Quality Risk Management for Quality system

质量风险评估在质量保证体系中的应用

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解馨

Agenda

Introduction to QRM

The QRM Process

The 10 step approach to QRM

Case Studies

Final Points

QRM - What is it?

- Structured approach to understanding and managing risk in the Pharmaceutical Industry
- Started from ICHQ9 “Quality Risk Management” working group
- Becoming more of a regulatory expectation
  - FDA guideline in June 2006
  - EU added to the EMEA website in January 2006
  - Japan adopted in Sept 2006
- Chinese GMP 2011Edition,effective March 1

QRM – Why do it?

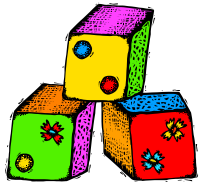
- Regulatory and Compliance
  - Becoming more and more a regulatory expectation
- Patients and Customers
  - Greater assurance of patient safety
    - Elements of risk a more visible
    - Risk reduction actions can be better identified and linked to each risk
- Business Case:
  - Makes decisions more robust
  - Prioritise/focus resources
  - Eliminate un-required activities and thus reduce workload
  - Support lean/agile endeavours/projects
  - Support our continuous improvement

QRM and other Methodologies

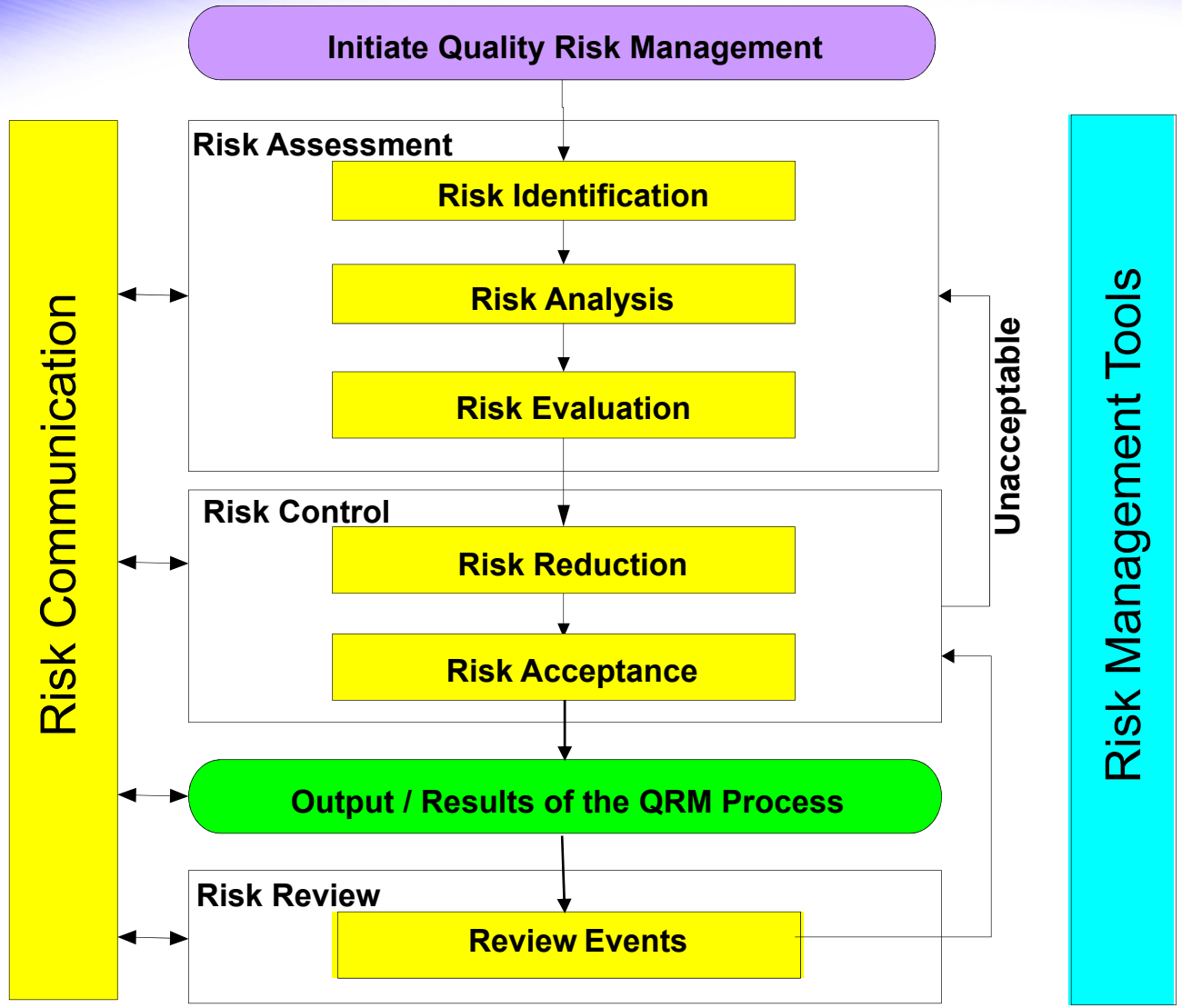
- Quality Risk Management may be new, but we are already using some of the thinking in the way our systems and processes are set up
- There is also a lot of other methodologies or approaches that are in place in Pfizer
- It's important to understand the differences and similarities between QRM and:
  - Root Cause Analysis
  - Commissioning and Qualification
  - Operational Excellence (eg. Six Sigma Green Belt Projects)

