Risk Management Applications

PDA New England Chapter

14th November 2012

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Introduction

26 years in the pharmaceutical industry which includes 4 in API and 2 in Excipient manufacture:

Solid dose, liquids/creams/ointments, p-MDI, SVP, transdermal

23 years as a lead auditor

10 years in supply chain quality management

Degree in Chemistry, 2 years study with DBA to become a QP

MSc in Pharmaceutical Quality and GMP

8 years as a Qualified Person, 2 years releasing IMPs

5 years as a QP Assessor

Fellow of the Royal Society of Chemistry / Chartered Chemist

Member of the Chartered Quality Institute . Chartered Quality Professional

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Qualified Person

The QP is essential to the safe control of medicines and needs to have extensive training and in-depth critical understanding of all the aspects associated with manufacturing and distribution.

QPs are responsible for undertaking their duties in accordance with a professional Code of Practice. The aims and objectives of the Code of Practice are to provide operational guidelines for carrying out the functions of the QP in accordance with Article 56 of Council Directive 2001/82/EC and/or Article 52 of Council Directive 2001/83/EC.

Annex 16 of the “Orange Guide” requires that for every batch a QP:

- Confirms compliance to MAA / PSF
- Confirms compliance to GMP and national law
- Certifies in a register

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QP Assessors

The MHRA and Veterinary Medicines Directorate (VMD) require the Royal Pharmaceutical Society of Great Britain the Society of Biology and the Royal Society of Chemistry ('Joint Professional Bodies') to assess the eligibility of their members for QP status.

Each professional body has a Panel of Assessors with a Chairman who review a 20 page application then ask knowledge and scenario based questions against a Study Guide for approximately 90 minutes.

Although it is the opinion of the professional body concerned whether a member meets the statutory requirements to become a QP, it is up to individual companies to satisfy themselves of the suitability of any individual applicant for a particular post. MHRA or VMD are ultimately responsible for determining who can be named as a Qualified Person on a particular Manufacturer's Licence.

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Objectives

Provide an overview and summary of Risk-based Management

Explain the benefits of this approach for all

Discuss GMP expectations

How should you aim to implement Risk Management?

What are the key points to consider / stumbling blocks to avoid?

Where does QRM feature in EU Inspection trends?

What have QA to do ?

Quality Assurance need to align all of their processes with the risk management guidance of ICHQ9

First of all, understand how Risk Management works

Decide what specific goals you want to achieve

Train the relevant people in the relevant risk assessment tools

Keep it simple - implement

Then repeat the cycle, evolve, integrate the process and repeat in another area

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Warning !

There is *'the potential for quality risk-management to degenerate into a non-value added exercise of identifying non-critical, improbable, low risk scenarios indefinitely'.* (J. Orloff, *Pharm. Technol.* **35** (2) 38–40 (2011)).

What is a Risk? …. Definition

This risk can best be expressed by the question:

- **“What if the project/activity/function fails to perform as expected?”**

Otherwise a risk is simply defined as a situation which would lead to negative consequences.

Risk = Severity (of event occurring) Vs likelihood (of event occurring)

The risk is then managed by

- Treat
- Transfer
- Terminate
- Tolerate

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Do we recognise Risk ?

Is avoidance just luck?

Our knowledge?

Our awareness?

Decision making?

Risk-Based Management

FDA GMPs for the 21st Century – A Risk-Based Approach

ICH Q9

Alignment with other industries / other quality standards

PDA Guide 44 Risk Assessment of Aseptic Processes

PQG Guide to Supplier Risk Management

MHRA / FDA inspections based on this principle

- MLX345 Risk Based Inspection program in UK

ISPE Good Practice Guide « Applied Risk Management for Commissioning and Qualification »

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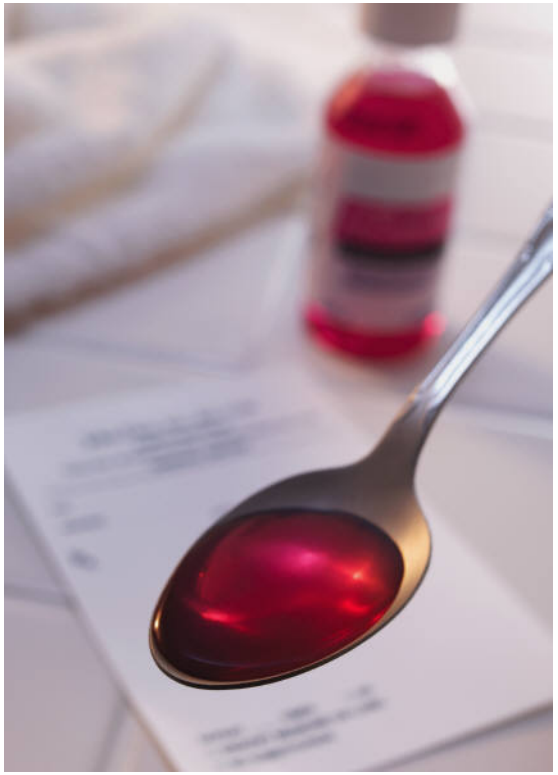
Recent issues

Contamination e.g. glycerol, heparin

Recalls

Counterfeiting e.g. Lipitor in UK

NEED TO AVOID THESE ISSUES TO BE HEALTHY BOTH IN TERMS OF PATIENTS AND FINANCIALLY



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Benefits to companies

Value adding compliance

More effective prioritisation

More efficient use of resources

Proactive not reactive → ongoing risk reduction

Lower risk to business and lower overall cost

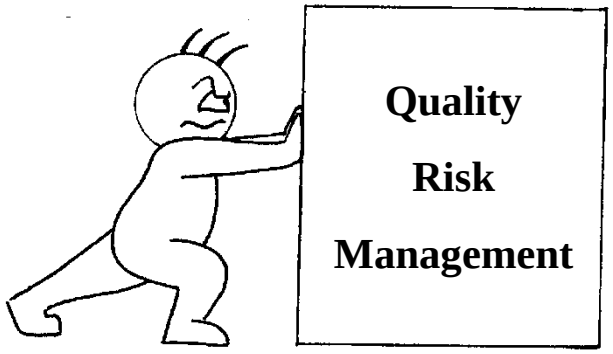
Improved customer satisfaction (patient / regulator / purchasing company)

Safer medicines

View of the Regulators?

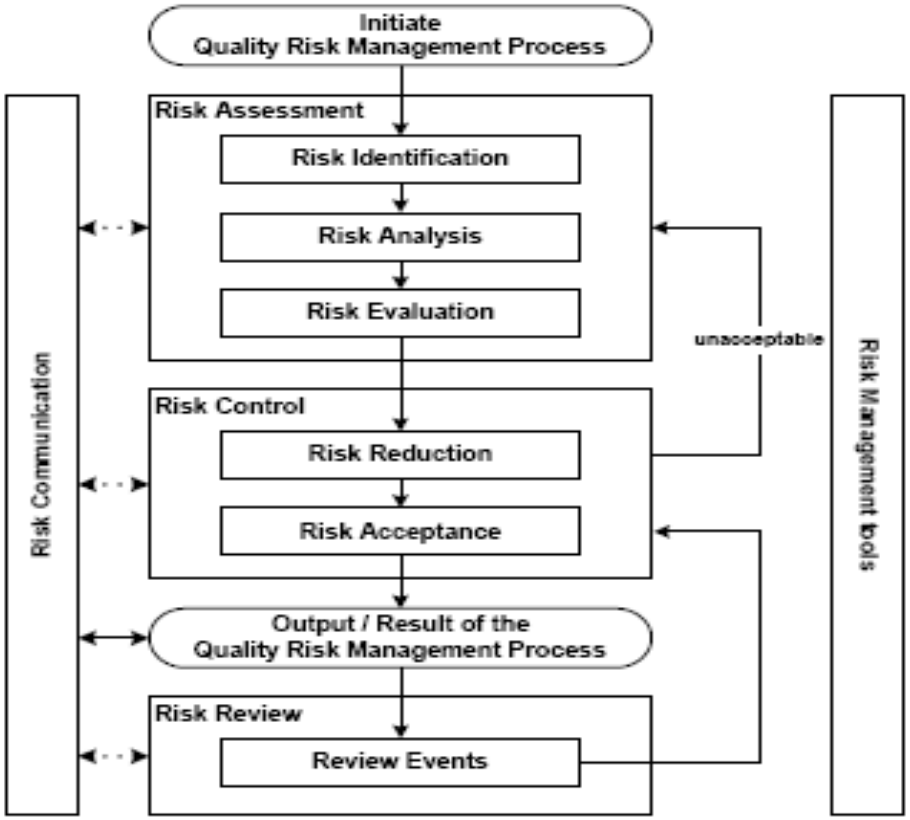
Quality Risk Management:

