Centre for Biopharmaceutical Excellence

Basics of Quality Risk Management

Module Topics

- Current Regulatory Expectations
- Some Important Definitions
- Risk Management Process
- Examples and modified FMEA

Module Objectives

On completion of this module you should be able to:

- State how Pharmaceutical Quality System (ICHQ10) and Quality Risk Management (ICH Q9) are integrated
- Conduct basic risk assessments
- Apply some basic QRM tools to industry examples
- Develop a simple FMEA for an example pharmaceutical product

Some Key Definitions

Risk

- Combination of the **probability of occurrence** of harm and the **severity** of that harm (ISO/IEC Guide 51:1999, definition 3.2)

Residual Risk

- Risk remaining after protective measures have been taken (ISO/IEC Guide 51:1999, definition 3.9)

Tolerable Risk

- Risk which is accepted in a given context based on the current values of society (ISO/IEC Guide 51:1999, definition 3.7)

Risk Management File

- The set of records and other documents, not necessarily contiguous, that are produced by a risk management process (ANSI/AAMI/ISO 14971: definition 2.19)

Some Key Definitions
(from AS4360 and ISO14971)

Risk analysis

- systematic use of available information to identify hazards and to estimate the risk. Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm

Risk evaluation

- process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

Risk criteria

- terms of reference by which the significance of risk is assessed

Risk reduction

- actions taken to lessen the **likelihood**, negate **consequences**, or both, associated with a **risk.**

Some Key Definitions

Hazard

- potential source of HARM (ISO/IEC Guide 51:1999, definition 3.5)

Hazardous situation

- circumstance in which people, property, or the environment are exposed to one or more hazard(s)

Harm

- physical injury or damage to health of people, or damage to property or the environment (ISO/IEC Guide 51:1999, definition 3.1)

Severity

- measure of the possible consequences of a hazard

Managing Risk

- We manage risk continuously, sometimes without realizing it.
- We mostly consider risk implicitly in our decision making.
- The alternative to risk management is "risky management" or reckless decision making.
- Important to maintain a balance between responsibility for risk and ability to control that risk.
- Perception of risk is increased when we have no control over circumstances.

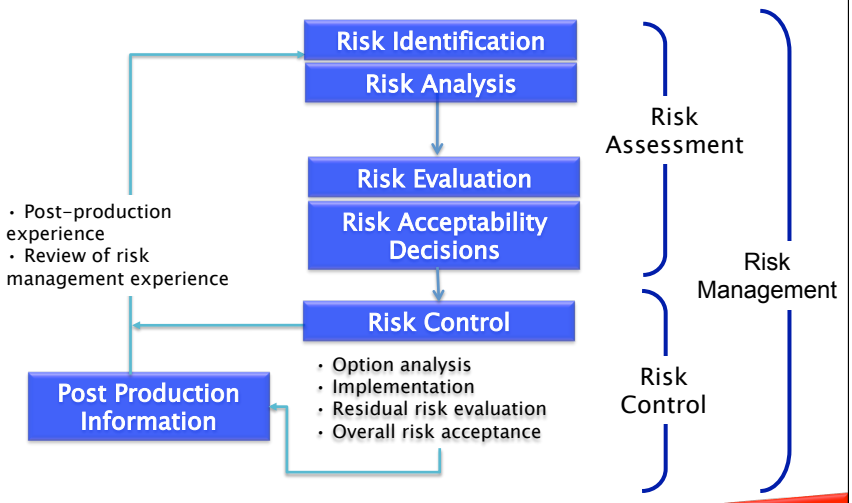
Some definitions to keep in mind
(ICH Q9 – Guidance - Quality Risk Management)

"It is commonly understood that *risk* is defined as the combination of the **probability of occurrence** of *harm* and the ***severity*** of that harm."

PRINCIPLES OF QUALITY RISK MANAGEMENT

The evaluation of the risk to quality should ultimately link back to the **protection of the patient**;

ICH Q9 and ANSI/AAMI/ISO 14971 Risk Model



PIC/S GMPs – 2009 and Risk (the part that's auditable)

- The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and **Quality Risk Management** are inter-related. (Ch. 1 Principles)
- **Quality Risk Management can be applied both proactively and retrospectively**. (Clause1.5)
- A risk assessment approach should be used to determine the scope and extent of validation. (Annex 15 Principles)
- The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. (Annex 15 Change Control)

PICS GMPs – 2009 and Risk

The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Clause 1.6

PIC/S GMPs - Annex 20 provides **voluntary** methodology for applying risk management to Pharmaceuticals.