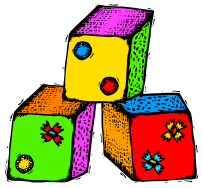
Overview - Principles

- **Two primary principles of QRM:**
  - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk



Overview – Process





The 10 step approach to QRM

1. Collect and organise information
2. Define the risk question
3. Choose tool
4. Determine risk factors
5. Define the scales for risk components
6. Define matrix
7. Determine the threshold for action
8. Apply the tool
9. Define risk reducing measures
10. Document and Approve

plus Ongoing Risk Review

Initiation and Identification

Analysis

Evaluation

Reduction

Output and Acceptance

Review

Step 1 – Collect and Organise information

- Gather relevant information and references
  - PQSs, Regulations, Data, etc.
- Identify any background or preliminary information
- Agree on assumptions
- Tools which can be used to organize available information
  - Brainstorming
  - Flow Charting
  - Process Mapping

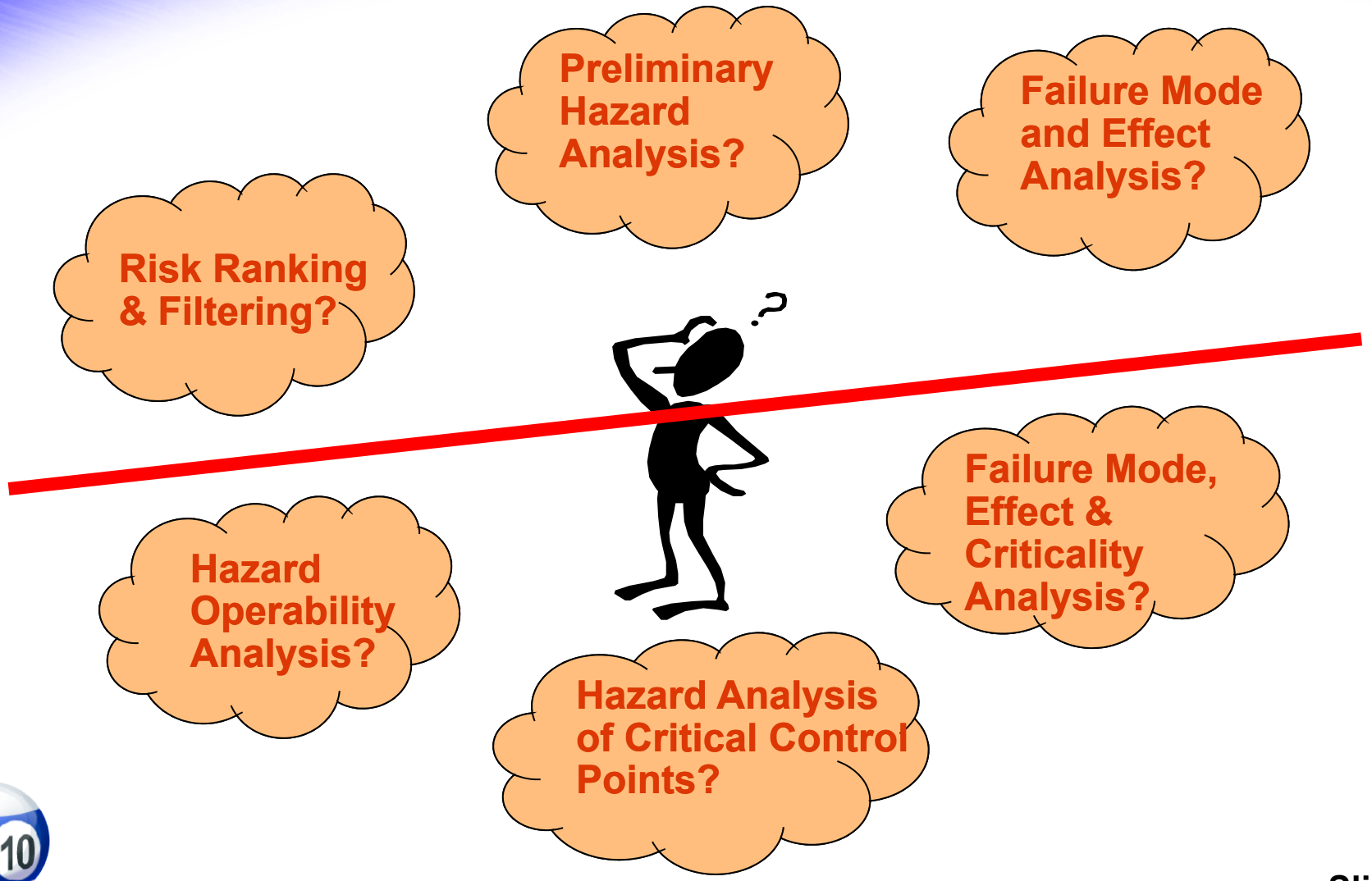
Step 2 – Define Risk Question

- Clearly defining the initial risk question or issue is essential for an effective QRM outcome.
- Clearly defining the risk question helps to:
  - Focus on the objective
  - Clarifies the scope
  - Assure resources are effectively applied
  - Provides context

