Quality Risk Management (QRM) Considerations for Introduction of New Products

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Abstract *— Quality Risk Management (QRM) is an optional tool to improve product effectiveness and safety by assuring that the recognized risk is at a desired level. Also risk management tools provide a methodology to evaluate risk levels and prioritize on risk mitigation and risk control strategies. For this design project an evaluation was performed to identify the factors and considerations that could be adopted from the QRM methodology during the technology transfer process and new product introductions. The technology transfer approach was used to see possible risks and take on preventive actions to mitigate risk and avoid to inherit the risks throughout product life cycle. ICH Q9 was used as a guide for risk assessment during a pilot program on whole to ICH Q10 Pharmaceutical Quality System. An evaluation was conducted by determining risk prioritization numbers during the different new product introduction stages. It was noticed that as the new product introduction process progressed closer to commercial manufacturing, launch and distribution, the risk decreased which was a result of increased process detectability and reduced occurrence.*

Key Terms*— FMEA, New Products, Quality Risk Management, RPN, Technology Transfer.*

PROBLEM STATEMENT

In order to keep the industry in a competitive market the constant development of new products and processes are necessary. The industry is regulated by various accrediting agencies to ensure the product safety, quality and efficacy. Currently there are some trends that are impacting the industry to improve its performance. The quality system is one of them; industries not only focus on the production of a product, but rather to comply with Good Manufacturing Practices (GMP) to prevent any risk to the consumer. 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 [1]. Existing guidelines are not mandatory but it benefits both the patient and the developer which help identify, assess and mitigate these risks.

Quality Risk Management (QRM) is defined by the guide ICH Q9 as a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. [1]. Therefore QRM could be a tool to be used since the discovery of a new product to its development and commercialization to mitigate or minimize the occurrence of any risk associated with the process during the life cycle of the product.

PROJECT DESCRIPTION

This project will consist in the development and interpretation of possible considerations for the implementation of quality risk management to introducing new products to mitigate the risks associated with product development using technology transfer for maintaining control and quality during development.

PROJECT OBJECTIVES

The project objective is to design and develop considerations for risk assessment methodology from the early stage of a product life cycle. Project Contribution

Quality: maximize the contribution of QRM in the process of introducing new products as part of the continuous and constant search for improvement the process of discovering and developing a new product, to ensure efficient and safe final product

that meets requirements and regulations from the accreditation agencies.

LITERATURE REVIEW

This section will summarize the most relevant topics that will give us the key to understanding this article.

Technology Transfer

The technology transfer (TT) is the documented process for transferring a product developed from research and development (R&D) through manufacturing or within or between manufacturing and testing sites. This argument reinforces the importance to transfer all the information through the development process. The most transfers start after develop the product, as shown figure 1.

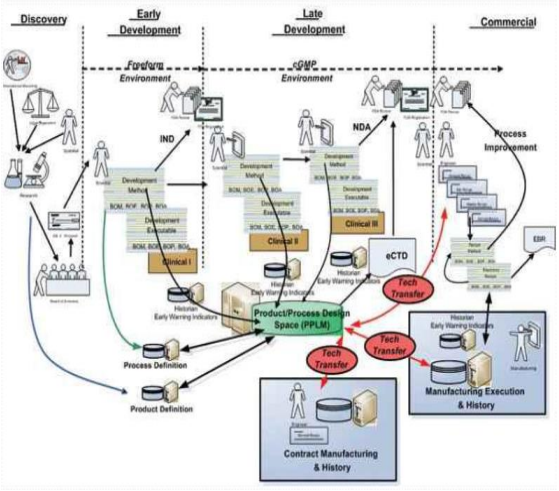

Figure 1
Product Cycle Life and Tech Transfer

Technology transfer is part of the technical activities for new and existing products explained in ICH Q10 guide. The purpose of this guideline is applied to product lifecycle activities [2].

- Pharmaceutical Development: Drug substance development; formulation development; manufacture of investigational products; delivery system development; analytical method development, manufacturing process development and scale up.
- Technology Transfer: New product transfer during development through manufacturing; transfers within or between manufacturing and testing sites for marketed products.
- Commercial Manufacturing: Acquisition and control of materials; provision of facilities, utilities, and equipment; production; quality control and quality assurance; release; storage; distribution.
- Product Discontinuation: Retention of documentation; sample retention; continued product assessment and reporting. [2]

The goals of these approaches work together for a continual improvement on quality through product lifecycle, as show Figure 2. The Technology Transfer (TT) goal is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control, strategy, process validation approach and ongoing continual improvement [2].