- Should either drive, or be consistent with, all decisions and activities
- **Must be proactive …** not a justification for poor GMP or bad decisions previously

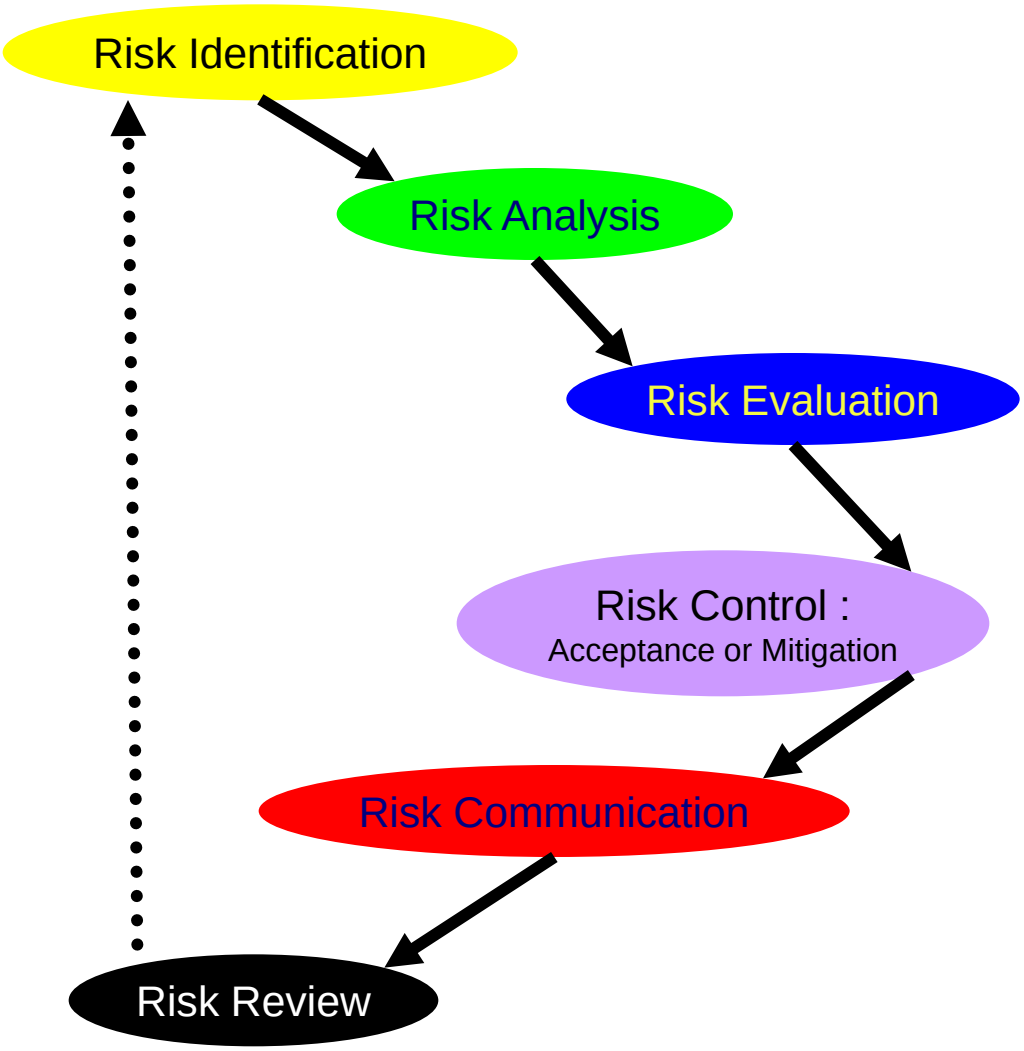


Risk Management Strategy

- Use a structured approacl
- Must cover the life-cycle c products
- Must be pro-active
- Must be reiterative
- Link into the QMS
- Use those trained in tools other activities



Simple Risk Management Process



Specific risks identified are agreed and documented

Data is refreshed and entered every 6 months

Risk is evaluated by the scorecard's macros to provide a rank list of risk total scores

A level is set of what is acceptable and anything above this requires a strategy of how to mitigate the risk

Proposals are communicated to the Quality Steering Team

A formal review starts the process again

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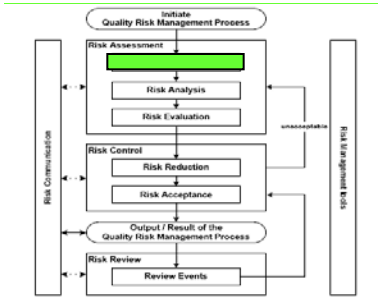
Implementation - Getting started is the hardest part

Risk Identification



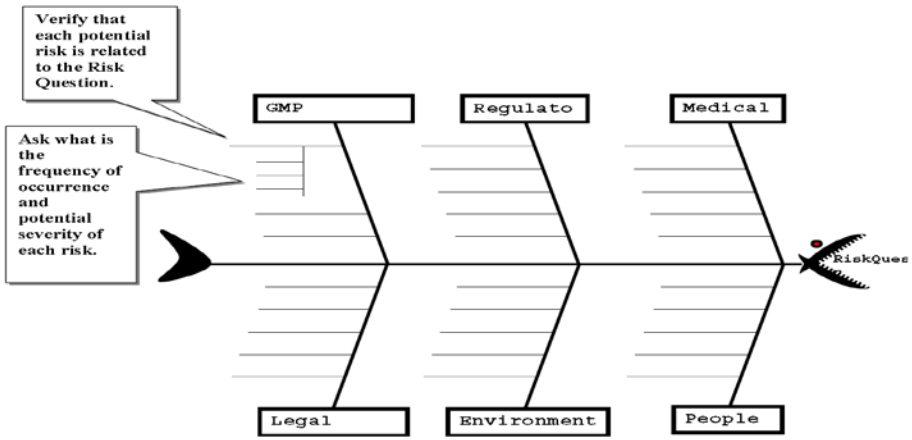
Known issues:

- Critical Control Points
- Deviations
- Complaints
- Audit findings
- Near misses
- Your customer's products e.g. route of administration, sterile, non-sterile
- Key Performance Indicators
  - *If these don't measure risks then they should !*

Risk Identification

Potential issues:

- Brainstorming
- Process mapping
- Fishbone / Ishikawa / Cause & Effect diagrams
- FMEA failure mode steps
- Trend analysis e.g. Pareto, Cusum, Cpk, etc
- Reliance on key personnel (expertise, knowledge)



Risk Identification

Knowledge in the public domain:

- News of fires, floods, earthquakes etc.
- Raw material availability e.g. crop failures
- Changes in legislation
- Regulatory findings
- Changes: site of manufacture, closure of site, takeovers,

Do you have a process to collect this information and react to it?