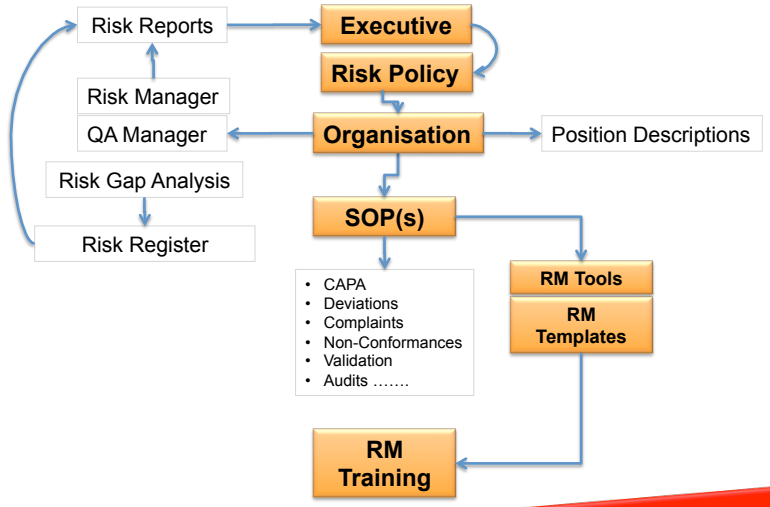
Applying QRM to the PQS Quality System

QS Element	Rationale for Application
Auditing Programs	Assign non-conformance criticality ratings based on risk to GMP compliance or product safety.
Complaints and Recalls	Assign initial risk evaluations to incoming incidents and again after post investigation.
CAPA System	Generally incidents or potential risks are qualified into the CAPA system from other QMS elements. The CAPA system manages the company higher level risk issues.Rational for Application
Deviations	Initial informal potential risks are assessed whenever a deviation occurs. If the risk is assessed as potentially significant then a formal deviations report is raised and risk is assessed within that document.
Quality Defects (Non-conformances)	Whenever a product or material does not meet specifications or in-house control limits a non-conformance report is raised. The final disposition of the Lot is not based on risk assessment however the potential for other related Lots to also be defective may be warranted based on a risk assessment.

Applying QRM to the PQS Quality System

QS Element	Rationale for Application
Computerised Systems	Computerised systems are assessed for risk levels based on GxP criticality and system complexity. This will drive the validation programs and the extent of formal controls.
Validation Programs	The cGMP requires that validation programs be driven by risk assessment (Annex 15 – 1 Principle. This is addressed in the VMP.
Change Control	Change control requires an impact assessment based on potential risks to marketing authorisation, compliance, maintenance of the validated state and patient safety.
Training and Documentation	The depth and extent of training and documentation should be directly related to the criticality of that operation to product quality. For example intensive competency training and documentation is required for aseptic operators but may not be warranted for non GMP related activities.

Risk Management System



Risk Forms and Templates

- Risk Reports Register
- Quality Records - Risk Analysis - Qualitative Summary Record
- Quality Record - Risk Analysis - Simplified FMEA Template
- Quality Record - Risk Analysis Full FMEA Template

Formal and Informal Risk Techniques (ICH Q9)

- It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures).
- The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

When should Risk Assessment be initiated ?

Event Occurs ……..	
If ……	**Then ……**
the event is judged to be insignificant or has negligible potential to impact a patient ……	do not initiate a formal risk assessment. Record the event as required by SOPs and GMP records. The reason for the decision to not to conduct a formal risk assessment is not needed.
the event may or may not be significant or may have some potential to impact a patient ……	consider moving to a formal risk assessment. Seek the advice of the QA Manager and other company management before proceeding. The reason for any decision to not to conduct a formal risk assessment is required.
the event has reasonable foreseeable potential to be significant or impact a patient ……	initiate a formal risk assessment.

Who should be involved in risk identification, analysis & assessment ?

- **Team based risk assessment is essential**
- Need the "voice of the customer" present – may refer to clinical advice ?
- Need a person with expert product or process knowledge
- Need a quality assurance /regulatory representative
- Need a production/engineering representative

Components of Product Risk Assessment

1. Risk identification and analysis

- What can go wrong? **(Hazards and their Failure Modes**)

2. Risk evaluation

- What are the consequences if it did go wrong? **(Hazard ……. Harm …… Severity)**
- What is the likelihood it will go wrong? **(Probability)**

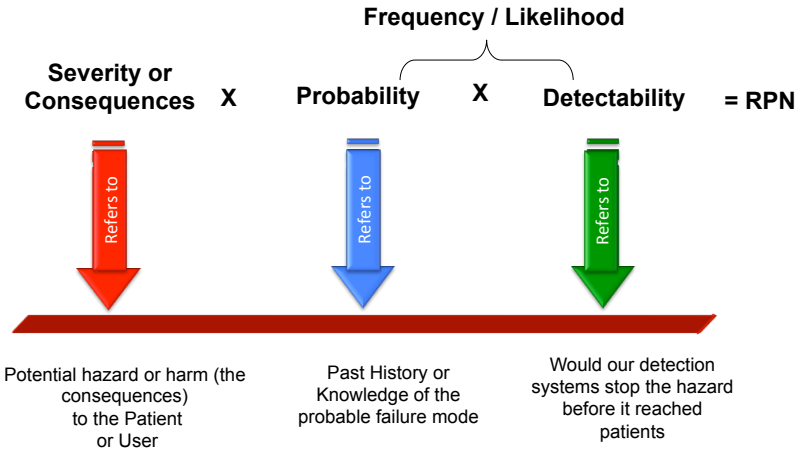
3. Risk acceptability decision

- Is the risk tolerable or acceptable ?
- Or should it be mitigated or controlled ?

