Essentials in Quality Risk Management

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Quality Risk Management (QRM) Principles

Quality risk management is an essential element of every aspect drug development and manufacturing throughout the product lifecycle. Quality risk management (ICH Q9) is designed to assure that drug critical quality attributes (CQAs) are defined and maintained from phase to phase during drug development and manufacturing and changes in drug product formulation, definition, analytical method and associated process changes are understood and managed to assure patient safety and drug efficacy. An effective QRM process can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential risks to quality during development and manufacturing.

Risk can be defined two ways:

1. Risk is the combination of the probability of occurrence of harm and the severity of that harm.

2. Risk is the potential influence of product and process factors on critical quality attributes and the uncertainty of that influence.

The first definition is traditional and takes into account potential failures and adverse events and the second takes into account influence of factors relative to critical quality attributes (CQAs) and how well we understand or know the influence of those factors on critical quality attributes of the drug product. In

modern drug development it is often the second definition that is a problem in that we don't know what we don't know. As we complete development activities the risk goes down because our knowledge and understanding of the factors associated with unit operations and analytical methods goes up relative to product acceptance and all associated CQAs.

There are two key principles in QRM, 1) risk assessment should be based on scientific knowledge associated with product and process understanding and 2) the level of effort and detail associated with risk assessment/management should be commensurate with the level of risk being identified and evaluated. Science guides us and facts/data minimizes and helps to control the risk. A common criticism of risk assessments they are just opinions and not backed by science. The higher the focus and dependence on scientific principles, thought experiments, literature/research, prior experimental results and understanding of our historical performance brings the best science into the QRM process. The major benefits of QRM and risk assessments are to improve the ability to develop drug products and drug substance and answer the question "*When, what, how much and where do we need additional development?"* Development activities reduce potential risks to safety and efficacy and help to +achieve the benefits of the drug for the targeted indication.

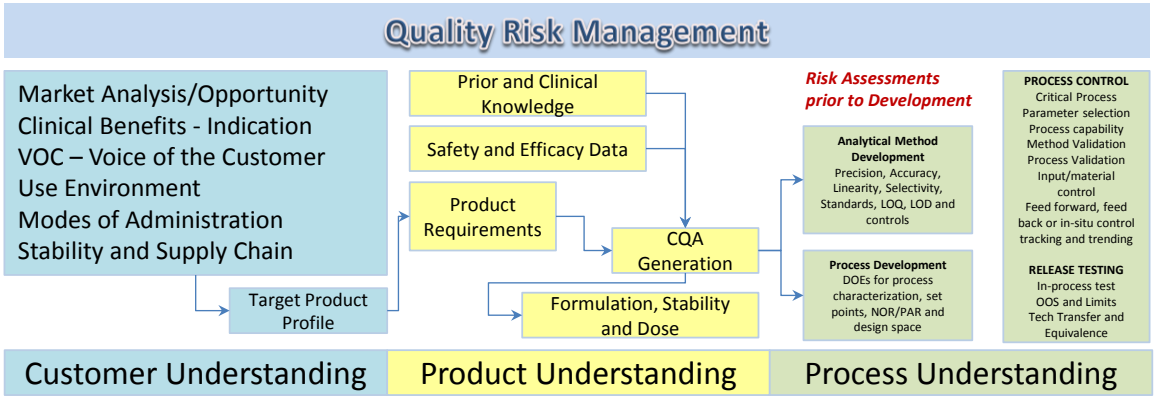


Figure 1 QRM and Systematic Drug Development

Systematic drug development and QRM ensure that we maintain line of site from the Target Product Profile, to the Quality Target Product Profile (QTTP), through CQA generation to analytical method selection, unit operation characterization, specification and acceptance criteria limit generation, critical process parameter and control selection and finally method and process validation. Q6, Q8, Q9, Q10 and Q11 detail the pharmaceutical development process and how to set limits. The QRM process is linked to product and process CQAs as they are the quality attributes of the drug we wish to assure.

Drug Substance Critical Quality Attributes

Product Development Team Leader: Approval/Review Date: Product Development Team Members:

	Drug Substance Design Requirements and Critical Quality Attributes										
DS Component	Attribute No.	Critical Quality Attribute Name	Critical Quality Attribute Purpose	Test or Measurement Method	Attribute Target	Attribute Upper Limit	Attribute Lower Limit	CQA Development Strategy	Process Capability (optional)	Prior Knowledge	CQA Risk*
API- Active Pharmaceutical Ingredient	1										10
	2										7
	3										5
	4										3
	5										1
Appearance and Description	1										
	2										
	3										
	4										
	5										

