Applying a Quality Risk Management Approach to a Cleaning Validation System

Jesús M. Medina
Master of Engineering in Manufacturing Engineering
Edgar Torres, Ph.D.
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract— *Cleaning Validation is a crucial step on assuring product effectiveness and safety by assuring that the equipment to be used has the appropriate condition to manufacture a new product without any foreign substances that could endanger the patient to ingest this product. A quality risk management approach was used to see possible risks on a cleaning validation system and give recommendations in order to mitigate and control those the risks by seeking options to access does risks in an effective and reliable manner. FDA 21 CFR 210-211 was used as a guide for regulations regards cleaning validation systems.*

Key Terms — *Cleaning Validation, FMEA, PAT, Quality Risk Management.*

PROBLEM STATEMENT

In order to meet the quality expectations in the pharmaceutical industry is crucial, the guaranteed that the equipment used in the manufacturing process, is clean and free of any undesired residue that could put on risk the manufactured product. To achieve this is important to have a cleaning validation system that validates all cleaning process within any pharmaceutical manufacturing plant. In the last two (2) decades the cleaning process have achieved an major emphasis by both, regulatory agencies and also the industrial pharmaceutical in order to have a consistent, validated manufacturing process; this new emphasis has been caused by several developments in the pasts decades for examples, new generation of products with a higher concentration doses, series of tragic contaminations that have as a result some serious personal injuries among others.

Quality Risk Management (QRM) is defined by the ICH Q9 as a systematic process assessment in control communication and review of risk to the quality of the medicine across the product life cycle [5]. Therefore QRM could be a powerful tool in order to identify, mitigate a minimize occurrence of any risk associate to final product which start when the equipment to be use is clean and release for use.

PROJECT DESCRIPTION

This project will consist in the design and development of a quality risk management approach to identify, reduce and control possible risk that could compromise the outcome of a cleaning process during a cleaning validation.

PROJECT OBJECTIVES

The project objective is to design, develop and document a quality risk management assessment on a cleaning validation system. Project Contribution

Quality – As part of the continuous search for complying and business improvement to achieve a product that meet the requirement and regulation from the accreditation agencies by assuring that the final product will be one safe and effective for the patients, is crucial to assure a cleaning program that compliance with regulation in a concise and effective manner.

LITERATURE REVIEW

This section summarizes the most relevant topic that will be key for the understanding of this article.

Cleaning Validation

Andrew Walsh describe in his article "Cleaning Validation for the 21ST Century: Overview of New ISPE Cleaning Guide" as a required activity within the pharmaceutical, biological, nutritional supplement and medical

device industries. The objective for any robust cleaning validation process is, to assure that the cleaning process meet the specification and regulation to protect the patient safety [7]. The basic reason to have a capable and consistent-cleaning program is to prevent contamination final product produce consequently using the same equipment. Although cleaning validation has boomed in the past two decades the Food Drug Administration (FDA) has maintained the approach to ensure the cleanliness of the equipment used in any manufacturing process before being performed, as the 1963 GMP Regulations (Part 133.4) stated "Equipment shall be maintained in a clean and orderly manner" (FDA, First USA GMP Regulation, 1963). Today in the FDA Code of Federal of Regulation (CFR) has regarding cleaning programs the following requirements [4].

- 21 CFR 211.65 "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, quality, or purity of the drug product beyond the official or other established requirements."
- 21 CFR 211.67 (a) "Equipment and utensil shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."
- 21 CFR 211.167 (b) "Written procedure shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product."
- 21 CFR 211.180-182 "Records shall be kept of maintenance, cleaning, sanitizing and inspection."

There is four (4) mechanisms of contamination that can be found of products with a poor cleaning process that could affect the patient (Hall, 2003): First is Cross – Contamination with Active Ingredient (API): The main danger with this method of contamination is based that the product becomes a multiple ingredient product and not a single active ingredient as it should be on the first place. The second mechanism of contamination is Microbiological Contamination: this contamination has the peculiarity of develop at any time that includes a product that was cleaned effectively. This contamination involves effects on the stability of the finished product. Storage of equipment in wet condition provides a natural medium for bacteria to grown. The third mechanism of contamination is Contamination by Cleaning or Sanitizing Agent: In some manufacturing cleaning process a detergent may be need in order to clean the equipment. It is important to be aware of the composition of the detergent to be used. The four mechanism of contamination is Contamination by Miscellaneous Other Material: Excipient, bristles from brushes, paper filters, micron filter among other can be a possible source of contamination depending of the nature of the product being manufacture [2].