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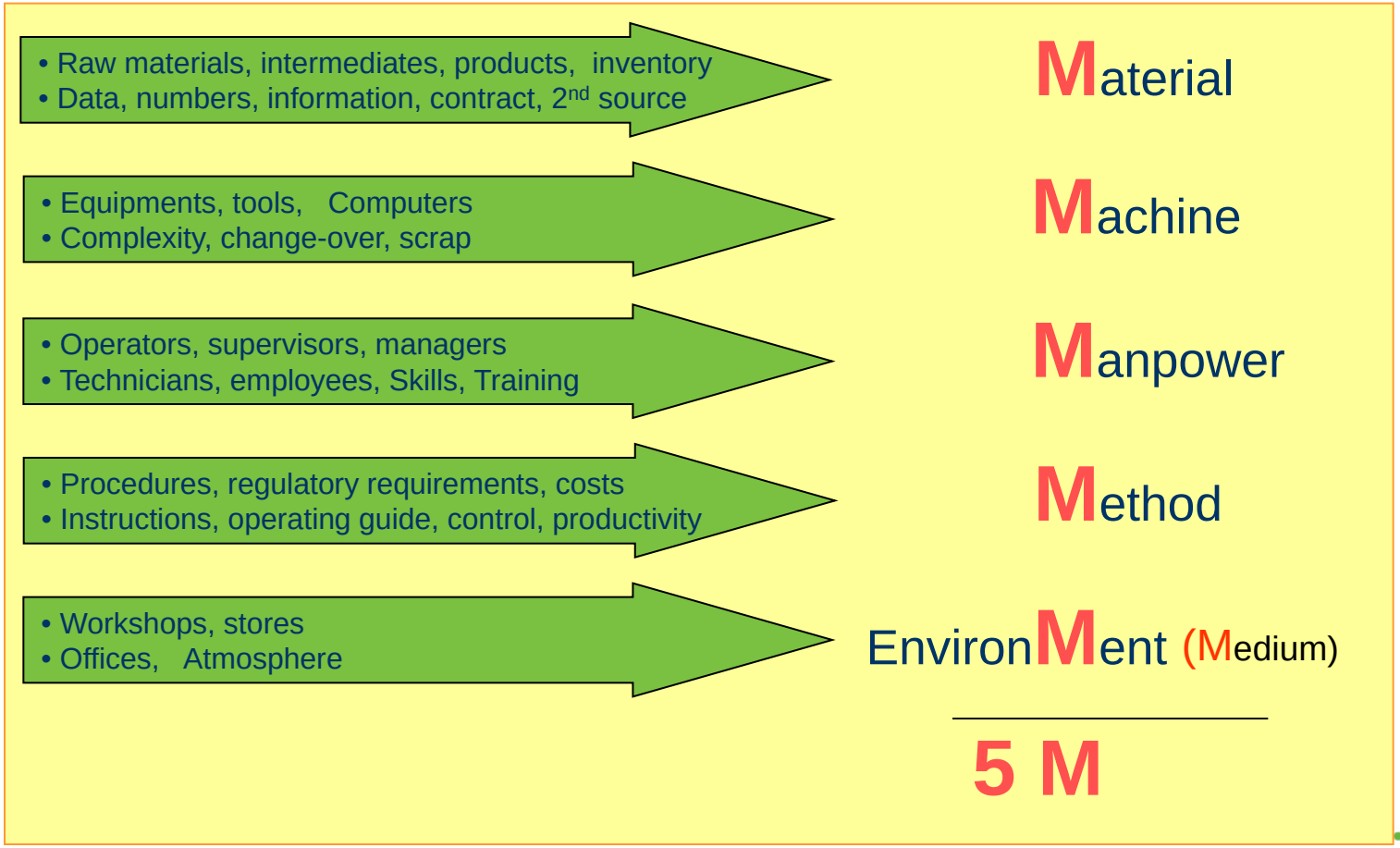
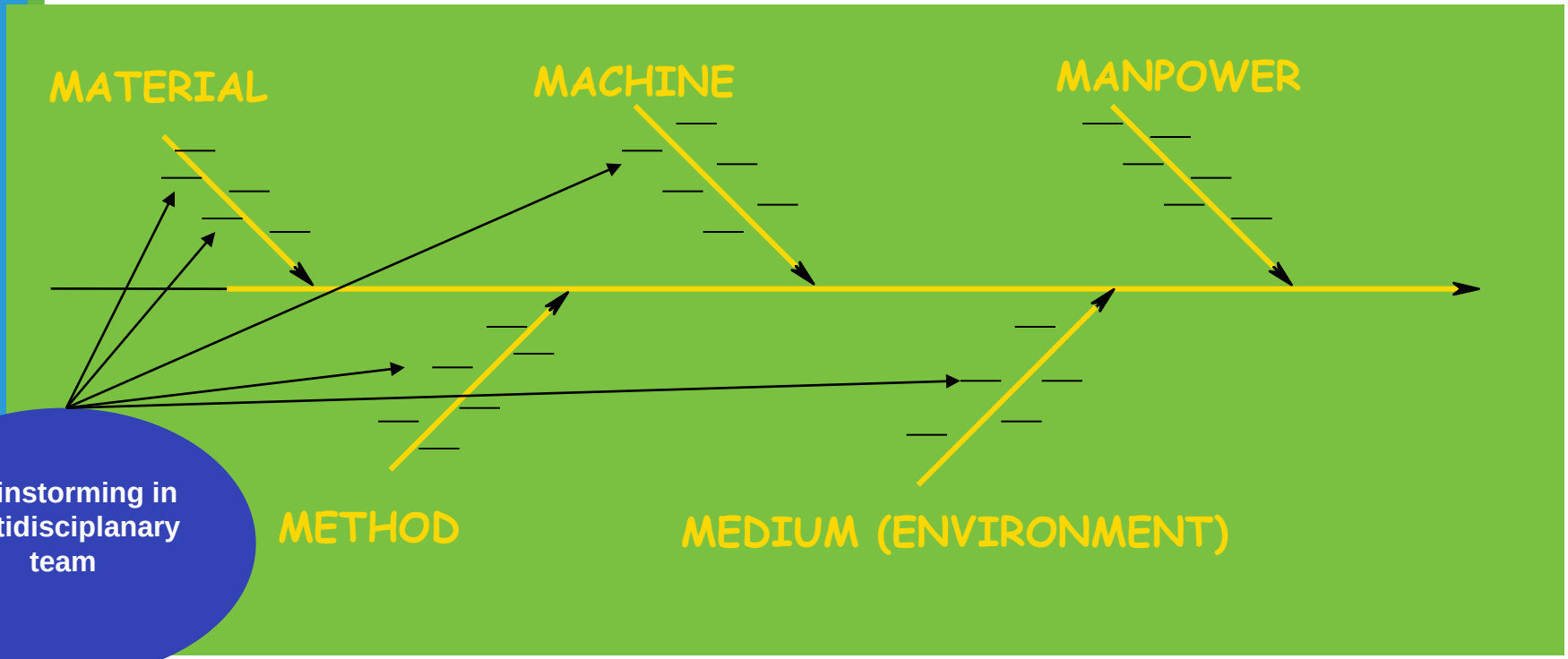
Risk Identification – Brainstorming using 5 M's



RISK IDENTIFICATION METHODOLOGY

Risk / ‘hazard’ identification: using the 5Ms methodology:

Simple & systematic, not too heavy



Brainstorming in Multidisciplanary team

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Risk Analysis

Which Tool to use?

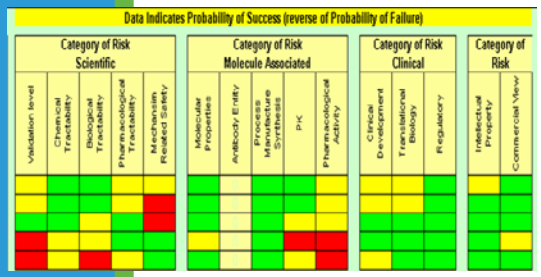
ICH Q9 gives lots of alternatives but does not specify which to use or in which circumstances to use it

Sometimes this is the most difficult and confusing part of Risk Management …

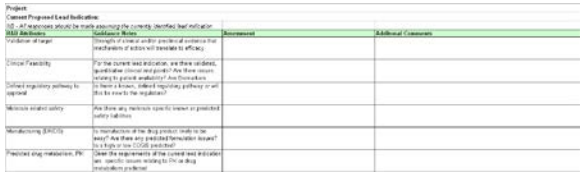
- Simple ? Fit for purpose ?
- Ranks / differentiates risks ?
- Accurate ?Or based on assumptions?
- Try it then evolve!