Figure 2 QTTP and CQA Identification and Line of Sight

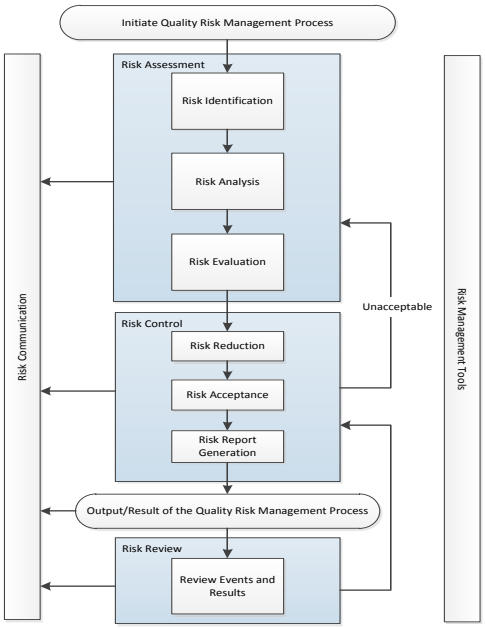
Quality Risk Management Process

QRM is a process and like any process has a series of operations, inputs and outputs. All unit operations, formulations, analytical methods, excipients, cell banks, working cell banks, equipment, reagents, chemistry, facilities and materials are evaluated for the potential influence they may have on drug CQAs and product requirements. Any time a change event is being recommended a risk assessment should be initiated. Any time an analytical method is being developed and or a process is being characterized a risk assessment should be generated prior to study design.

Pharmaceutical Development Process

Product/Process Development Interdisciplinary Teams

Management Involvement and Direction



Risk Management Tools

Technical risk assessment
Business risk assessment
FMEA
Fault Tree Analysis
Hazard analysis
Pareto
DOE
Regression
Sniper Plots
Simulation, tolerance analysis
Process mapping
Margin/capability analysis
Super Fishbone

Figure 3 QRM Process (Q9)

1. Risk Assessment

The QRM process is linked to product and process CQAs as they are the quality attributes of the drug we wish to assess. Risk assessment includes risk

identification, risk analysis and evaluation. This is generally a team effort to work through the product/process step-by-step to identify and evaluate each potential risk. Outcome from the assessment should be a set of identified and prioritized risks that either require action and or are considered acceptable with an associated rational. Risk assessments should generally be done in advance of development or change control rather than as a justification of changes after the fact.

All risk assessments begin with a clear risk question. The risk question focuses the risk assessment team as to the risk area to be assessed. It is recommended that a list of CQAs be identified to there is line of site from CQAs to unit operation and or other drug attributes. Two types of risk assessment templates are commonly used; 1) QRM high level risk assessment (FMEA like) and 2) a low level detailed DOE Factor Response Matrix.

Drug Substance Technical Risk Assessment

Product, Project or CMC Activity:

Date:

Background, Problem, Business Objectives and Goals:

Team Leader and **Team Members:**

What is the problem you are trying to solve, risk needing assessment? What is the background, purpose and/or goals?

Risk Question(s):

What is/are the specific product, process or assay development risk question(s) that need to be assessed?

CQAs

ICH Parameter	CQA/assay name (release)	USL	Target	LSL	Assay/Test name for Characterization Only
Safety					
Identify					
Purity/impurity					
Potency					
Stability					
Yield					

Process Step and or Process Changes					Risk Analysis					
Unit Operation Number	**Unit Operation Name**	**Baseline** (optional)	**Change** (optional)	**Difference** (optional)	**Potential Risk, Influence** or **Failure Mode**	**Severity** and/or **Influence (1,3,5,7,10)**	**Probability** and/or **Uncertainty (1,3,5,7,10)**	**Detectability** (optional) **(1,3,5,7,10)**	**Risk Score (RPN) Severity x Probability Only**	**Risk Score (RPN) Severity x Prob x Detect**
	Description			**Unit Operation Delta (Δ)**						
1						5	3		15	0
2									0	0
2									0	0
2									0	0
3									0	0
3									0	0
3									0	0
4									0	0
5									0	0
6									0	0
7									0	0
9									0	0
10									0	0
11									0	0
12									0	0
13									0	0
14									0	0

Figure 4 QRM Template, High Level Risk Assessment

DOE Factor/Response Matrix

Experiment Name:

Date:

Experimental Problem, Objectives and Goals: Experimenter(s):

What is the problem you are trying to solve? What is the purpose, study questions and goals?

			Responses (Y)							
		Goal (Max, Min, Target)	Match Target	Minimize	Maximize	None				
		Upper Limit								
		Target								
		Lower Limit								
		% GR&R - 1 stdev ME								
		Responses (Y)	Response 1	Response 2	Response 3	Reponse 4	Reponse 5	Reponse 6	Reponse 7	
Experimental Factors Xs			Relative Importance of the Ys (weight)							
Ease of Randomization	Factor Types	Factors (X)	1	3	1	1	1	1	1	Totals*
Easy	Continuous	Factor 1	0	0	0	0	0	0	0	0
		Factor 2	0	0	0	0	0	0	0	0
		Factor 3	0	0	0	0	0	0	0	0
		Factor 4	0	0	0	0	0	0	0	0
		Factor 5	0	0	0	0	0	0	0	0
		Factor 6	0	0	0	0	0	0	0	0
		Factor 7	0	0	0	0	0	0	0	0
		Factor 8	0	0	0	0	0	0	0	0

Figure 5 DOE Factor Response Matrix, Low Level Risk Assessment

2. Risk Control

Risk control has two potential outcomes, either we take action to minimize and control risks and or we consider the risks are acceptable and there is a scientific rationale as to why the risks are acceptable. There are many potential activities that can control risk. In general we reduce the severity, lower the probability and or improve detectability to lower the risk. Adding redundancy and/or increasing robustness are also key considerations to design out and control risk. PAT/SPC and the associated control logic design are also important concepts in designing out risk and designing in input and output control loops.

