAZOP.

These are two principles of ICH Q9:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process should be commensurate with level of risk.

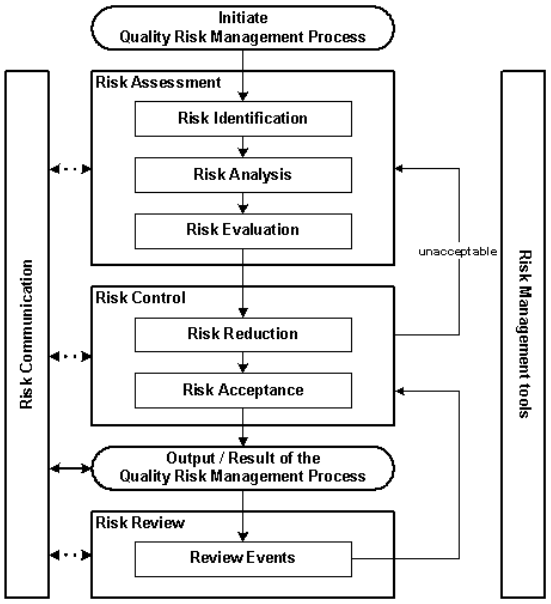

Figure 1
ICH Q9 Flow Chart

ISPE's GAMP 5 guide describes a flexible risk-based approach to compliant GxP regulated computerized systems based on scalable specification and verification, while Risk-MaPP provides a scientific risk-based approach to manage the risk of cross-contamination in order to achieve

and maintain an appropriate balance between product quality and operator safety.

GAMP 5 is applicable to a wide range of information systems, lab equipment, integrated manufacturing systems, and IT infrastructures. The GAMP guidance aims to achieve computerized systems that are fit for intended use and meet current regulatory requirements, by building upon existing industry good practices in an efficient and effective manner.

GAMP 5 Drivers:

- The need to develop a guidance that will satisfy the regulatory requirements for Computer System Validation.
- Scaleable approach to GxP Compliance through the complete life cycle.
- Drive towards Risk Based Approach.
- Effective Supplier Relationship.
- Use of existing documentation and knowledge.
- Continuous improvement within QMS.
- Quality design.
- Effective governance to achieve and maintain GxP compliance.

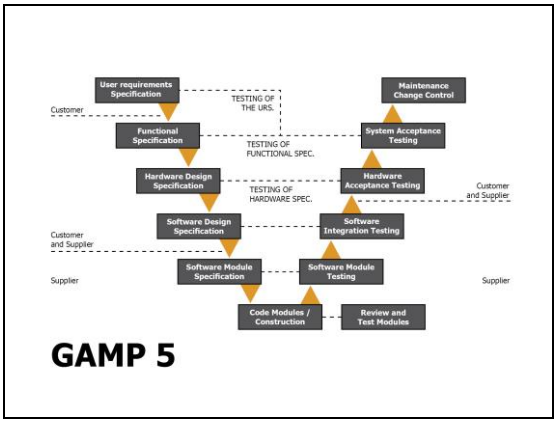

Figure 2
GAMP 5 V Model

RESEARCH METHODOLOGY

The methodology which will be followed is the Six Sigma project solving model called DMAIC (refer to Figure 3) which stands for: Define, Measure, Analyze, Improve, Control.

DMAIC has proven itself to be one of the most effective problem solving methods ever used because it forces teams to use data to confirm the nature and extent of the problem, identify true causes of problems, find solutions that evidence how are linked to the causes, establish procedures for maintaining the solutions even after the project is done.

Figure 3
Six Sigma DMAIC Model

DEFINE – The purpose of this project is to solve how to align two different processes. One process of Risk Assessment and the other is the GAMP 5 process. The problem of this is to align these processes with the best methodology of both processes.

This can affect in the way of taking a decision on the way someone is going to decide what process or method will use for any project. Some result can reflect the problem by deciding to take two different ways: a risk-based approach or risk assessment.

These processes must be align in a simple way in which companies and industries can use one process which contain risk assessment with Computer System Validation (CSV) process. This would the goal for any industry.

Instead of taking constantly decisions about which method will be used to apply a CSV process, the best option is to align both methods to include everything in just one.

MEASURE – In quality risk management (ICH Q9) the performance is based in three different trends that can impact any industry or company. These three trends are approach to computer system validation where a system is evaluated Quality, Sustainability and Risk. GAMP5 is a risk based approach to computerized systems provides a framework for the risk-based approach

to computer system validation where a system is evaluated and assigned to a predefined category based on its intended use and complexity.