Relating Hazards to Harm – Example

Potential Hazard	Foreseeable sequence of events (Failure Mode)	Hazardous situation	Harm (Severity)
Chemical (cleaning residue)	1) Incomplete cleaning of equipment used in prod'n 2) Use wrong cleaning agent	Patient receives undetected dose of impurities	• Adverse reaction • Acute injury • Complaint
Biological (Microbial contamination)	(1) Excessive bioburden in bulk mix due to: (1) poor cleaning (2) extended/ wet storage of equipment (3) Environmental	Bioburden grows through the filter and contaminates product. Lower SAL	• Fails sterility test • Bacterial infection • Death
Pyrogens (biological contamination)	(1) Excessive pyrogens in product due to: (1) HAO cycle failure (2) Inadequate vial wash	Undetected pyrogens appear in finished product.	• Fails LAL test • Febrile reaction by patient • Acute / chronic injury

Risk Assessment Components - Risk Priority Number (RPN)



Suggested Severity Levels

Severity level (Quantitative)	Severity level (Qualitative)	Example description of consequences
1	**Negligible**	Will not result in harm requiring attention.
2	**Marginal**	Results in customer inconvenience and/or harm requiring local first aid treatment.
3	**Moderate**	Results in serious harm or a customer / community health problem requiring medical treatment.
4	**Critical**	Results in extensive harm or a customer / community health problem requiring hospitalisation or prolonged medical treatment.
5	**Catastrophic**	Results in death or extensive harm; a general community health problem attracting public interest and requiring significant medical treatment or hospitalisation for those effected.

Suggested Likelihood Levels

Likelihod level (Quantitative)	Likelihood level (Qualitative)	Example description of probability (based on events/time)
1	Rare	May occur every 10–30 years
2	Unlikely	May occur every 5-10 years
3	Possible	May occur every 1-5 years
4	Likely	May occur more than once per year
5	Almost Certain	May occur several times per year

Example Risk Evaluation Table

		Severity				
		Negligible (1)	Marginal (2)	Moderate (3)	Critical (4)	Catastrophic (5)
Probability	Almost certain (5)	Medium (5)	High (10)	High (15)	High (20)	High (25)
	Likely (4)	Low (4)	Medium (8)	High (12)	High (16)	High (20)
	Possible (3)	Low (3)	Medium (6)	Medium (9)	High (12)	High (15)
	Unlikely (2)	Low (2)	Low (4)	Medium (6)	Medium (8)	High (10)
	Rare (1)	Low (1)	Low (2)	Low (3)	Low (4)	Medium (5)

Example Analysis

The company manufactures microdose, narrow therapeutic prescription tablets. **The mixing process is not validated**

Hz #	Hazard Statement	Potential or Foreseeable Failure Modes:	Potential Harm:	Score
1	The patient receives a dose that is outside the therapeutic window	The mixing process is not validated for the new blender. The bulk product is not mixed to acceptable homogeneity (less than 3% rsd)	(a) the patient receives **excess dose** - leads to patient acute discomfort and a complaint (b) the patient receives **insufficient dose** – which could lead to inadequate treatment and complaint / adverse event but no chronic harm.	8 6

Example Likelihood (Frequency) Analysis

Hz#	Probability of Occurrence	Score
1	These records were examined • In- process testing records for last 12 months (23 batches) • Non-conforming (failed) batches history - last 2 years • Complaints history • Maintenance history of the blending equipment • Adverse events profile • Internal audit reports for the process line • Tested multiple samples from the current manufactured Lot **The risk team concluded that the process potentially that it was possible that 1 in 10 batches would produce defects.**	8

Example
Detectability (Frequency) Analysis

Hz#	Detectability	Score	Frequency Score
1	The risk team identified, via examination of batch records and process instructions: • There was no in-process testing for bulk blend uniformity. • The QC laboratory tested 20 tablets for content uniformity from an average batch size of 200,000 tablets • **Occasional units are checked for defects**	8	The **Frequency** was calculated as: [Pr(occur) (8) X Detect. (8)] $^{0.5}$ = 8

Risk Rank = Severity (8) x Likelihood (8) x Detectability (8) = 512 …. Unacceptable

Typical Risk Acceptance Criteria (based on analysis)

Unacceptable Risk	Cannot accept the risk - must re-design product/ processes or not proceed
High/Major Risk	Cannot accept the risk - must mitigate or control the risk eg via validation of processes
Medium Risk	Should or may mitigate or control the risk eg. increase verification/ testing or other controls
Low (ALARP) Risk	**As Low As Reasonably Practical Risk** - broadly acceptance - action is optional. Document procedures and Train personnel
Negligible Risk	The risk is inconsequential and no action is warranted - business as usual.