Step 3 – Choose Tool

- There is no wrong tool
- Simple tools are valuable
- Various methods of analysis are largely interchangeable
- Methods/tools can be modified to meet needs
- Available information and the risk question will drive selection of tools

Step 3 – Choose Tool (cont.)



Step 3 – Choose Tool (Summary)

Tool	*Includes*	*Scales*	*Scale Items*	*Threshold*
RRF - Risk Ranking and Filtering	S x P	Words (only L,M,H)	Not defined	Use standard matrix. Action taken when High outcome. (Medium to be considered)
PHA - Preliminary Hazard Analysis	S x P	Words (L,M,H or other)	Each scale item defined	Prepare matrix and define action requirements
FMEA - Failure Mode and Effect Analysis	S x P x D	Numbers	Each scale item defined	Define action requirements by RPN

Step 4 –Determine Risk Factors

- Severity
  - What are the factors which must be considered that will have an impact on the patient / compliance / company (consequences)?
    - Probably covered in your risk question
- Probability
  - What is the likelihood that the impact on the patient/compliance/company will occur?
- Detection
  - Can you detect the risk?
  - Remember low detection → high risk

Step 5 – Define Scales

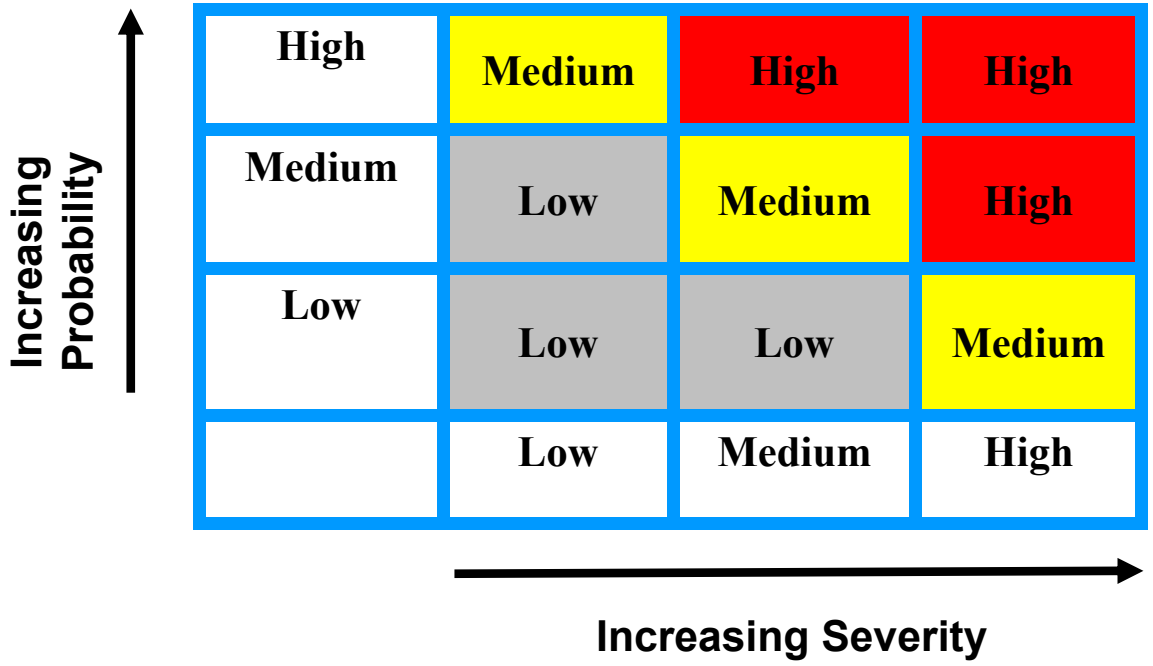
- **Use of different scales:**
  - High, Medium, Low
  - Severe, Major, Minor, Negligible
  - Linear: 1, 2, 3, 4
  - Exponential: 1, 2, 4, 8
  - Logarithmic: 1, 10, 100, 1000
  - Self made: 1, 3, 7, 10

Step 5 – Define Scales (cont.)

Severity Term	*Description & Definition*		*Probability (Frequency)*	*Description & Definition*
Severe	Potential death or permanent injury		Frequent	Continual occurrences
Major	Potential serious injury, but not permanent		Probable	Occurrences are frequent probable reoccurrence
Minor	Potential minor injury, but not permanent		Occasional	Isolated occurrences
Negligible	Potential minor discomfort, but not permanent		Remote	Isolated occurrences possible; Don't expect reoccurrence

Step 6 – Define Matrix

Example RRF – Matrix



Step 6 – Define Matrix (cont.)