Risk Analysis

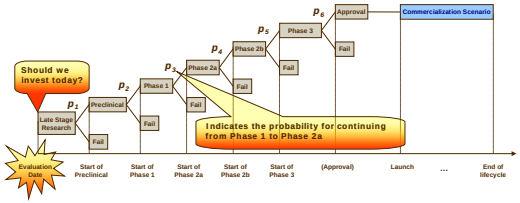
Different techniques can be used throughout the lifecycle:



Basic attributes / Qualitative



Attribute Scoring



Quantitative Analysis

Beginner **Intermediate** **Expert**

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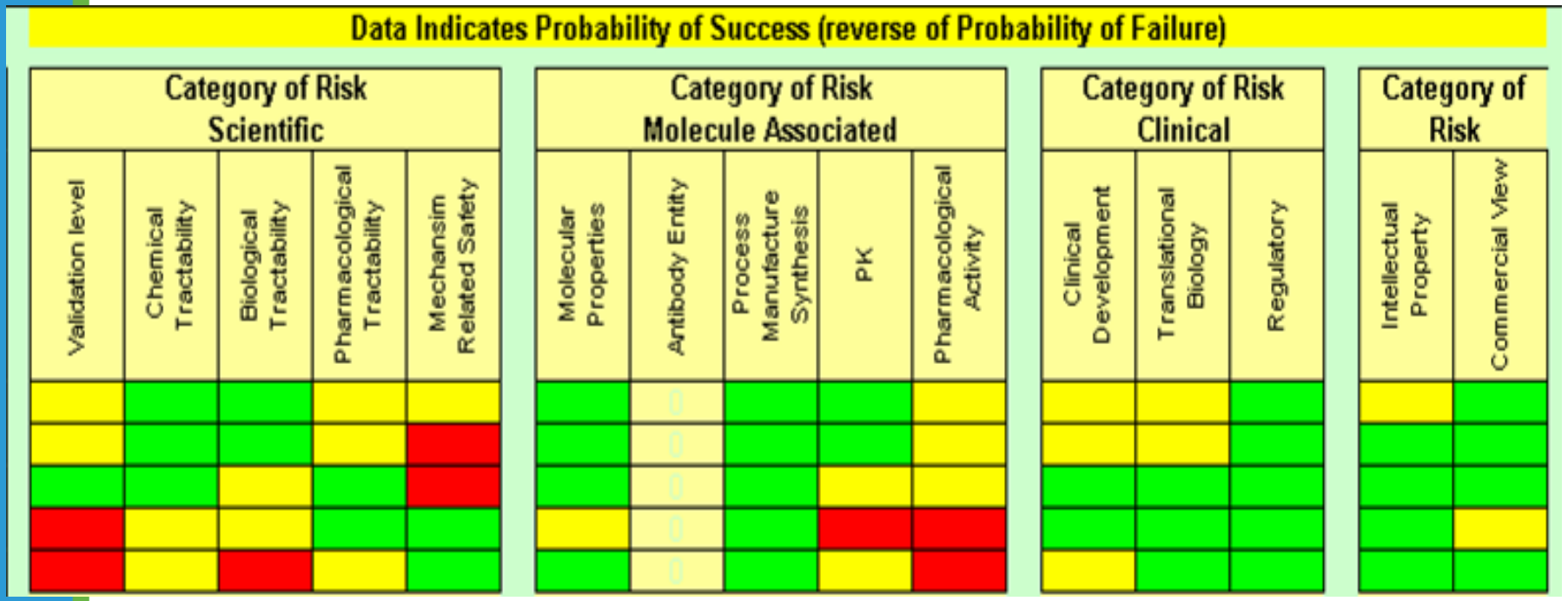
Qualitative Risk Assessment

Example from clinical development:



Risk Rating Scales – Example 2 Corporate

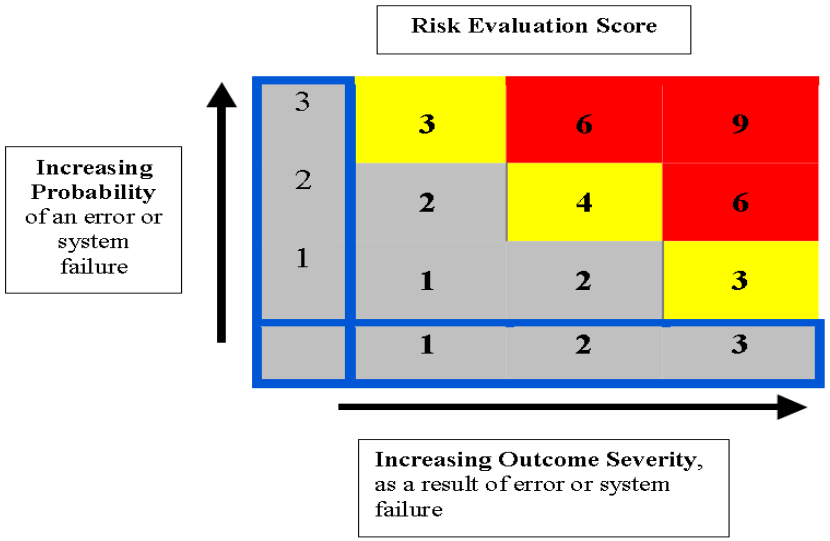
Impact

Ranking	Description	Sales / Reputation	Duration	Value
5	Catastrophic	> 500M / or Complete loss of confidence	Irrecoverable	Collapse of market capitalization
4	Critical	<500m / or Sustained loss of confidence	Recoverable in the long term (i.e. 24-36 months)	> 50% reduction in market capitalization, accession liquidity reserve
3	High	<100m / or Moderate loss of confidence	Recoverable in the short term (i.e. 12-24 months)	>30% reduction in market capitalization, minimal operating cash flow, maintenance of liquidity reserve
2	Moderate	<30m / or limited to minor / short term loss of confidence	Temporary (i.e. less than 12 months)	Miss forecast and or budget
1	Minimal	<10m	Relatively insignificant impact on the achievement of business objectives	

Simple Quantitative Risk Assessment

Risk Ranking

Potential Risks (Risk Identification)	Risk Analysis		Risk Evaluation
	Probability	Severity	Score
Risk 1	Low (1)	High (3)	Low (3)
Risk 2	Med (2)	Low (1)	Low (2)
Risk 3	Med (2)	Med (2)	Med (4)
Risk 4	Med (2)	High (3)	High (6)
Risk 5	Low (1)	Low (1)	Low (1)
Risk 6	High (3)	High (3)	High (9)
Risk 7	Low (1)	Low (1)	Low (1)



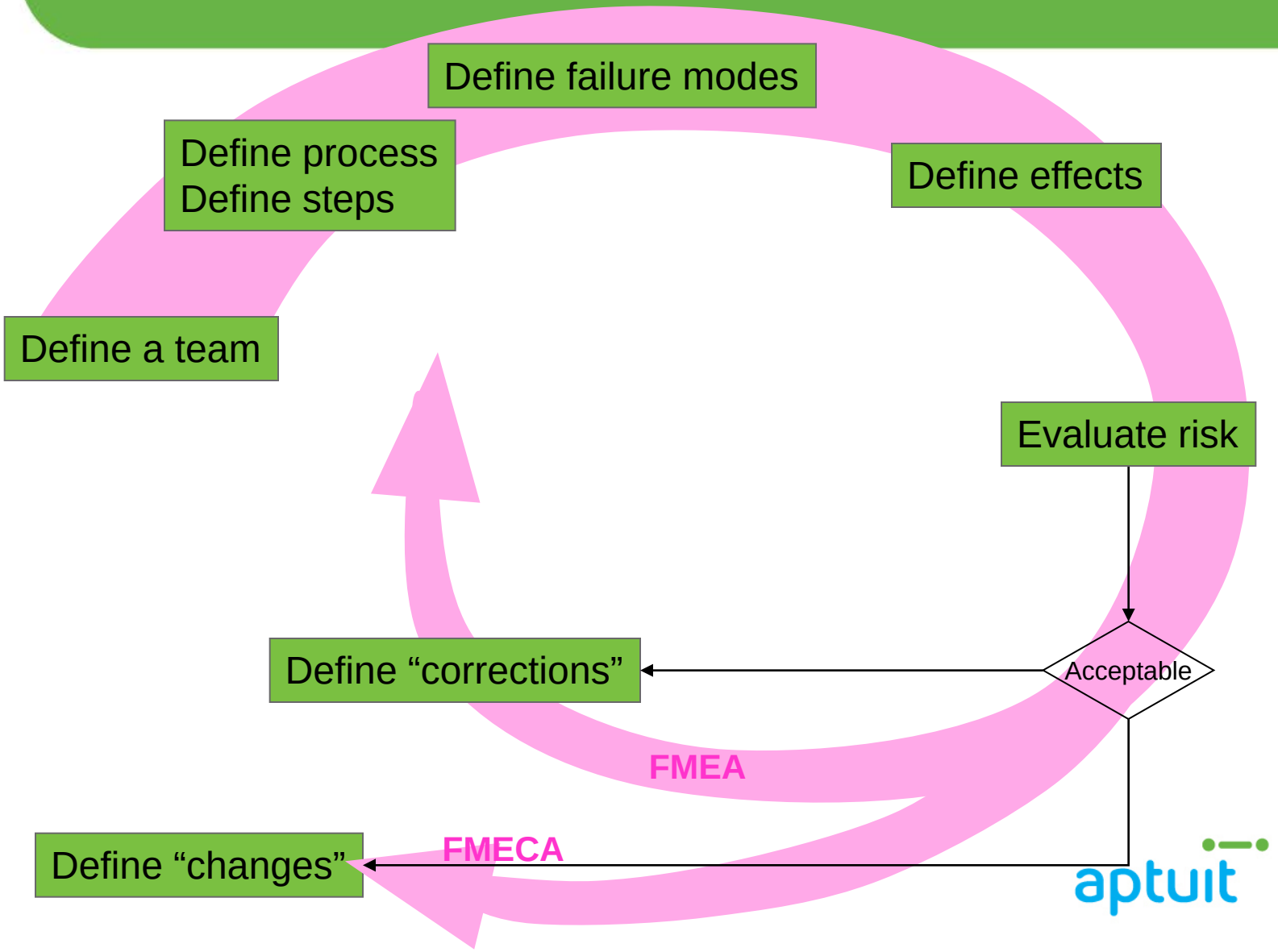
Quantitative Risk Assessment: FMEA Example