The Cleaning Validation process consists of 4 stages [8]. In the first stage the first step is to determine the most appropriate cleaning procedure for the equipment. During this step the acceptance criteria data for the contaminant will be generated. Then the process, equipment the cleaning agents and the cleaning techniques available, will determine the cleaning method. Finally all aspects of the cleaning procedure should be clearly defined in de the Standard Operation Procedure (SOP) Cleaning In Place (CIP) or Cleaning out of Place (COP) equipment. The second step is to develop and validate the sampling and chosen analytical methods for the compounds(s) being cleaned. During this step is important to decide is the sampling will be gather by swabbing the surface or by a sampling of the rinse during cleaning, this depend of the kind of product and the equipment to be cleaned. Also is important to determine the percent of recovery, the limit of detection limits of quantitation, accuracy of method, the reproducibility, and the stability over time among

other process. The third step of stage one is to evaluate equipment surfaces and determine the worst-case location to sample (swab sampling), the volume and type of rinse solvent to be employed (rinse sampling) and the equipment surface area, which is necessary to calculate carryover into subsequent batches.

The second stage of the cleaning validation process consists in developing a cleaning validation protocol for the product and the equipment being cleaned. This protocol should include: an introduction, the scope of the validation to be performed, the equipment that will be cleaned, the cleaning procedure to be validated, the sampling procedures, the analytical testing procedure, the Acceptance limits, and the acceptance criteria for the validation to be performed.

The third stage of the cleaning validation process is the development of the interim report. In this report the goal is to generate an interim cleaning validation report on a clean by clean basis detailing the acceptability of the cleaning procedure for the equipment and the product. This stage is required is there is a long period of time between manufacture and validation runs.

Quality Risk Management

Quality Risk Management (QRM) is defined by ICH as a systematic process for the assessment, control, communication and review of risk to the quality of the drug product across the product lifecycle [5].

The basic steps used to initiate and plan a QRM process includes the following (ICH, Quality Risk Management Q9, 2005):

- Define the problem and/or risk question.
- Assemble background information and/or data on potential hazard, harm or human health impact relevant to the risk assessment.
- Identify a leader and critical resources.
- Specify a timeline deliverables and appropriate level of decision making for the risk management process.

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with the exposure to those hazards.

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.

Risk Analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process linking the likelihood of occurrence and severity of harms.

Risk Evaluation compared identified and analyzed risk, against given risk criteria. It considers the strength of evidence for all three of the fundamental questions.

Risk control purpose is to reduce the risk to an acceptable level. The final decision might be obtained by the use of different processes, which includes benefit-cost analysis, for understanding the optimal level of risk control.

Risk reduction focuses on process for mitigation or avoidance of quality risk when it exceeds a specified level. It might include actions taken to mitigate the severity and probability of harm. Process to improve the detectability of risks might be used as part of the risk control strategy. Risk reduction implementation reduction measures could introduce new risk into the system or increase the significance of existing risks.

Risk Acceptance is a decision to accept risk It is important to understand that for some types of harm, even the best QRM practices might not eliminate risk entirely [5].

Risk Communication is the sharing of information about risk and risk management between the decision makers and others.

Some tools that could be uses as part of a QRM are [5].

- Basic risk Management facilitation methods (flowchart, check sheets, etc.);
- Failure Mode Effect Analysis (FMEA);
- Fault Tree Analysis (FTA);

Process Analytical Technologies

FDA considers Process Analytical Technologies (PAT) to be a system for designing,

analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and process, with a goal of ensuring final product quality. It includes chemical, microbiological, mathematical, and risk analysis in an integrated manner. The main purpose or goal of PAT is to enhance understanding and control of manufacturing processes that is consistent with the current quality system: quality cannot be tested intro products; it should be by design [3].