Example PHA – Matrix

Frequency / Probability	***Severity***			
	Negligible	***Minor***	***Major***	***Severe***
Frequent	Low Risk	Intermediate Risk	High Risk	High Risk
Probable	Low Risk	Intermediate Risk	High Risk	High Risk
Occasional	Trivial Risk	Intermediate Risk	Intermediate Risk	High Risk
Remote	Trivial Risk	Low Risk	Intermediate Risk	Intermediate Risk

Step 7 – Determine Threshold for Action

Action thresholds:

■ High	Risk must be reduced
■ Intermediate Medium	Reduce risk to As Low as Reasonably Possible (ALARP)
■ Low	Reduce risk to ALARP, considering cost/benefit
■ Trivial	Generally acceptable level of risk

Step 8 – Apply Tool

- List the potential risk items
- Organise by risk category (Consumer/Patient, Compliance, Business/Producer)

- Example for a batch/product deviation:
  - Consumer /Patient
    - Is it a product efficacy issue?
    - Is it a product strength issue?
    - Is it a medically necessary supply issue?
  - Compliance
    - Did we breach GMP?
- Example for a decision to remove/discontinue a certain test:
  - Consumer/Patient
    - Could we have an an issue with product identity?
  - Compliance
    - Is this test registered?

Step 8 – Apply tool (cont.)

Example RRF – Application of Tool

Potential Risk	Probability	Severity	Outcome
Consumer Risk A	*Low*	*Med*	*Low*
Consumer Risk B	*Med*	*Med*	*Med*
Compliance Risk A	*High*	*Med*	*High*
Producer Risk A	*Low*	*High*	*Med*

Note: Table will be different for PHA and FMEA.

Step 9 – Define Risk Reduction Measures

Two basic risk control strategies:

- Prevent
  - Stop the hazard occurring at all
- Protect
  - Decrease the severity/impact
    - E.g. If severity unknown, get a medical opinion
    - E.g. Installing an eye-wash station
  - Decrease the probability
    - E.g. Slow down the machine rate
    - E.g. Perform maintenance less frequently
  - Increase the detection
    - E.g. Perform 100% visual inspection
    - E.g. Implement additional routine checking

Step 9 – Define Risk Reducing Measures

- Once measures have been implemented, reapply tool to show:
  - How each individual potential risk was reduced
  - What the overall level of risk is

- Shows that we have:
  - Followed the QRM process
  - Understood and accepted the residual risk
  - Effectively completed the analysis

Step 10 – Document and Approve

Risk Question:

Assessment Team:

Potential Harm	Risk Analysis		Risk Evaluation	Recommended action	Responsible party and target date	Risk Analysis		Risk Evaluation
	Probability (P_1)	Severity (S_1)	Initial Score (P_1 x S_1)			Probability (P_2)	Severity (S_2)	Final Score (P_2 x S_2)

Prepared By: _____ Date _____
Business Unit Approval: _____ Date _____
QA Approval: _____ Date _____

Ongoing Risk Review

- **At Pfizer**
  - SQRT/AQRT
  - Site Validation Committee
  - Corporate Auditors
- **Outside Pfizer**
  - Inspectors
  - Regulatory Authorities

QRM – What can we do with QRM?

- Retro-actively:
  - Making decisions around product and quality risk for deviations/issues/complaints
- Pro-actively:
  - Qualification & Validation
  - Change Management - Impact assessments
  - PM Programs and Calibration
  - Audit Frequencies
  - Materials Management
  - Training Optimisation
  - …….

Sharing practices

QRM used in quality system

Case 1: Supplier Auditing

1. **Collect and organise information**

   What are the different types of suppliers used by the site? What do we know about each supplier?

2. **Define the risk question**

   What is the supplier audit schedule that will ensure that suppliers presenting a high risk to the patient are audited in a more frequent manner?

Case 1: Supplier Auditing

3. **Choose Tool – FMEA**

4. **Define the meaning of risk components**
   - Severity
     - Type of products
     - Number and significance of quality defects
   - Probability
     - Complexity of the site (multi products)
   - Detection
     - Robustness of the quality system
     - Audit history

Case 1: Supplier Auditing

5. Scale for Severity

Factor	Definition	Example
10	Sterile products or recall of product	*Sterile products, sterile APIs, sterile packaging material*
6	Product orally administered or product rejected	*Tablets, capsules, primary packaging material*
3	Topical products and compounds not directly used by patient or backlog of release of lots due to deviations	*Creams, ointments, non-sterile API's, secondary pre-printed packaging*
1	Compounds used during manufacturing process	*Starting materials, raw material, excipients*

Case 1: Supplier Auditing

5. Scale for Probability

Factor	Definition	Example
8	Highly complex structure of the site	*Multi products including products to be produced under strict separation schemes*
4	Complex structure of the site	*Multi products*
1	Dedicated site	*One product*