Failure Mode and Effects Analysis

EXAMPLE FMEA table:

Before Action										After Action(s) taken			
Risk	**Failure Mode**	**Effect of failure**	**Severity**	**Potential Cause(s)**	**Occurrence**	**Current Controls**	**Detection**	**Risk Score**	**Recommended Action**	**Severity**	**Occurrence**	**Detection**	**After Action Risk Score**

The FMEA procedure

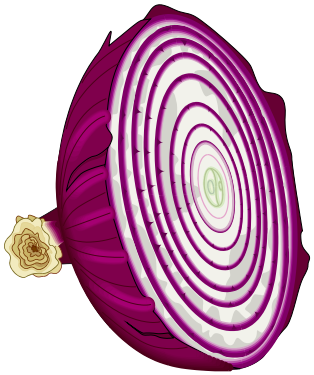


FMEA Tree - Onion

- A layered approach is highly recommended as FMEA can get complex.

- FMEA are like ONIONS/LAYERS.
  - Each layer is more detailed
  - Each layer is closer to the root cause

  ➔ But ... do too many, and you will cry.



Full FMEA is not simple or quick, therefore where you can, use a more qualitative approach

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Quantitative Risk Assessment e.g. C&E Matrix

Business team together decide on specific risks and weight these to reflect the level of risk

The Risk Total score is calculated

How to reduce the Risk Total Score is summarised here

Some of this data might not be easily available and systems need to be developed !!!

SUMMARY				SUPPLIER RISK EVALUATION													
								Weighting	6	10	10	4	7	Distribution	
							Weighted rating of risk	9	None	Weak (High risk of supply interruption)	High Risk (Corrective actions required on a regular basis)	High Risk of not meeting 100% OTIF	GXP - 9 or no audit rating.	#VALUE!	1st Quartile
							9 = extremely important	3	In Process	Vulnerable (Moderate risk of supply interruption)	Medium Risk (Corrective action required occasionally)	Medium Risk of not meeting 100% OTIF	GXP 3	#VALUE!	Median
							0 = not important	1	Expiring within 12 months	Stable (Minimal risk of supply interruption)	Low Risk (Corrective actions required rarely)	Low Risk of not meeting 100% OTIF	GXP-1 or satisfactory historical audit.	#VALUE!	3rd Quartile
								0	Current/NA	Secure (No risk of supply interruption)	No Risk (No corrective actions required)	No Risk (Always meets OTIF)	No requirement to audit and/or satisfactory	#VALUE!	Maximum
Supplier Name	Risk Total	Supplier Interface Contact / Responsible Person	Risk Management Strategy	Supplier Number	Supplier Location	Commodity / Supplier Type (Manufacturer, Service, Agent / Distributor)	Scored By (BR, BU, SLH, ROC, etc.)	2008 Total Spend in Euro	Sourcing Situation: Supply Agreement &/or Quality Agreement	Continuity of Supply	Quality	Delivery	Compliance: Audit Rating	RPN Score	Absolute RPN Risk rating (H,M,L)
Example 1	142					CMO	BR	6,120,000	1	3	3	1	0	142	
Example 2	105					Laboratory	BR	98,000	3	0	3	3	3	105	
	#VALUE!							Needs to come from Purchasing	Needs to come from both Purchasing and Quality	Where is the data?	Where is the data?	Where is the data?	Do the Compliance group have a system for scoring audits?	#VALUE!	#VALUE!

Quantitative Risk Assessment (continued)

How to decide whether to perform a planned audit?

		IMPACT ASSESSMENT				AUDIT / VENDOR ASSURANCE						
		3	9	5		Weightings used in the calculation of Audit Risk total are specified in the formula.						
		<50K Euro	Significant impact to current OI and future OI. (9 = Group 1: Cimzia, Keppra, etc)	Very Involved include US Registration or EU Type 2 Variation (3 - 24 months). Requires a CBE Supplement, a CBE 30 Supplement or a Prior Approval.		9 = Significant Impact	9 = Finished Product (CMO) or APIs	9 = >1000K Euro	Last audit more than 3 years ago, never audited			
		>50K Euro	Moderate impact to current OI and future OI. (3 = Group 2: Neupro, Vimpat, Roticadine etc.).	Medium Involvement e.g. Type 1B Variation (1 - 3 months) For US may be captured in an annual report.		3 = Moderate Impact	5 = Major Services (Labs or Engineering) / Software Audits	3 = >250K Euro	Last audit between 2 and 3 years ago			
		>250K Euro	Minimal impact to current OI and future OI. (1 = Group 3: All other Products i.e.???).	Internal Data Only Required or EU Type IA Variation (< 1 month, Tell and Do) e.g. name change.		1 = Slight Impact	3 = Excipient / Major Component	1 = >50K Euro	Last audit between 1 and 2 years ago			
		>1000K Euro	Products to be discontinued and/or no impact to current OI and future OI.	No Impact		0 = No Impact	1 = Minor Component or 0 = Minor Services	0 = <50K Euro	Audited less than 1 year ago			
Relative RPN Risk Rating (H,M,L)	Ability To Detect (H, M, L)	Sourcing Situation: Spend (Leverage)	Strategic Importance	Regulatory Impact of Change	Impact Assessment Total	Significant Changes/ Compliance History	Finished Product or Service	Spend (Impact on UCB Business)	Time Since Last Audit	Audit Risk Total	Material Classification	Audit / Vendor Assurance Comments	Date of Last Audit (dd-mmm-yy)
#VALUE!		0	9	9	126	0	9	9	3	192			
#VALUE!		3	9	3	105	3	5	1	9	247			
#VALUE!		Calculated from Spend (Column I)		Needs to be performed by Regulatory	#VALUE!	Needs to be performed by UCB Manufacturing		Calculated from Spend (Column I)	Needs to be calculated from date in Column AE (provided by Compliance or QA)	#VALUE!			

What is the potential impact of change?

See the “big picture” …

Focus too much on one source of information……

And you might just miss something important!

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WARNING

The output prioritises your future actions. If you get this step wrong

- It means that you may not work on the most important issues
- You will waste time, resource and may still end up ‘’fighting the fire’ you were trying to avoid
- You will have to go back and address the issue(s) you missed (i.e. prioritised incorrectly/inaccurately)

CHECK your output:

- Does it feel right?
- Does it make sense?