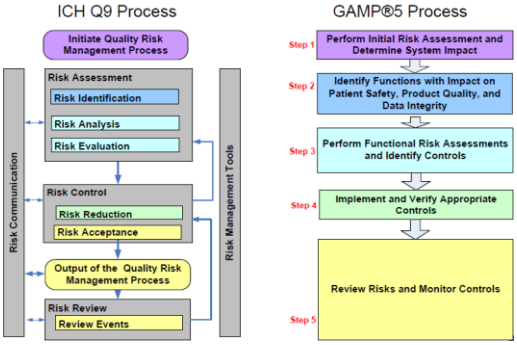

Figure 4
ICH Q9 & GAMP 5 Process Alignment

Above an illustration of the two process and the alignment of both.

ANALYZE - Possible causes can be a risk-based approach in computer system validation. Considering or selecting an approach to implementing a validated computerized system, the size, complexity, functional criticality and standardization must be taken in consideration. It also accounts for the risk of the business process regarding product quality, patient safety, and data integrity.

The High Level Risk Assessment as such is not a validation deliverable, as for any Computerized System classified as GxP relevant, further risk analysis and assessment shall be performed and documented in the validation plan.

IMPROVE - The purpose of Improve is to make an alignment of both processes to make a risk assessment process combined with Computer System Validation Process. This will eliminate all gaps and causes of problems by having only one method with all the requirements.

CONTROL –The objective of controls in the process are to ensure that the method works as intended. Controls for the alignment of Quality Risk Management and GAMP5 includes the main categories of risks with a critically matrix. Traceability is an essential ability to control the process and know the history throughout the process. FMEA is another type of control that can be used to ensure safety. This will help monitoring the process for any gap and ensuring the best product quality and patient safety.

RESEARCH RESULTS

Two different processes that are completely different but can work together as one to improve the way of one method by making it a risk based method.

Today, quality risk management improvement efforts in healthcare organizations are rallying behind patient safety and finding ways to work together more effectively and efficiently to ensure that their organizations deliver safe, high-quality patient care and continue to minimize risks.

Automated Manufacturing Practices (GAMP) is not legislation; it is an important guideline for companies regarding computer system validation. The objective of computer system validation is to demonstrate the system functions as intended. Computer system validation can be successfully accomplished by using the requirements and specifications as an objective standard to which the system is tested. If the test passes, the executed test scripts serves as documented evidence that all the requirement and specification were met.

Adding Risk Assessment, Risk Control and Risk review before the GAMP5 process will help make the Computer System Validation process a safer and controlled method in terms of risks. When risks reviewing some of the events are: Review system and events; evaluate needs to go back to Risk Control and Risk Reduction, Risk Mitigation to reduce severity, Risk Reduction to reduce Probability of Occurrence and Risk Acceptance. The risk of a change must be assessed for its potential impact on the performance of the Computerized System.

Traceability is a big part on the alignment of these methods. Traceability has to be ensured for all GxP relevant Computerized Systems. It provides a mapping of critical requirements to test. It allows forward and backwards mapping throughout all

phases of the life cycle. These are some relationship among deliverables:

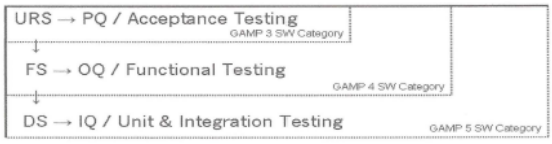

Figure 5
Relationship among Deliverables

Traceability must be demonstrable and documented from the URS to test cases as shown in Figure 6.

System Description	Traceability Path	Comments
Internally developed systems- Applications with Customization	URS→FS→DS→ Testing	If any of the documents are combined, e.g., FS/DS, adjust accordingly
Configured systems	URS→Configuration specification→Testing	Not all functionality will require configuration — for that the path is URS→Testing
Simple COTS (Commercial off the Shelf) systems and Non-Configurable systems	URS→Testing	N/A
End user applications (e.g., spreadsheets)	URS→Testing	For end user applications all information may be collected in a single document.

Figure 6
Approaches to Traceability

Gamp Validation approach is based on different categories of software product. To ensure the best quality in the Computer System Validation process we must comply with the categories listed below:

Category	Software Type	Validation Approach
1	**Operating System**	Record version (including service pack). The Operating System will be challenged indirectly by the functional testing of the application.
2	**Firmware**	For non-configurable firmware record version. Calibrate instruments as necessary. Verify operation against user requirements.
		For configurable firmware record version and configuration. Calibrate instruments as necessary and verify operation against user requirements.
		Manage custom (bespoke) firmware as Category 5 software.
3	**Standard Software Packages**	Record version (and configuration of environment) and verify operation against user requirements. Consider auditing the supplier for critical and complex applications.
4	**Configurable Software Packages**	Record version and configuration, and verify operation against user requirements. Normally audit the supplier for critical and complex applications.
		Manage any custom (bespoke) programming as Category 5.
5	**Custom (Bespoke) Software**	Audit supplier and validate complete system.