Lean Six Sigma

Lean and Six Sigma are a combination of the methodology of Lean Manufacturing and Six Sigma that looks for elimination activities that add no value and reducing the variation of any process.

Lean manufacturing is as a systematic identification and elimination of wastes; the implementation of the concepts of continuous flow; and customer pull. Waste or activities that add no value in a process that lean manufacturing defined in seven (7) major areas: overproduction, inventory, waiting, motion, transportation, rework, and over processing [6].

Six Sigma is a highly disciplined process that focuses on developing and delivering near-perfect products and service consistently. Six Sigma is also a management strategy to use statistical tools and project work to achieve breakthrough profitability and quantum gains in quality. The main purpose of Sig Sigma is the variation reduction of process in other to have a consistent quality final product [6].

Six Sigma and Lean Six Sigma phases on most organizations is describes as DMAIC. DMAIC is an acronym for define, measure, analyze, improve and control These 5 phases can be described as follows:

- Define: On the define phase the goal to seek is to define in a way that can be measure the problem (Y's) to be improve.
- Measure: On the measure phase the goal is to measure the current state of the process in an objective and well-planned manner using even historical data or in time data from the organization.
- Analyze: On the analyze phase the goal is to identify the root causes in the process that are causing the process to not meet the desire output.
- Improve: On the improve phase the goal is to look for innovative initiatives to eliminate or minimized the root causes that are causing the process not to meet the desire output and measure that improvement.
- Control: On the control phase the goal is to develop a control plan that assure the continuity of the improvements made on the process and to help identify future problem that could occur on process as part of the continuous improvement mentality.

METHODOLOGY

The Methodology to be used during this project will be the DMAIC methodology. This methodology is define in 5 phases as previously discussed in the literature review and consist on the define phase, the measure phase, the analyze phase the improve phase and the control phase.

During the Define phase a CTQ diagram will be develop to focus on the most critical areas in which the QRM needs to assess risk with the bigger impact in the achievement of compliance on the cleaning validation system. Finally this phase will end with a SIPOC Diagram to help us have a high-level understanding of the scope of the process and to give us the key outputs of the process.

During the measure phase it will be decided the possible risks and its ranking system to be used for the QRM of the cleaning validation system.

During the analyze phase 3 FMEA will be performed in order to analyze the most critical risks and would it be their impact to the cleaning validation. The first FMEA will be using as an example a 100% manual process; the second one will be for a CIP process; and the last one will be for a COP Process.

The improve and control phase will focus on PAT strategies recommendation that could be

implemented in a cleaning validation system focusing more on CIP and COP to increase efficiency a reliability of the process. Also another recommendation to mitigate the risks defined in the FMEA's. This is the key on controlling the process and assures the reliability of the process going forward.

RESULTS

Define Phase

A CTQ was used to assess the critical attributes needed to be address during a cleaning validation system in order to assure compliance with the regulator agency to assure the elimination of residues for API, Excipients, detergent or any miscellaneous that could affect the security, integrity, potency purity and quality of the product as specified on cGMP's CFR 21 part 210 and 211 for pharmaceutical products. Refer to Figure 1 for Cleaning Validation CTQ diagram.

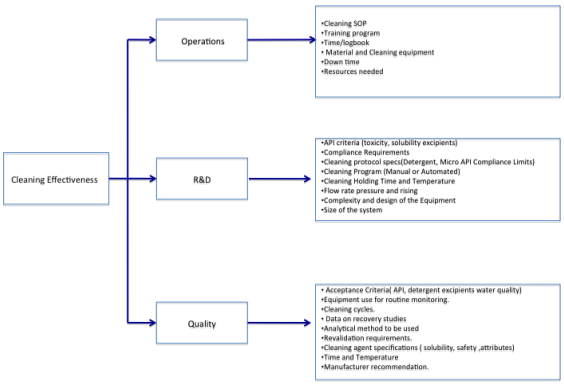

Figure 1
CTQ Diagram for Cleaning Validation System

A SIPOC diagram was used in order of develop a better understanding of a cleaning program and identify key output crucial for the compliance and efficiency of the cleaning validation system process that help us in the identify the best strategy to used and what is needed to apply this strategy. Refer to Figure 2 for Cleaning Validation SIPOC diagram.