Case 1: Supplier Auditing

5. Scale for Detection

Factor	Definition	Example
8	Compliance status is unknown or defects in the Quality Systems are definitely not known	*Never audited, last audit more than five years ago, result of last audit had critical observations*
4	Compliance status could be affected by time or changes or defects in Quality System might not be known	*Last audit three to four years ago, change in site owner, global reorganisation, results of audit had major observations*
2	Compliance status has good reputation or defects in the Quality System might be possible	*Last audit two/three years ago, result of last audit resulted in minor observations*
1	Compliance status has been recently assessed or defects in the Quality System has been assessed	*Last audit was up to 2 yeas ago, satisfactory audit results (comments)*

Case 1: Supplier Auditing

6. **Define Matrix**
7. **and Threshold**
   - When RPN is at least 96 (6S x 4P x 4D) = schedule audit
8. **Apply the tool**

Supplier	Severity Score (S)	Probability Score (P)	Detectability Score (D)	Total Risk Score (SxPxD)
Supplier A				
Supplier B				
Supplier C				
Supplier D				

Case 1: Supplier Auditing

9. Define risk reducing measures

Supplier	Total Risk Score (SxPxD)	Recommended action and target date
Supplier A		Audit on month, year
Supplier B		
Supplier C		
Supplier D		

10. Document and Approve

- SQRT to approve QRM and Audit Schedule

Case 1: Supplier Auditing

Last comments on audit scheduling:

- Use of a risk based audit scheduling will make the fixed frequency approach obsolete
- A rolling schedule that can be adapted if new information becomes available, *e.g*. recall situation can raise the priority of the audit
- This tool does not define the focus areas within each audit
- Additional risk factors, applicable to individual suppliers, can also be considered. *e.g.* availability / relationship with the supplier

Case 2: Using QRM to determine SOP review date

Step 1 – Collect and Organise Information

- Sites employ a default frequency for periodic review of SOPs.
- There are no regulations specifying a required review period for SOPs,
- Clear expectation that SOPs are current.

Case 2: Using QRM to determine SOP review date

Step 2 – Define the Risk Question

- What is the optimal frequency of periodic review, for all SOPs, that ensures that product quality and regulatory compliance is maintained?

Case 2 Using QRM to determine SOP review date

Step 3 – Choose tool

- Risk Ranking and Filtering
- Simple but sufficient for this analysis.

Case 2 Using QRM to determine SOP review date

Step 4 – Determine Risk Factors

- ***Probability*** – what is the likelihood of having non-compliant or deficient procedures which have the potential to impact product quality or regulatory compliance attributed to lack of timely document review that could remain unchecked or undetected?
- ***Severity*** – what is the impact on product quality and regulatory inspection outcomes from having an SOP in a non-compliant (out of currency) status?

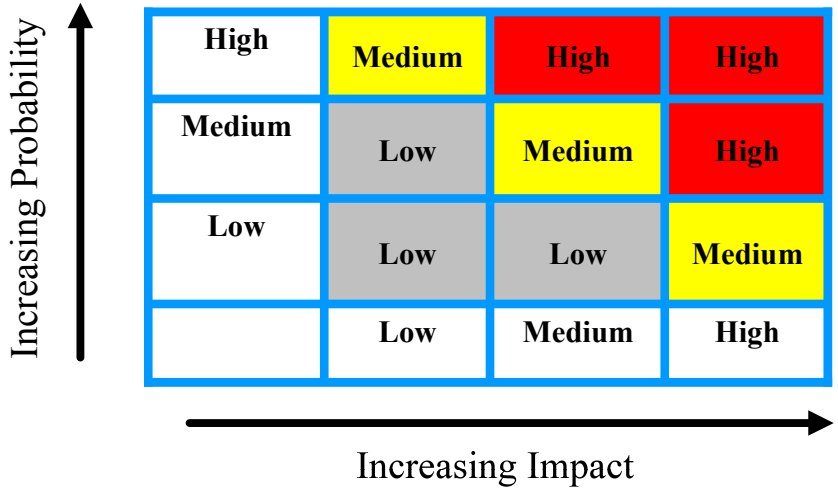
Case 2 Using QRM to determine SOP review date

Step 5 – Define the Scales

- Probability – low, medium, high
- Severity – low, medium, high

Case 2 Using QRM to determine SOP review date

- **Step 6 – Define the Matrix**



Case 2 Using QRM to determine SOP review date

Step 7 – Determine the Threshold for Action

- Low – Periodic Review of 5 years
- Medium – Periodic Review of 2- 3 years
- High – Periodic Review of 1 year