Risk Control/ Risk Mitigation

1. Risk Control - Option Analysis

- What can be done to mitigate risks?
- What options are available?
- What are the trade-offs in terms of risks, benefits and costs?

2. Existing Controls

- What controls are already in place ?

3. Monitoring and Control Plans

- Can we detect the failure mode ?
- What monitoring and reporting feedback are in place ?

ICH Q9 - Some Risk Tools

- Below is a non exhaustive list of some of these tools:
  - 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

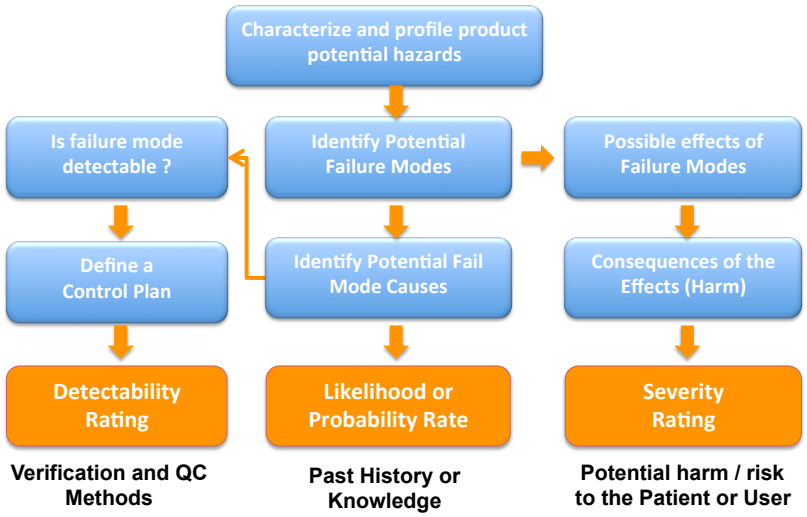
Types of tools

Facilitation (Qualitative) Tools	Analytical (Semi) Quantitative Tools
Brainstorming	Failure Mode Effects Analysis (FMEA);
Cause and Effect Diagrams	Hazard Analysis and Critical Control Points (HACCP);
Flowcharts	Preliminary Hazard Analysis (PHA);
Risk ranking and filtering	Supporting statistical tools

Summary of Main (Semi) Quantitative Risk Tools

Feature	PHA	FTA	HACCP	FME(C)A
Purpose	Preliminary risk identification	Identify probable fault paths	Identify process risks and controls	Assess product / process failure modes and quantitative risk
Focus	Simple version of FMEA	Root cause(s) of process faults	Process hazards eg contaminants	Identify and risk rate failure modes
Strengths	Easy application with limited data	Shows multiple factors effect on one fault	Identify CPPs for a unit process	Rank and prioritize risks
Limitations	Limited value for complex systems	No risk ranking or prioritisation	Must understand the process – relies on SME	Analysis complex and tedious
Severity ?	Yes	No	Yes	Yes
Likelihood ?	Yes	Optional	Yes, SME needed	Yes
Detectability ?	No	Optional	Yes	Yes
Output	Tables	Charts/ graphics	Tables	Tables
Rank / Metric	Rank – Semi Q	No rank/ Qual.	Partial/ Qual.	Rank – Quant.

How is an "FMEA Risk Analysis" done ?



Simplified FMEA Template

	Quality Record – Simplified FMEA Record			QR xxx - 01
	Participants in RA			
	RA Prepared by:		RA Approved by:	
			RAR Number: yy/##	

Product/Process Name	Title:	Lot #	
Classification/Source	☐ QMS ☐ Product ☐ Design ☐ Audit/Compliance ☐ Deviation ☐ Non Conformance ☐ Other		
		Source Ref. #	

Present Risk							Remaining or Residual Risk				
Ref	Hazard/Patient Harm (Consequences) Potential Failure Mode	(S)	Likelihood of Failure Mode Occurring Pr. (O) and Detection (Frequency)**	Freq. (F)	RPN S x F	Recommended Action / Mitigation Or Current Controls	(S)	Freq (F)	RPN S x F	Comments	Evaluation Report

** Frequency: combination of the Likelihood of the failure mode occurring X the Detectability = [Pr(O) x Detect]$^{0.5}$ Where there is no detectability, just use Likelihood.

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