Supplier	Input	Process	Output	Customer
R&D Department	Disassembly of system		Approved protocols	Operation Department
R&D Department	Precleaning requirements		Trained Personnel	Quality Department
R&D Department/ Quality Department	Cleaning, agent, concentration, solution, volume and water quality		Acceptance Criteria	Regulatory Agencies
R&D Department	Flow Rate, pressure and rising		Approved Cleaning SOP.	R&D Department
Regulatory Agencies	Government Regulations		Compliance Requirements	
Buyer/R&D Department	Complexity and design of the equipment		Cleaning Agent to be used.	
R&D Department/Training Department/Operations Department	Training of operation		Revalidation requirements	
R&D Department	Size of system		Data on recovery studies	
R&D Department	Time and Temperature		Safety Criteria	
R&D Department/ Operations and Quality Department.	Personnel Resources		Product Attributes	

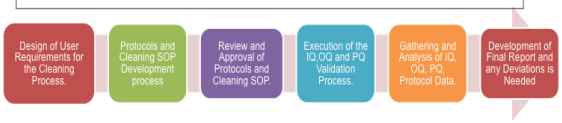

Figure 2
SIPOC Diagram for Cleaning Validation System.

Measure

Risk Assessment/Control Acceptability:

Risk Assessment:

Based on the Critical to Quality Diagram, potential risks are asses to meet these regulatory requirements necessity to comply in order to achieve an effective cleaning validation system.

Risk Control:

The risk associated will be evaluated based on the FMEA assessment of severity, occurrence and detectability. Failure mode and effect analysis (FMEA) is a risk management tool that provides an evaluation for potential risk in a process/product.

Risk Acceptability:

Risk priority number (RPN) will be used to characterize risk.

- RPN= Severity X Occurrence X Detection.
- ALARP= "As Low As Reasonable Possible".

A pharmaceutical consultant company quantitative and qualitative ranking/risk indexing to rank severity occurrence and detection will be used to rank the 3 FMEA of cleaning validation system for the 3 cleaning process to be addressed. This three (3) process are: a 100 % manual cleaning process; a CIP cleaning process; and a COP cleaning process. Refer to table 1, table 2, and table 3 for information regarding severity, occurrence and detection respectively. Table 4 is the risk

acceptability table that will determine the risk is tolerated or not.