Case 2 Using QRM to determine SOP review date

Step 8 – Apply the Tool

- Categorize SOPs

Case 2 Using QRM to determine SOP review date

SOP Category	Subject	Sub-group	Probability	Outcome	score
1.Plant	1.Safety		low	low	low
	2.Plant Process	Labels management	low	high	medium
		Project Management	low	high	medium
	3.Plant Cleaning		low	medium	low
	4.Plant Equipment		low	medium	low
	5.Plant Training / Administration	Documentation	low	medium	low
		Training	low	medium	low
		Validation (System, Cleaning & Process)	medium	high	high
		Security	low	low	low
		Compliance	low	high	medium
		RFT	medium	medium	medium
		Change Control	medium	high	high
		Health	low	low	low

Case 2 Using QRM to determine SOP review date

SOP Category	Subject	Sub-group	Probability	Outcome	score
2.Quality Operation	1.QO Safety		low	low	low
	2.QO Process	Sampling, Testing and Release	low	high	medium
		IPC	low	high	medium
		Investigation	medium	high	high
		Analytical Method Validation	low	high	medium
		GLP	low	high	medium
	3.QO Cleaning		low	medium	low
	4.QO Equipment		low	medium	low
	5.QO Training / Administration	Quality Assurance	medium	high	high
		Quality Control	low	high	medium
		Documentation	low	medium	low
		Training	low	medium	low

Case 2 Using QRM to determine SOP review date

Step 9 – Define Risk Reducing measures

- Determine appropriate review period for each SOP based on QRM

Case 2 Using QRM to determine SOP review date

PLANT TRAIING/ADMINISTRATION	
Management Of Plant Procedure	2 Y
Plant Training System	3 Y
Correct Documentation.	3 Y
Management of Batch Documents	2 Y
Process Validation Protocols	1 Y
Revalidation Policy	1 Y
The General Visit PPL Procedure	5 Y
GMP Training Procedure	2 Y
Procedure of Using the out-permission ticket	5 Y
Visitor Reception and Traffic Managerment	5 Y
Handling Procedure of Security Incidents	5 Y
Plant Security Patrolling Procedure	5 Y
Security Guard's Working Regulations	5 Y
Manipulate procedure of security alarm and monitor system	5 Y

Case 2 Using QRM to determine SOP review date

Step 10 – Document and Approve

- Change control request.
- Implement these review periods.
- SOP review system to ensure that this SOP review occurs within 3 months of the specified requirement.

Key learning of case 2

- Reduce Non-value added activities
- Improvement on SOP review efficiency
- Example of science and risk based quality