Figure 7
Categories of Software

These categories above are the ones listed in GAMP 4. Later these categories were revised in GAMP 5, and category number 2 was eliminated, just leaving 4 categories.

The software categories identified in GAMP 5 do not fit with determining the risk to product quality, efficacy or data integrity and no longer plays an integral part to determining that a computer system is fit for purpose. This is why we need a risk assessment in the beginning of the process, to identify possible risk.

The complexity and the maturity of the software can be used to support and mitigate identified risk but should not be used to determine the validation / verification deliverables.

Types of Risks and Main Categories

Main Categories	Low	Medium	High
Patient Safety Failure of the system can directly or indirectly lead to:	Does not lead to serious patient harm Minor patient harm would be indirectly attributable to failure of the function only if multiple other process or system failures occur	Severe Injuries Serious reversible adverse health effects	Severe irreversible adverse health effects (Full disability cases) Several cases of adverse/ irreversible health effects resulting in death
Product Quality Failure of the system could have regulatory impact such as:	Insignificant impact on product quality or patient and/or the impact is under control / acceptable Unlikely to result in a regulatory citation and is non reportable No GxP impact	Health Authority inspection observations, e.g., FDA Form 483 observations that might require significant commitment of resources or money for remediation	Unsatisfactory Health Authority inspection results, e.g., Warning letter Seizure of goods Recalls or more serious regulatory penalties

Figure 8
Types of Risk and Main Categories

It is to be noted that depending on the system in scope additional risks such as Business Impact, HSE, Information Security, Data Privacy, Data Integrity, and size and complexity of the system have to be identified and taken into account, and mitigated. Furthermore, risk categories have to be put into perspective of the system in scope in order to be able to draw realistic conclusions from the assessment.

Criticality Matrix

	Low	Med	High
1 - Infrastructure Software	(A)	(A)	(A)
3 - Standard (Non-configured) Software	(A)	(A)	(B)
4 - Configurable Software	(B)	(B)	(C)
5 - Custom Developed Software	(B)	(C)	(C)

Figure 9
Critically Matrix of Categories Software

Some of the Resulting Deliverables by category are explain in the following table:

Category	1 – Infrastructure Software											
Deliverables	VP	URS	VA	FS	FRA	DS	IQ	OQ	PQ	TM	VR	OH
(A)		X*					(X)			X		X
Category	3 – Standard (Non-configured) Software											
Deliverables	VP	URS	VA	FS	FRA	DS	IQ	OQ	PQ	TM	VR	OH
(A)	X	X					(X)		X	X	X	X
(B)	X	X	X				(X)		X	X	X	X
Category	4 – Configurable Software											
Deliverables	VP	URS	VA	FS*	FRA	DS	IQ	OQ	PQ	TM	VR	OH
(B)	X	X	X				(X)	(X)	X	X	X	X
(C)	X	X	X	(X)	(X)		(X)	X	X	X	X	X
Category	5 – Custom Developed Software											
Deliverables	VP	URS	VA	FS	FRA	DS	IQ	OQ	PQ	TM	VR	OH
(B)	X	X	X	(X)	X	(X)	(X)	(X)	X	X	X	X
(C)	X	X	X	(X)	X	(X)	(X)	X	X	X	X	X

Figure 10
Deliverable by Category

It is to be noted that the table represents a generic classification, defining the minimal set of validation deliverables. Individual assessments are to be performed for each Computerized System in order to determine sufficiency, as in most cases a mix of different categories exists within Computerized Systems. For those systems, the establishment of a Master Validation Plan is recommended, defining the validation strategies for the different sub-systems based on their criticality identified.

CONCLUSIONS

As part of this project, the DMAIC problem solving method helped me providing solutions for the gaps found in GAMP 5 process and the alignment with ICH Q9. This problem solving toll provided a reliable method to analyze the problem and provide methods to ensure to keep the problem from reoccurring. As a result the best way to align ICH Q9 with GAMP 5 is to provide the Computer System Validation process with a Quality Risk Assessment method that can identify the risk, prevent them from occurring and have controls over them. The best way to align these processes is to start first with a risk assessment, risk control and continue with the Computer System Validation process. This will help the different industries and companies to have a better product quality and patient safety.

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