Table 1
Severity Classifications

Classification	Category	Description	Rank	
			Quantitative	Qualitative
Negligible	Product	No real effect on performance	1	Low
	Process	Does not affect equipment performance		
	Regulatory/ Compliance	Submission- Agency contacts us with minor comments. No impact to schedule or submission		
Negligible	Product	Cosmetic issue that does not affect product performance	2	
	Process	Minor disruption of process. May cause additional documentation.		
	Regulatory/ Compliance	Submission- Agency contacts us and requests information; response is provided via teleconference with no impact the schedule or submission.		
Negligible	Product	Performance degradation of a single non-critical quality attribute	3	
	Process	Minor disruption of process. A portion of product may be non-conforming. Event is identified by in-process control tests.		
	Regulatory/ Compliance	Submission- Agency contacts us and requests information; response is provided in writing with no impact the schedule or submission.		
Negligible	Product	Performance degradation of multiple non-critical quality attributes	4	
	Process	Results in an event. Minimum impact to the manufacturing schedule. Event easily recognizable.		
	Regulatory/ Compliance	Inspection- FDA status – No action indicated Routine inspection by a Health Authority		
Negligible	Product	Performance degradation of a single critical quality attribute	5	
	Process	Results in an event. Slight impact to the manufacturing schedule.		
	Regulatory/ Compliance	Notification - Biological Product Deviation Report (BPDR) is sent to the Agency, no action is requested. Notice of violation (Untitled letter) – Notification of a "non serious" GMP violation that may or may not require a response		
Marginal	Product	Performance degradation of multiple critical quality attributes	6	Medium
	Process	Equipment or process failure impacting a non-critical process parameter and resulting in an event. No impact to batch release. Recoverable impact to mfg schedule.		
	Regulatory/ Compliance	Submission - Lot release –Several regions must pre-approve lots for commercial sale. Failure to obtain approval causes delay in schedule Inspection - Focused (for cause) inspection by Health Authority		
Marginal	Product	Product malfunction or product is ineffective without potential for injury, serious injury or death	7	
	Process	Equipment or process failure impacting a non-critical process parameter resulting in an event. May cause revalidation or change request.		
	Regulatory/ Compliance	Submission - Agency requests filing categorization upgrade, impacts schedule and causes delays Inspection - FDA status – voluntary action indicated Health Authority inspection report with deficiencies indicated Form FDA 483 received		
Marginal	Product	Potential of non serious injury	8	
	Process	Failure impacts a critical process parameter resulting in an event. May delay batch release or have a major impact to manufacturing schedule.		
	Regulatory/ Compliance	Submission - Agency delay of filing, due to incomplete information or the request of additional information. Filing on hold pending response, impacts schedule and causes delays Notification - BPDR resulting in a class 3 recall		
Critical	Product	Potential of serious injury	9	High
	Process	Equipment failure effecting a critical process parameter. May be outside of license claims. Requires revalidation or change request. Results in delayed batch release or major impact to manufacturing schedule. Batch may be rejected.		
	Regulatory/ Compliance	Submission – Refusal to file or non-approvable letter received. Inspection - FDA status – official action indicated Consent decree/Warning letter/Health Authority sanctions Fail Pre-Approval Inspection		
Catastrophic	Product	Potential of death	10	
	Process	Catastrophic equipment or process failure resulting in employee hazard or harm. Process is shut down. Batch rejected		
	Regulatory/ Compliance	Submission - Revoke license Notification - BPDR resulting in a class 1 or 2 recall Enforcement - Seizures; injunctions; prosecutions		

Table 2
Occurrence Classifications

Classification	Description	PROBALITY RATINGS			Rank	
		Likelihood				
		DPO*	Chronological	CpK	Quantitative	Qualitative
Very High	Failure is almost inevitable	≥1 in 2	More than one occurrence per day	< 0.33	10	High
		1 in 3	One occurrence every three to four days	≥ 0.33	9	
High	Repeated failures	1 in 8	One occurrence per week	≥ 0.51	8	
		1 in 20	One occurrence every month	≥ 0.67	7	
Moderate	Occasional failures	1in 80	One occurrence every three months	≥ 0.83	6	Medium
		1 in 400	One occurrence every six months to one year	≥ 1.00	5	
		1 in 2000	One occurrence per year	≥ 1.17	4	
Low	Relatively few failures	1 in 15000	One occurrence every one to three years	≥ 1.33	3	Low
Very Low	Only isolated failures	1 in 150000	One occurrence every three to five years	≥ 1.50	2	
Remote	Failure is unlikely	≤1 in 1500000	One occurrence in greater than five years	≥ 1.67	1	

*Defects per opportunity

Table 3
Detection Classification

Classification	Description	Detectability	Rank	
		Failures Undetected by Control Systems	Quantitative	Qualitative
Almost certain	Existing controls will almost certainly detect a failure. Failure would be evident to trained personnel and/or would be detected prior to execution.	≤1 in 1500000	1	High
Very High	Very high chance that existing controls will detect a failure. Events identified by on-line, at-line instrumentation.	1 in 150000	2	
High	High chance that existing controls will detect a failure.	1 in 15000	3	
Moderately High	Moderately high chance that existing controls will detect a failure. Failure would be detected early allowing corrective actions to be taken.	1 in 2000	4	Medium
Moderate	Moderate chance that existing controls will detect a failure. Failure would be evident to experienced personnel	1 in 400	5	
Low	Low chance that existing controls will detect a failure. Failure would be evident to a technical expert or a subject matter expert.	1in 80	6	
Very Low	Very low chance that existing controls will detect failure. Failure would be detected when data is being reviewed but possibly after execution.	1 in 20	7	Low
Remote	Remote chance that existing controls will detect a failure. Failure would not be detected without further analysis and/or testing.	1 in 8	8	
Very Remote	Very remote chance that existing controls will detect a failure.	1 in 3	9	
Almost Impossible	Almost impossible chance that existing controls will detect failure. Failure would not be detected by data review or testing.	≥1 in 2	10	