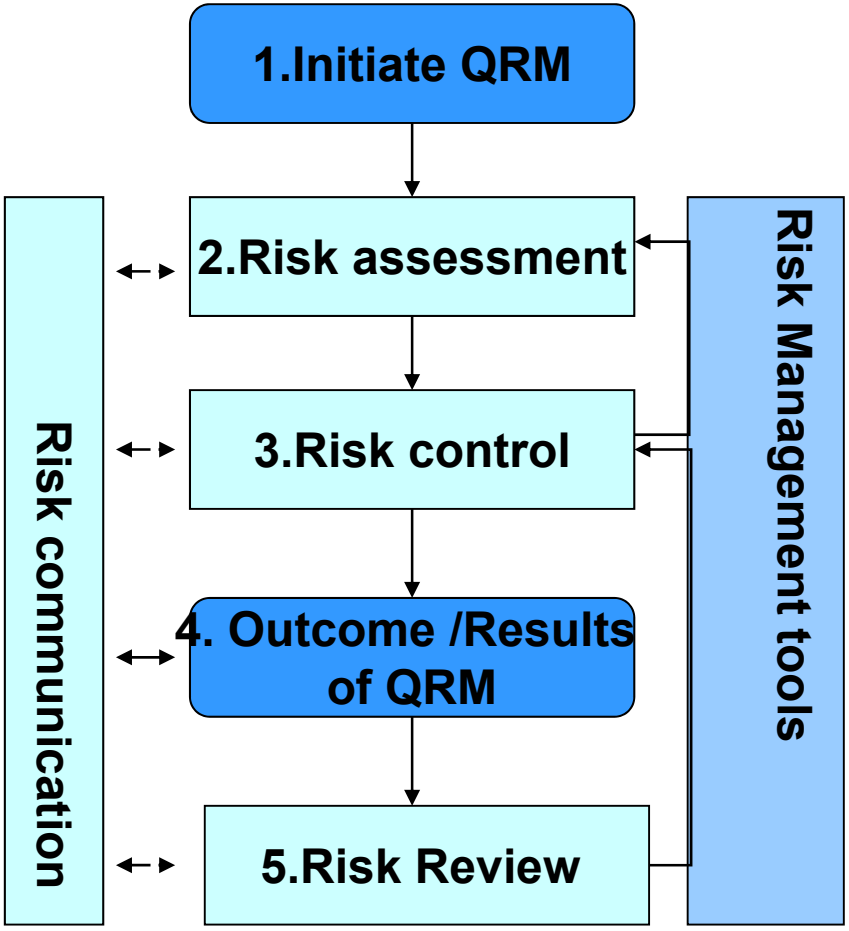
Case 3 Change control system with QRM

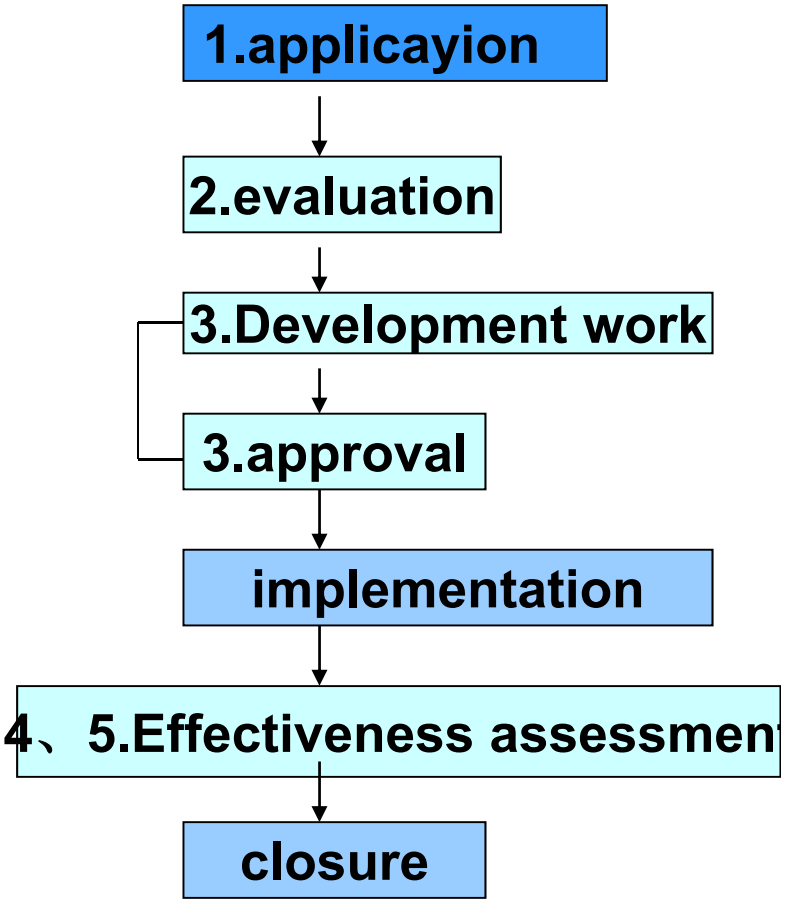
- Change Control is an important element in pharmaceutical quality system. Establishment of effective change control process is key to ensure continuous improvement and manufacture of quality products.

- China GMP Edition 2011

  There should be change control system established in plant, to evaluate and manage all changes impacted on product quality.

Case 3 Change control system with QRM





Case 3 Change control system with QRM

- Take the manufacturing location change of API for a solid dosage as an example to explain the rationality of the methodology discussed by implementing QRM

Case 3 Change control system with QRM

- **Step 1 information collection**

- A solid dosage API will change manufacturing location from Site A to Site B. The process in the two sites are both three-step method except for one-step reaction path, an original material as well as a little difference of the solvent system. 3 respective batches of new and old API comparative test by current specification shows: Chemical property matches. Physical property also matches except for particle size distribution difference. The initial dissolution rate data shows particle difference impacts dissolution.

- The location change impacts single market registration. The EIR （Establishment Inspection Report）from FDA is required by the target market.

Case 3 Change control system with QRM

- **Step 2 Identify Risk question**

What is the quality and regulatory risk caused to the solid dosage by API manufacturing location change? What action should be taken?

Case 3 Change control system with QRM

- **Step 3 tools selection**

RRF (Risk Ranking & Filtering)

Case 3 Change control system with QRM

- **Step 4 Determine Risk Factors**

- Severity：

  Quality risk to product caused by the product quality property's incompliance with the accepted specification.

  Regulatory risk caused by the change over the limitation of register and GMP .

- Possibility：

  The possibility of the product quality property's incompliance with the accepted specification

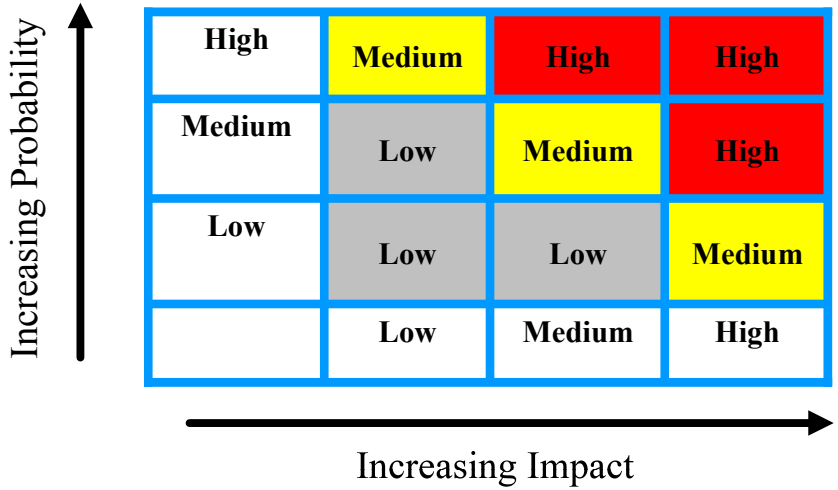
  The possibility of the change over the limitation of register and GMP