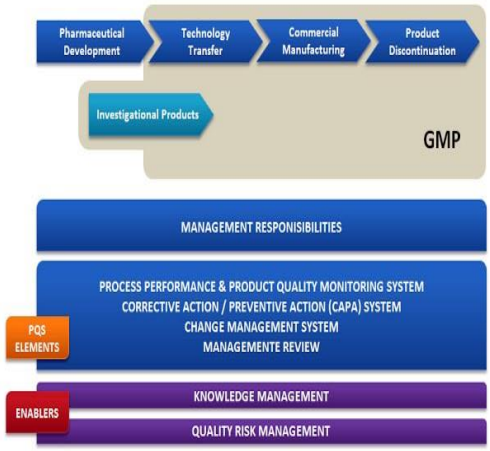

Figure 2
Diagram of the ICH Q10
Pharmaceutical Quality System Model

Quality Risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement

of process performance and product quality throughout the product lifecycle.

It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the product remain consistent with those used in the clinical studies. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality [1].

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 through the product lifecycle. Two primary principles are evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality and documentation should be commensurate with the level of risk. [1]

Possible steps used to initiate and plan a QRM process might include the following [1]:

- 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.

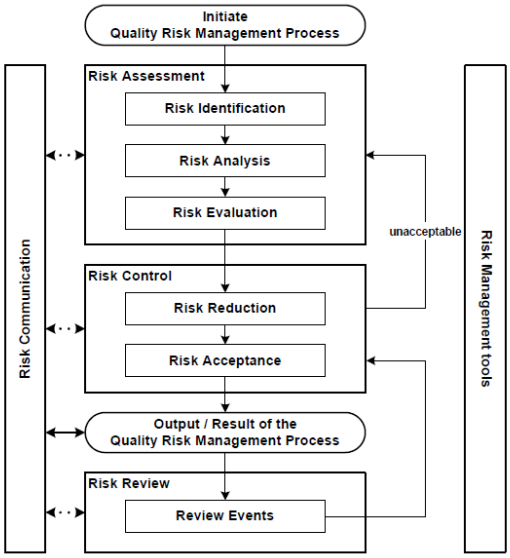

Figure 3
Overview of a Typical QRM Process

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 [1].

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

The pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools that could be uses are [1].

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);

- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

DMAIC

Most of industries or companies implementing Six Sigma utilize the DMAIC methodology to keep continual improvement. This methodology can be thought of as a roadmap for problem solving and product/process improvement. DMAIC is an acronym for five interconnected phases; Define, Measure, Analyze, Improve, and Control. These 5 phases can be described as follows:

- Define the problem, improvement activity, opportunity for improvement, the project goals, and customer (internal and external) requirements;
- Measure process performance;
- Analyze the process to determine root causes of variation, poor performance (defects);
- Improve process performance by addressing and eliminating the root causes;
- Control the improved process and future process performance [3].

Failure Mode Effects Analysis (FMEA)

FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures [1].

FMEA can be used to prioritize risks, monitor the effectiveness of risk control activities, equipment and facilities and to analyze a manufacturing process in order to identify high risk steps.

METHODOLOGY

The Methodology used during this project was a combination between DMAIC methodology and Quality Risk Management tools as per referenced guidelines. The DMAIC methodology consisted of five (5) phases as previously discussed in the literature review. The phases consisted on the define phase, the measure phase, the analyze phase, the improve phase and the control phase.

During the define phase, a flowchart diagram was developed to focus on the product life cycle process. The flowchart diagram helps to show the actual state of QRM assessment on the process. This visual is to help us have a high-level understanding of the scope of the process and to give us the key of the process.

During the measure phase the possible risks characterizations and its ranking system were determined and used for the QRM of the product lifecycle.

During the analyze phase 3 FMEAs were performed in order to analyze the most critical risks and their impact through the process.

The improve and control phase will focus on technology transfer strategies to improve and control the risk through the cycle and will be to give us a relation between the product lifecycle process and the risk priority number. On this step a flowchart was developed to show the “after” to use of QRM during all product process lifecycle.

RESULTS

In this section results obtained will be explained and analyzed.

Define Phase

A technology transfer is the documented process for transferring a product developed through their lifecycle. This information could to give us a parameter to research the critical and priority risk through all the process or product lifecycle to an

introductory product. The information will be our source to see potential areas to high risk or critical parameters on the product lifecycle process. The product life cycle technology transfer is compound to 3 phases; discovery, development and commercial. To help us to identify the areas develop process was created a flowchart, as shown the figure 4.