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Risk Evaluation

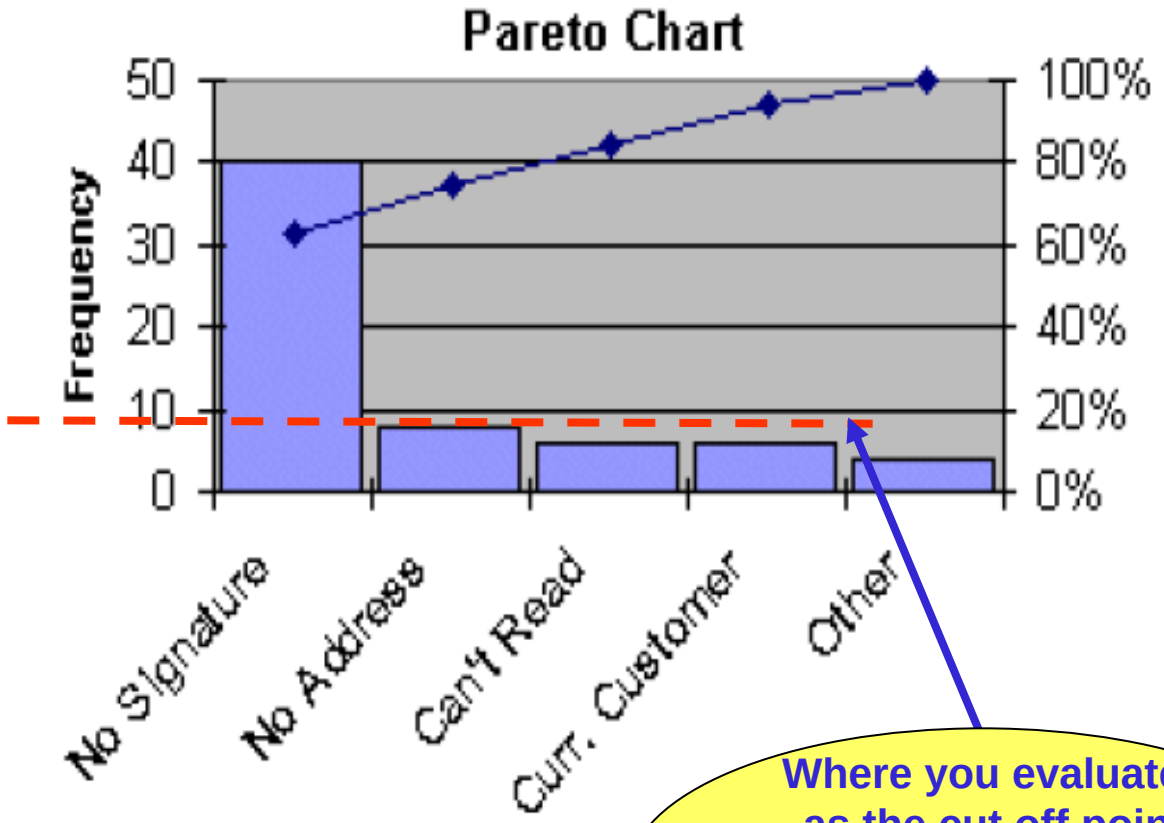
A sorting or ranking process How do you decide where to draw the line?

- Over time (as risks are reduced and systems for data collection are introduced/refined) risk scores may reduce
- Often part of the tool e.g. FMEA
- **<u>Leads to a clear decision and action</u>**

QUESTION:

Is it the risk score that is important <u>OR</u> is it your interpretation of the data and the decision you make that is the key step?

Risk Evaluation using Pareto Analysis



Risk Mitigation strategies

Mitigation strategy and actions based on the "4 T's":

TREAT a risk to prevent it occurring or reduce its potential impact.

- Have processes in place that improve the control effectiveness.
- The amount of effort to control risk should be proportional to the significance of the risk

TRANSFER the risk to someone else

- Risk financing, insurance, contracting out, etc.
- Some of the impact of the risk is transferred, not the responsibility the business has for managing the risk.

TERMINATE the risk – i.e. stop doing whatever it is that is exposing the business to the risk.

TOLERATE the risk after deciding that the risk has been reduced to an acceptable level.

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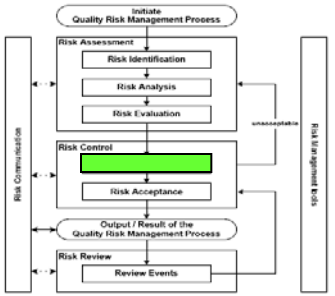
Risk Reduction

High risks need to be reduced

Risk Mitigation Strategies need to be formally defined and documented

Resource, cost and time estimates are needed to enable approval

Vulnerabilities and contingency plans may be needed to run in parallel



- **Keep actions SMART**

Risk Mitigation Plan Template

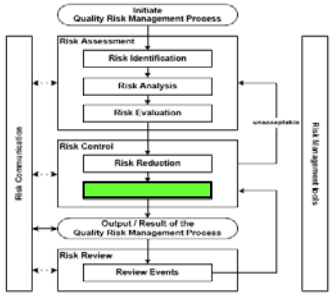
Risk# :.... Area:	Ownership & Partners		
Risk factors	**Total score**	**Before mitigation:**	**After mitigation:**
	LIK		
	IMP		
	MC		
Mitigation Plan Strategy	**Timelines and deliverables**		
Barriers:	**Needs:**		

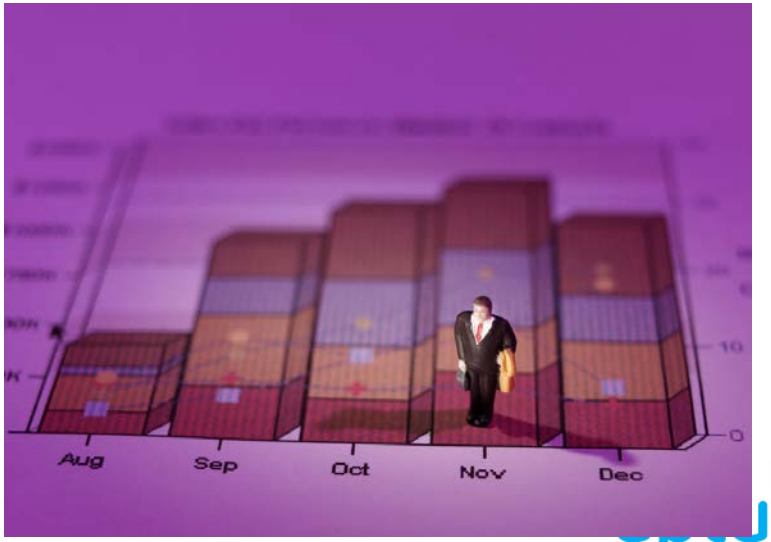
Risk Acceptance

Determines when inaction is appropriate, justified and agreed

Risk acceptance is not automatic nor implied

It is an output of the risk evaluation proposal that is communicated to stakeholders for their input





Risk Acceptance

A critical step that requires formal Senior Management signature

- *Needs to be auditable*
- *Anyone can propose acceptance of a risk but only the Head of Department makes the decision / is accountable*

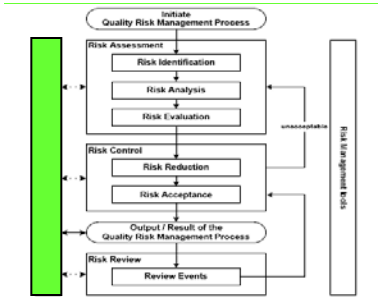
This Risk Acceptance is timebound since a periodic review is routinely required