Table 4
Risk Accessibility Table

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

Analyze

Three (3) FMEA were performed to asses, characterize and evaluate the risk on the following cleaning systems: a 100% manual cleaning process, a CIP process and a COP process. Refer to Tables 5, 6 and 7 for the FMEA results. To ascertain the ranking process of a cleaning validation system the help of the same pharmaceutical consulting company was used during the FMEA's developing and analysis.

Note: To refer to Severity, Occurrence and Detection on the following tables the letters S, O and S was used.

Table 5
100% Manual Cleaning Process FMEA [1]

RISK	S	O	D	RPN
Incomplete SOP	9	4	6	216
Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	10	3	2	60
Untrained Personnel	8	4	3	96
Wrong Water Quality	9	2	1	18
Wrong Retention Time	10	2	1	20
Lack of Equipment	8	5	1	40
Calibration Problems	9	3	1	27
Failed Cleaning	7	6	1	42
Prolonged Downtime	5	7	3	105
Personnel Injury	10	1	1	10

Table 6
CIP Cleaning Process FMEA [1]

RISK	S	O	D	RPN
Incomplete SOP	9	4	6	216

Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	10	3	2	60
Untrained Personnel	8	4	3	96
Wrong Water Quality	9	2	1	18
Wrong Retention Time	10	2	1	20
Lack of Equipment	8	5	1	40
Calibration Problem	9	3	1	27
Equipment Malfunction	9	5	1	45
Failed Cleaning	7	6	1	42
Prolong Downtime	5	7	3	105
Personnel Injury	10	1	1	10

Table 7
COP Cleaning Process FMEA [1]

RISK	**S**	**O**	**D**	**RPN**
Incomplete SOP	9	4	6	216
Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	10	3	2	60
Untrained Personnel	8	4	3	96
Wrong Water Quality	9	2	1	18
Wrong Retention Time	10	2	1	20
Lack of Equipment	8	5	1	40
Calibration Problems	9	3	1	27
Equipment Malfunction	9	5	1	45
Failed Cleaning	7	6	1	42
Prolonged Downtime	5	7	3	105
Personnel Injury	10	1	1	10

The results decision of the FMEA's performed are showed in the following tables:

Table 8
100% Manual Cleaning Process Risk Accessibility

Risk	Accessibility
Incomplete SOP	Intolerable
Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	ALARP
Untrained Personnel	ALARP
Wrong Water Quality	ALARP
Wrong Retention Time	ALARP
Lack of Equipment	ALARP
Calibration Problems	ALARP
Failed Cleaning	Broadly Acceptable
Prolonged Downtime	ALARP
Personnel Injury	ALARP

Table 9
CIP Cleaning Process Risk Accessibility

Risk	Accessibility
Incomplete SOP	Intolerable
Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	ALARP
Untrained Personnel	ALARP
Wrong Water Quality	ALARP
Wrong Retention Time	ALARP
Lack of Equipment	ALARP
Calibration Problems	ALARP
Equipment Malfunction	Broadly Acceptable
Failed Cleaning	Broadly Acceptable
Prolonged Downtime	ALARP
Personnel Injury	ALARP

Table 10
COP Process Risk Accessibility

Risk	Accessibility
Incomplete SOP	Intolerable
Wrong Acceptance Criteria (API Residue, Temperature, Toxicity)	ALARP
Untrained Personnel	ALARP
Wrong Water Quality	ALARP
Wrong Retention Time	ALARP
Lack of Equipment	ALARP
Calibration Problems	ALARP
Equipment Malfunction	Broadly Acceptable
Failed Cleaning	Broadly

	Acceptable
Prolonged Downtime	ALARP
Personnel Injury	ALARP

Improve and Control Recommendation

The FMEA's showed that an incomplete standard operation procedure (SOP) is the only intolerable risk following the acceptance criteria used for this analysis. It important to understand that an SOP is critical for any process because is the document that will be followed on the execution of any process. As a recommendation to minimize the occurrence of this risk it will be helpful to apply the following steps:

- Assure that all the important process step will be including on the document.
- Use visual aids to ease the understanding of the execution.
- Develop a checklist with all the information that an SOP needed in order to execute the process successfully.
- Use a Video showing how the process needs to be executed for training and analysis purposes.
- Review at least every 6 months and ask the personnel executing the procedure their feedback and recommendation for improvement if needed.