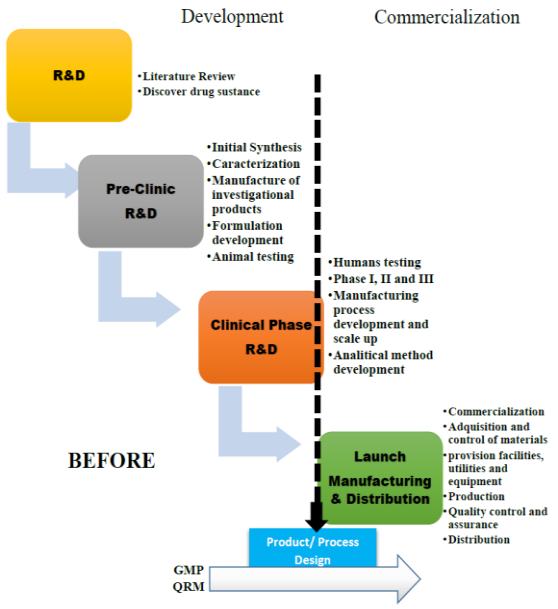

Figure 4
Flowchart for New Product Lifecycle

A flowchart is used to a better understand the process and the relation between the TT, product lifecycle and the QRM. Actually, the pharmaceutical industry is limited to work QRM only with GPM regulations. The goal is to show how the QRM assessment could be applied to all the cycle and their direct relation with risk priority number.

Measure

Risk Assessment/Control Acceptability:

Risk Assessment: Based on the QRM principles, the risk should be based on scientific knowledge and ultimately link to the protection of the patient in order to achieve an effective and safe product.

Risk Control: The risk associated will be evaluated based on the FMEA assessment of severity, occurrence and detectability.

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

RPN = Severity X Occurrence X Detection (1)

Table 1, table 2, and table 3 refer to information about the characterization created to severity, occurrence and detection respectively. Table 4 and 5 is the risk acceptability table that will determine the risk is tolerated or not.

Table 1
Severity Classifications

Ranking	Severity	Description
1	None	(Failure would not be noticeable to the customer)
2	Minor	(Failure could be noticed by the customer but is unlikely to be perceived as significant)
3	Moderate	(Failure causes a high degree of customer dissatisfaction)
4	High	(Failure leads to customer perception of safety issue, cause high degree of patient dissatisfaction)
5	Extremely High	(Failure could lead to injury to customer)
6	Dangerously high	(Failure could lead to death or permanent injury to customers)

Table 2
Occurrence Classifications

Ranking	Occurrence	Description
1	Remote	(Failure don't have probability to repeat, unlikely)
2	Low	(Failure happen infrequently)
3	Moderate	(Failure happen in a low frequency)
4	High	(Failure happen frequency)
5	Very High	(Failure happen regularly)

Table 3
Detection Classification

Ranking	Detectability	Description
1	Almost Certain	(The defect is obvious, failure can and will detected in all cases)
2	High	(Failure is detected by automatically inspected)
3	Moderate	(Failure will normally be detected with some statistical programs)
4	Low	(Failure is detected manually inspected in the process)
5	Remote	(Product is accepted based on no defects in a sample)
6	Absolute Uncertainly	(Failure is not detectable because the product is not inspected)

Table 4
Risk Accessibility Table

occurrence/probability			severity/consequences		
very unlikely	1	unlikely to happen	negligible	1	not impact
unlikely	2	expected to happen infrequently	marginal	2 3	cause a minor impact in quality
occasional	3	happen in low frequency			
moderate	4	happen frequency	critical	4 5	cause significant impact in quality
frequent	5	happen regularly	catastrophic	6	severe impact in quality

Table 5
Risk Accessibility Table

	OCURRENCE				
SEVERITY	Very unlikely	Unlikely	Occasional	Moderate	Frequent
Negligible	Acceptable	Acceptable	Acceptable	High	High
Marginal	Acceptable	Acceptable	Acceptable	High	High
Critical	Acceptable	Acceptable	High	High	High
Catastrophic	Acceptable	High	High	High	High

Analyze

One (1) FMEA was conducted to characterize and evaluate the risk through product lifecycle process. There are three (3) factors of risk that are identified as priority for the process development; stability of product, customer safety and the product efficiency. To each parameter a ranking was allocated and assigned according to documentation obtained from the process.

The results of the FMEA's performed are showed on Table 6.