- The risk needs evaluating every X months

Risk Communication

Takes place throughout the process of Risk Management

Needs formalising at end of process every X months



Tell management ? *Yes*

Tell customers ? *Possibly*

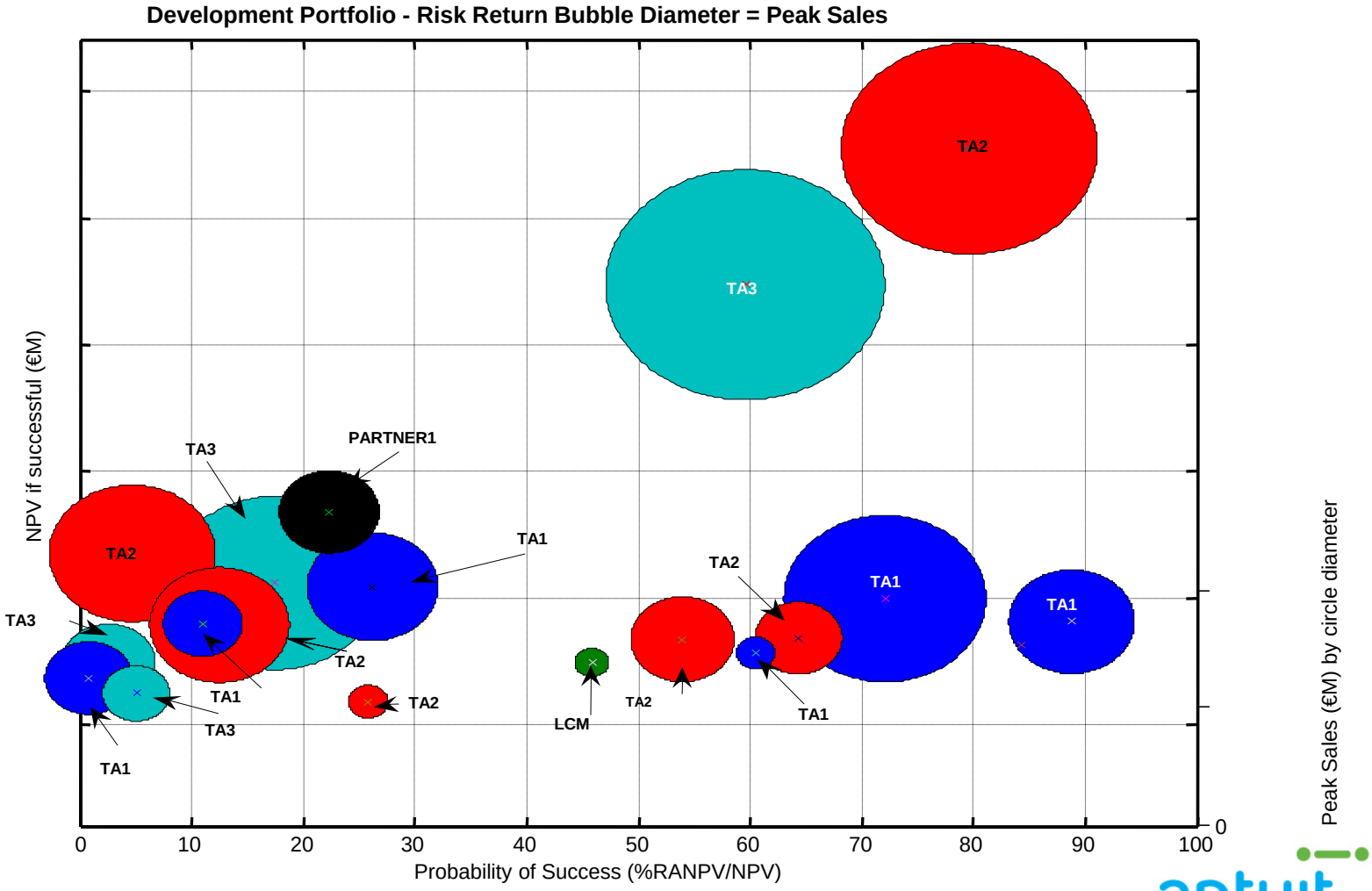
Tell suppliers ? Sometimes

Tell regulators, patients, media etc. ? Rarely / *Unlikely*

How to communicate ?

- Dashboard
- Boston box
- Report

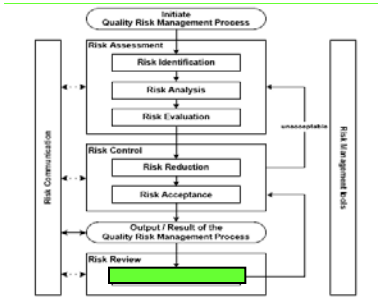
Risk Communication



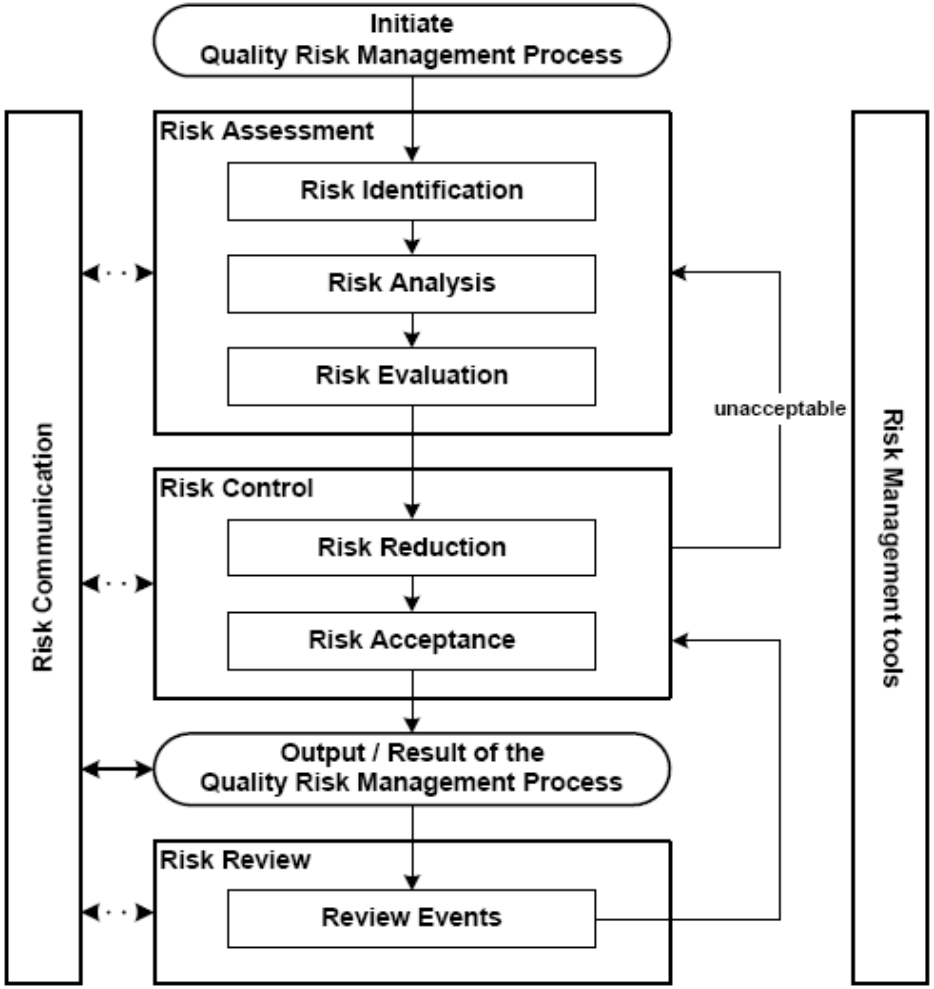
Risk Review

Periodic assessment that the output of Risk Management process hasn't changed

Reactive assessment when new and potentially significant information is identified



Risk Management Process … again



Stumbling blocks during Risk Management

Chapter 1 of the EU GMP guide states that '...the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk'. Companies can get this wrong e.g. too little of one or all of these:

- Strategy not linked clearly to objectives
- Responsibilities not defined
- Key departments 'opt-out' / do not contribute
- System gaps not filled i.e. too reliant on opinion and accurate data not available
- Risk Mitigation actions not completed / no successful
- Considered a 'one-off' exercise i.e. no review
- Communication to stakeholders & customers not performed / too late / too little

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How to evolve your current RM approach?

Learning opportunities should be captured

Precision of data can be improved

Qualitative tools can be made quantitative in order to provide greater accuracy and discrimination

Quantitative tools can be made slicker

The ‘umbrella’ can cover the whole business and all functions

FDA Globalisation Act will drive suppliers to be integrated into companies’ "Quality Risk Management Plans".”