Risk Control and Risk Reduction Evaluation								
Risk Reduction Actions	Name: (who will do it?)	Due Date	New Severity and Influence (1,3,5,7,10)	New Probability and/or Uncertainty (1,3,5,7,10)	New Detectability (optional) (1,3,5,7,10)	New Risk Score (RPN) Severity x Probability Only	New Risk Score (RPN) Severity x Prob x Detect	Scientific/Technical Rational if Risk is Acceptable
			3	3	3	0	27	
						0	0	
						0	0	
						0	0	
						0	0	

Figure 6 Risk Control

3. Risk Communication and Review

Once the risk assessment and the control actions have been determined it is critical in the QRM process to communicate the actions to process owners and

key stakeholders. CMC team leaders, key managers and development teams will need to know the actions required to minimize the identified risks. Clear action owners, implementation timelines and an effective documentation and review process are needed to make the needed and identified changes happen.

Risk Communication		Development Priority
Name: (Who needs to know?)	**Organization/Dept.**	**Development Priority for Unit Operation**
		High
		Medium
		Low

Figure 7 Risk Communication

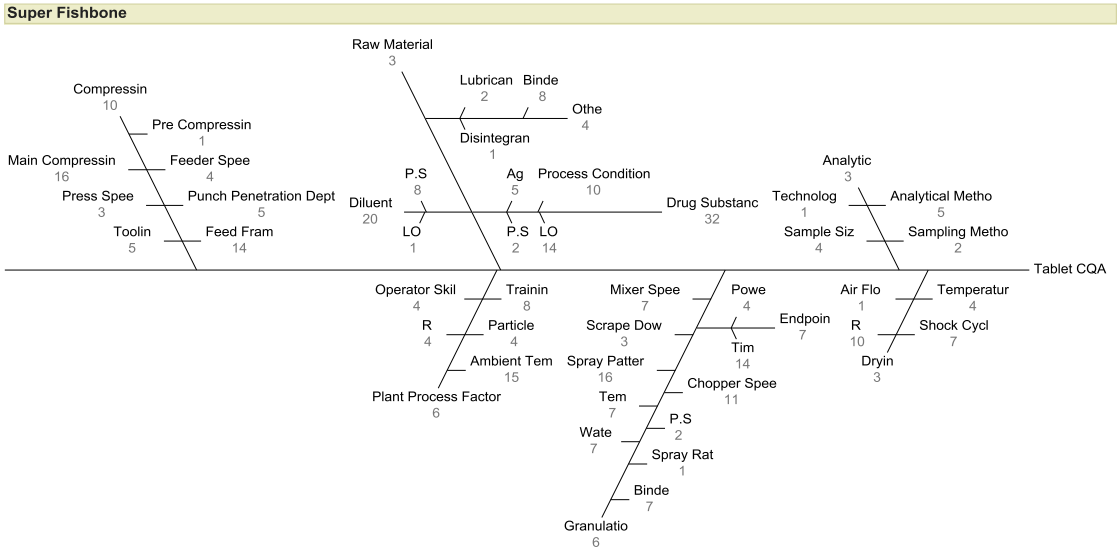


Figure 8 Super Fishbone Diagram

QRM Tools

QRM tools are typically used in the risk identification, risk analysis, evaluation and control. There are two types of tools, 1) risk assessment and control and 2) statistical/analytical tools. Risk assessment and control tools aid in the risk identification, risk control and risk communication. Statistical/analytical tools aid in variation analysis, identification of risk areas and determining the probability and frequency of potential risks. Analytical and quality tools further help to

identify and prioritize risk. Knowing the right tool for the right job is fundamental to proper risk identification and control.

- Risk Assessment Tools
  - Failure Modes and Effect Analysis (FMEA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
- Statistical/Analytical Tools
  - Pareto and Risk Weighted Pareto analysis
  - Process flow and Risk Priority Numbers (RPN)
  - Super Fishbone (Cause and Effect Diagram with RPN)
  - Histograms and process capability
  - Control charts
  - Sniper Plots
  - ANOVA and hypothesis testing
  - DOE (product and process)
  - Variation studies, POV and REML

QRM Implementation

Every company that is involved in drug development needs to take QRM very seriously. An implementation plan with tools, training and SOPs are needed to build a low risk development and manufacturing platform. Management involvement is needed to trigger risk assessment generation, form teams, communicate risk reduction or acceptance actions and establish a formal review process to measure results and progress. Clarification of roles and responsibilities for QRM within a company also will need to be formalized.

References:

ICH Q6 Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, 2000

ICH Q8 Pharmaceutical Development, 2009

ICH Q9 Quality Risk Management, 2006

ICH Q10 Pharmaceutical Quality System, 2009

ICH Q11 Development and Manufacture of Drug Substances, Draft

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004