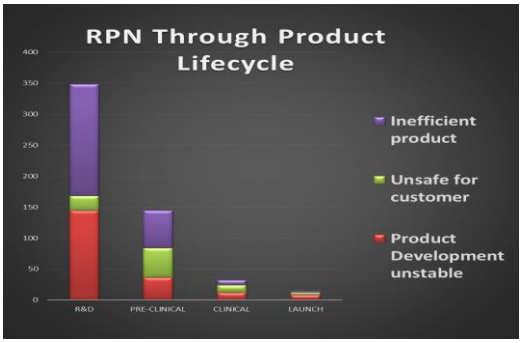

Figure 5
Graphic Result to FMEA

Table 6
Product Lifecycle FMEA

Process	Potential Failures Mode	Potential cause	S	O	D	RPN
R&D	Product Development unstable	Unknown formulation Insufficient base of knowledge	6	4	6	144
	Unsafe for customer	Specification are being developed unknown	1	4	6	24
	Inefficient product	Test Methods being developed, unknown damage to humans or environment	6	5	6	180
			Total RPN: 348			
Pre-clinical	Product Development unstable	Failure synthesis and characterization Chemically and fiscally unstable Unknown pharmacokinetics (PD)	4	3	3	36
	Unsafe for customer	Specifications and characterization in process	3	4	4	48
	Inefficient product	Doses are not defined Pharmacokinetics (PK) uncertain	5	4	3	60
			Total RPN: 144			
Clinical	Product Development unstable	Unknown process development Problems with reproducibility the product	3	2	2	12
	Unsafe for customer	Document do not have the IND approval	2	2	2	8
	Inefficient product	Dosing ranges are being developed I and II On develop PK and PD	2	2	3	12
			Total RPN: 32			
Launch	Product Development unstable	Product Validated	2	2	2	8
	Unsafe for customer	Safety and PK data satisfactory	2	2	1	4
	Inefficient product	Mfg. processes validated	1	2	1	2
			Total RPN: 14			

Improve and Control Recommendation

The results demonstrated the direct relation between the RPN throughout the product lifecycle.

As each phase is completed the RPN is reduced for the potential fail mode. The results are varied because the use of technology transfer works to minimize the risk throughout the process. The relation between RPN and all the process is shown very parallel, where as you go through the process, the RPN is reduced and improve the control of the process and minimize risk.

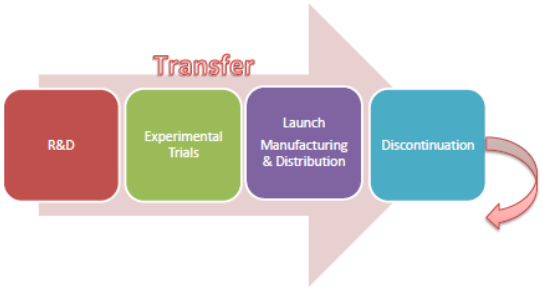

Figure 6
Flowchart for Technological Transfer to New Product

The transfer of documentation on each station improves the next station to achieve a process control, as shown next (figure 6). The technology transfer works as a facilitator to control the risk and improve the process. Using RPN as indicator of high risk from the beginning of the cycle, we could obtain a controlled process.

Controlling the risk on all phases of the process can reduce the hazards to customer and open a pathway to possible continual improvement, as shown in figure 7.

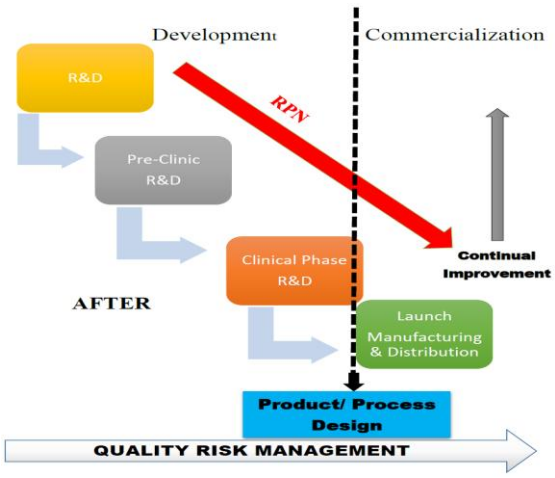

Figure 7
Flowchart for New Product Lifecycle

CONCLUSION

QRM helped us to understand risk and how critical is the effect on compliance, effectiveness and reliability of the product. Technological transfer is helpful in order to obtain all the documentation to keep the control, stability and quality of the product during all processes. Also it gives us the necessary tools to prevent, minimize or eliminate the risks that affect the product process.

Kevin & Arthur say on his article "GAMP 5 Quality Risk Management Approach": The companies need to focus skilled resources where the risks are highest, thus minimizing risk to patients while maximizing resource utilization and efficiency [4]. Definitely the utilization of QRM plays an important role for the industry. Regrettably the use of this tool is not mandatory to the industry at this time.

An evaluation was conducted by determining risk prioritization numbers during the different new product introduction stages. It was noticed that as the new product introduction process progressed closer to commercial manufacturing, launch and distribution, the risk decreased which was a result of increased process detectability and reduced occurrence.

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