Supplier Management – a key application

Funnel down …

- Use available tools to understand your processes, improve processes / products and reduce risks e.g.

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PQG Guidance

''A Guide to Supply Chain Risk Management for Suppliers to the Pharmaceutical Industry''

Bridges the gap between ISO and ICH approaches

Provides additional guidance and examples specific to supply chain for implementing ICH Q9 et al

Published 2010

An electronic version available on PQG website

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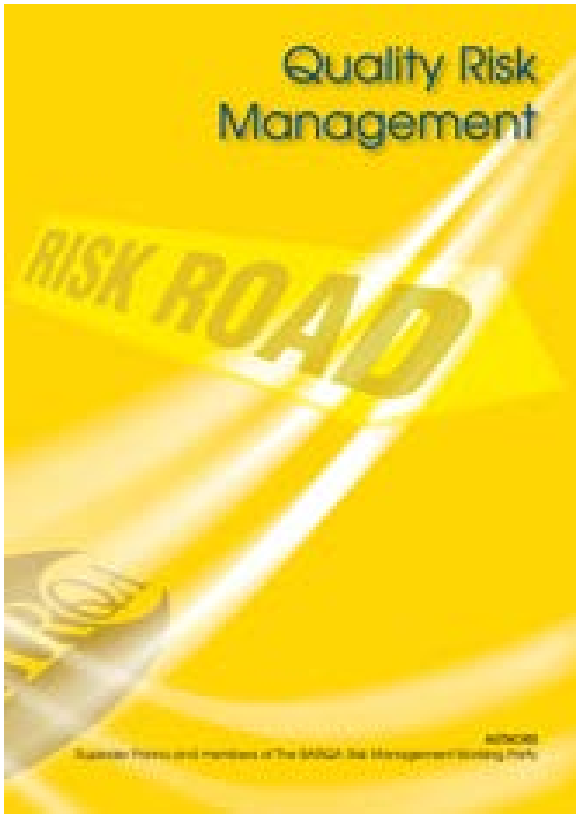
BARQA

Risk Management Guide
issued to support ICH Q9
(mainly for Development QA)



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ISPE Guide – Applied Risk Management for Commissioning and Qualification”

- Provides a roadmap for a migration from traditional qualification practices towards science and risk-based approaches
- Practical methods for applying QRM to equipment, systems and facilities
- Concepts to “cross the bridge”
  - Introduce Good Engineering Practice (GEP)
  - Use product and process understanding as its basis
  - Focus on achieving suitability for intended use
  - Refocus the Quality Unit
  - Use QRM as the basis for the extent of verification activities

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Quality by Design - Gerald Heddell, MHRA June 2012

Focus being given to key audience by the Head of the MHRA, referring to QRM:

"QbD … based on sound science and quality **risk management**"

Product Knowledge and Process Understanding requires acceptance criteria based on patient needs and **risk assessment**

Quality Attributes become critical when there is a probable or actual impact on safety, quality and efficacy

ICH Q11 – development and manufacture of Drug Substances 1st May 2012, Step 4

Section 8.1:

- *Quality risk management can be used at different stages during process development and manufacturing implementation. The assessments used to guide and justify development decisions (e.g., risk analyses and functional relationships linking material attributes and process parameters to drug substance CQAs) can be summarised in section 3.2.S.2.6.*

Section 10.2 (case study)

- ***iterative*** *quality risk assessment*
- *Risk Ranking Histogram (*i.e. a pareto chart)
- *Risk should be reassessed throughout the lifecycle as process understanding increases*
- Changes in level of risk (from data / experience) may lead to updates of the dossier / filing

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IPEC Proposal for Excipient Risk Assessment

Required by 2011/62/EC Falsified Medicines Directive requires that the holder of a manufacturing authorisation shall ensure that excipients are suitable by ascertaining what the appropriate GMP is on the basis of a formal risk assessment.

21CFR 314.94(a) and 331.1(e) require that NDAs show (excipients) are safe and do not affect the safety or efficacy of the drug product.

An appropriate Risk Assessment Model is being worked on by IPEC, PQG and EFPIA

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PDA Technical Reports

PDA Technical Report No. 54 (TR 54) Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

- provides detailed guidance for the application and implementation of quality risk management (QRM) principles throughout the product lifecycle
- Intended to present information that can be helpful on how to implement QRM
- emphasizes QRM application during commercial manufacturing and integrating QRM into the pharmaceutical quality system.

PDA Technical Report No. 58 (TR 58) Risk Management for Temperature-Controlled Distribution

- assist stakeholders in the supply chain to preserve the quality, safety and efficacy of these products during distribution
- serves to complement ICH Q9 guideline (Quality Risk Management) and previously published PDA Technical Reports No. 39, 46, 52 and 53 by assessing, controlling and reviewing risks in systems and processes during distribution.

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PIC/S - ASSESSMENT OF QUALITY RISK MANAGEMENT IMPLEMENTATION Mar 2012

- To contribute to a harmonised approach for inspection of QRM in industry
- This document …reflected the current state of the art
- QRM is not intended to be a barrier to technical innovation or the pursuit of excellence
- QRM should not be an isolated System of QA, it should be fully embedded into the QA or QM-System.
- gather evidence that:
  - The use of QRM is planned;
  - The key elements of the QRM program are clearly defined and documented;
  - Senior Management provides visible support to QRM;
  - Key outcomes of QRM are communicated to and acted upon by Senior Management

Review of *residual risk* and improvement of QRM processes

WHO - Draft Guideline on Quality Risk Management
August 2012

- largely based on ICH Q9 but the WHO draft presents detailed explanations as well as detailed provisions e.g.at least one "Risk Review" should be signed by quality assurance. Verification of the QRM processes and specific QRM applications should be performed by a third party. In addition, a risk matrix in a tabular form describes examples and risk management tools (methods, description of the methods, potential applications). A publication of the "Manufacturing Technology Committee" from the "Pharmaceutical Quality Research Institute" (PQRI-MTC) dated from 2008 is explicitly quoted for the examples presented.

- COMMENTS
- a flowchart is recommended to be able to perform the risk-based analysis of a process. In the draft, the use of a flowchart is described as "if needed" and not really binding ("may use").
- inconsistencies exist with regard to responsibilities. E.g. the signature of QA is required for "Risk Review" but the responsibility is not mentioned in the respective chapter 3.2.
- regarding the use of QRM for qualification activities (chapter 3.4), the document concedes that often only IQ, OQ, PQ are being performed. In this context, DQ plays a decisive role in the qualification life cycle and should be therefore integrated in the QRM process - except for the qualification of older facilities.

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Inspection Trends

Italian (AIFA) require risk matrix for manufacturing site risks to be catalogued and scored

Danish require raw materials to be held in quarantine until a satisfactory audit of the supplier is performed

MHRA website states "*The legislative focus for risk-management systems is on forward planning that is dynamic and proportionate to risk.*

There is also a focus on methods to try to monitor the effectiveness of any risk-minimisation measures.
PSURs are retrospective benefit-risk assessments."

MHRA Vigilance Risk Management of Medicines Division

Inspection Trends

Deficiency Data Review 2012 – 16 out of 670 Critical or Major findings due to Risk Management failings

http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con149837.pdf

1. Investigation of anomalies
2. Quality management (Change Control)
3. Corrective action/preventive action (CAPA)
4. Complaints and Product Recall
5. Quality management
6. Supplier and Contractor Audit
7. Contamination, Chemical/Physical –Potential For
8. Documentation –PSF/Procedures/Technical Agreements
9. Documentation –Manufacturing
10. Process Validation

Summary

Clearer guidance on exactly ***what*** and ***how*** is coming out

More examples of applications / best practice

Better knowledge from regulators = tougher & more observations

Not a one-off … needs to be iterative, repeated and a life-cycle approach

Value adding, especially if you move from qualitative to quantitative

Are your people ***fully*** trained? Do you have experts (or just people who talk a lot)?

Are you doing it because you have to or because it makes real and lasting improvements for your company and its patients?

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Key point to remember

QRM is about avoiding large risks through an ongoing process of risk awareness and reduction

- Avoid deaths, recalls, companies going bust
- Supports improvement / investment