In addition is important to assure an effective sampling method that help to assure the cleaning process. PAT is a useful approach to develop a robust analytical process for times to come. As previously discussed PAT stands for Process Analytical Technologies and is define as a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and process, with a goal of ensuring final product quality.

Examples of PAT used today to help assures an effective cleaning process are NIR and HPIMS. NIR spectroscopy is defined as a measurement system of the wavelength intensity of the absorption of near-infrared light by a specific sample. HPIMS which stand for High Performance Ion Mobility Spectrometry is a rapid separation technique based on the size and shape of molecular ions.

Both techniques has showed success on detecting API, Detergent and Excipient residues as shown in the Excellims article "Electrospray Ionization- High Performance Ion Mobility Spectrometry for Rapid On-site Cleaning Validation in Pharmaceutical Manufacturing" and the Patrick J. Cullen, Ph.D., Ian Jones, Laura Alvares-Jubete, Ph.D., Jaya Mishra and Carl Sullivan, Ph.D article "Cleaning Validation Using Direct NIR Imaging".

Excellims results showed a robust way to analyze 14 API's drug molecules using HPIMS. Cullen, Jones, Alvares-Jubete, Mishra and showed a lineal model with a R^2 of 96% and 99% of detection for 2 different API.

A PAT constraint is in Microbiology analysis because of the bacterial grown time needed in order to obtain an effective analysis of any microbial activity.

CONCLUSION

QRM approach is an effective systematic approach that allows us to manage risks and seeks for way to mitigate, eliminate and control them. QRM on a cleaning validation system helped us understand risk and how critical their effect could be on compliance, effectiveness and reliability of the cleaning process in order to obtain a cleaning process that meet regulatory agencies and safety requirements while being profitable for the company. PAT is helpful in order to obtain a robust analytical method to assure the effectiveness of a cleaning process by giving the ability of sample the hall cleaning area and giving us if implemented correctly a useful tool to obtain analytical on time data that help on the assurance and compliance of a cleaning validation process.

REFERENCES

[1] Leblanc, D,A. *"Validated Cleaning Technologies for Pharmaceutical Manufacturing", Interpharm/CRC, Boca Raton London New York Washington DC, 2000*, pp. 135-203.

[2] *Hall, W. E. "Validation and Verification of Cleaning Processes"*. In A. H. Robert A Nash, Pharmaceutical Process Validation, Marcel Dekker Inc., 2003, pp. 500-541.

[3] FDA. "*Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*", FDA, July 2010. Retrieved from: http://www.fda.gov/downloads/Drugs/Guidance's/ucm070305.pdf.

[4] FDA. "*FDA Current Good Manufacturing Practice for Finished Pharmaceuticals", Federal Drug Administration, July 2010.* Retrieved from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=211.

[5] ICH. *"Quality Risk Management Q9"*, International Council of Harmonization, November 2005, Retrieved from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf.

[6] LSS Primer, 1st ed., Quality Council of Indiana, West Terre Haute, IN, 2007, pp. II 7-9.

[7] Walsh, A. *"Cleaning Validation for the 21 Century: Acceptance Limits for Active Pharmaceutical Ingredient (API's)"*, July/August 2011, Retrieved from http://www.stevens.edu: http://www.stevens.edu/ ses/ documents/ fileadmin/ documents/ pdf/ Cleaning_ Validation_ for_ the_ 21st_ Century_ - Acceptance_Limits_for_APIs_-_Part_I.pdf.

[8] APIC. *"Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants"*, Active Pharmaceutical Committee, September 1999, pp. 11. Retrieved from http://apic.cefic.org/ pub/4CleaningVal9909.pdf.