Case 3 Change control system with QRM

- **Step 5 – Define the Scales**
- Probability – low, medium, high
- Severity – low, medium, high

Case 3 Change control system with QRM

- **Step 6 – Define the Matrix**



Case 3 Change control system with QRM

Step 7 – Determine the Threshold

- Low – Risk could be accept no further action needed
- Medium – Risk could be recued if possible
- High – Risk must be reduced

Case 3 Change control system with QRM

Step 8 Apply the tools

Quality Risk	Risk Analysis		Risk Evaluation
	Possibility(P)	Severity(S)	Risk Score (P x S)
Quality Risk			
Specification(Impurity, Residual Solvent, Particle Size Distribution)	High	High	High
Test Method Applicability	High	High	High
Dissolution Rate	High	High	High
Process Validation	High	High	High
Stability	High	High	High
Compliance Risk			
Registration	High	High	High
GMP(EIR)	Low	High	Medium

Case 3 Change control system with QRM

Step 9 Define risk reducing measures

	Rank	Action	Responsible Party and Target Date
Quality			
Specification(Impurity, Residual Solvent, Particle Size Distribution)	High	1. Improve process: Investigation demonstrates drying process variation is the cause of particle size difference. New API site is required to optimize drying process parameter to make the particle size distribution reaching the current specification. 2. Set up new specification: Update impurity, residual solvent control specification to adapt to the new process. 3.Complete 3 batches test result comparison.	2007.12
Test Method Applicability	High	Evaluate the applicability of the method	2008.5
Dissolution Rate	High	Complete Dissolution comparative test.	2008.5
Process Validation	High	Complete 3 batches process validation	2008.5
Stability	High	Carry out accelerated and ongoing stability study	2008.8
Compliance			
Registration	High	Complete Registration	2009.3
GMP(EIR)	Medium	Provide EIR	2008.8

Case 3 Change control system with QRM

- **Step 9 Apply tools again**

	Risk Evaluation	Risk Analysis		Risk Evaluation
	Initial Score	P	S	Final Score
Quality Risk				
Specification(Impurity, Residual Solvent, ,Particle Size Distribution)	High	Low	Low	Low
Test Method Applicability	High	Low	Low	Low
Dissolution Rate	High	Low	Low	Low
Process Validation	High	Low	Low	Low
Stability	High	Low	Low	Low
Compliance Risk				
Registration	High	Low	Low	Low
GMP(EIR)	Medium	Low	Low	Low

Case 3 Change control system with QRM

- **Step 10 – Document and Approve**

Potential Harm	Risk Analysis		Risk Evaluation	Recommended Action	Responsible Party and Target Date	Risk Analysis		Risk Analysis
	Possibility (P1)	Severity (S1)	Initial Score (P1 x S1)			Possibility (P2)	Severity (S2)	Final Score (P2 x S2)
Quality Risk								
Specification(Impurity, Residual Solvent, ,Particle Size Distribution)	High	High	High	1.Improve process:Particle size Reaches specification 2.Set up new specification 3.Compare 3 batches test	2007.12	Low	Low	Low
Test Method	High	High	High	Evaluate Method	2008.5	Low	Low	Low
Dissolution Rate	High	High	High	Dissolution Rate Test	2008.5	Low	Low	Low
Process Validation	High	High	High	3 batches process validation	2008.5	Low	Low	Low
Stability	High	High	High	Accelerated long-term stability study	2008.8	Low	Low	Low
Compliance Risk								
Registration	High	High	High	Complete Registration	2009.3	Low	Low	Low
GMP EIR	Low	High	Medium	Provide EIR	2008.8	Low	Low	Low

Case 3 Change control system with QRM

- Change Control is an important element in pharmaceutical quality system.
- Establishment of effective change control process is key to ensure continuous improvement and manufacture of quality products.
- Design and optimization of pharmaceutical products change control process based on quality risk management concept.

Final Points

- Tips to successfully embed QRM:
  - Have leadership support /accountability for QRM
  - Need all functions involved – not only Quality
  - Provide clear guidance to your colleagues on where and how QRM should be used
    - Incorporate philosophy into existing SOPs
    - Provide training in tools and methodology
  - Identify site QRM Champions
    - Across all functions/departments, not just Quality
  - Have a proactive approach to finding opportunities to use QRM
  - Communicate QRM analysis and outcomes
  - “Listen” to your QRM analysis
    - Take active decisions and actions

Final Points

- Bad decisions cannot be “made right” by applying QRM
- QRM works best with multi-disciplinary perspectives
- Even if the tool is simple (informal), you must document how you reached your decision
- There are no strict rules for applying tools and adapting tools is okay
- Each situation is different but all situations should relate back to consumer and compliance risk

Thank you