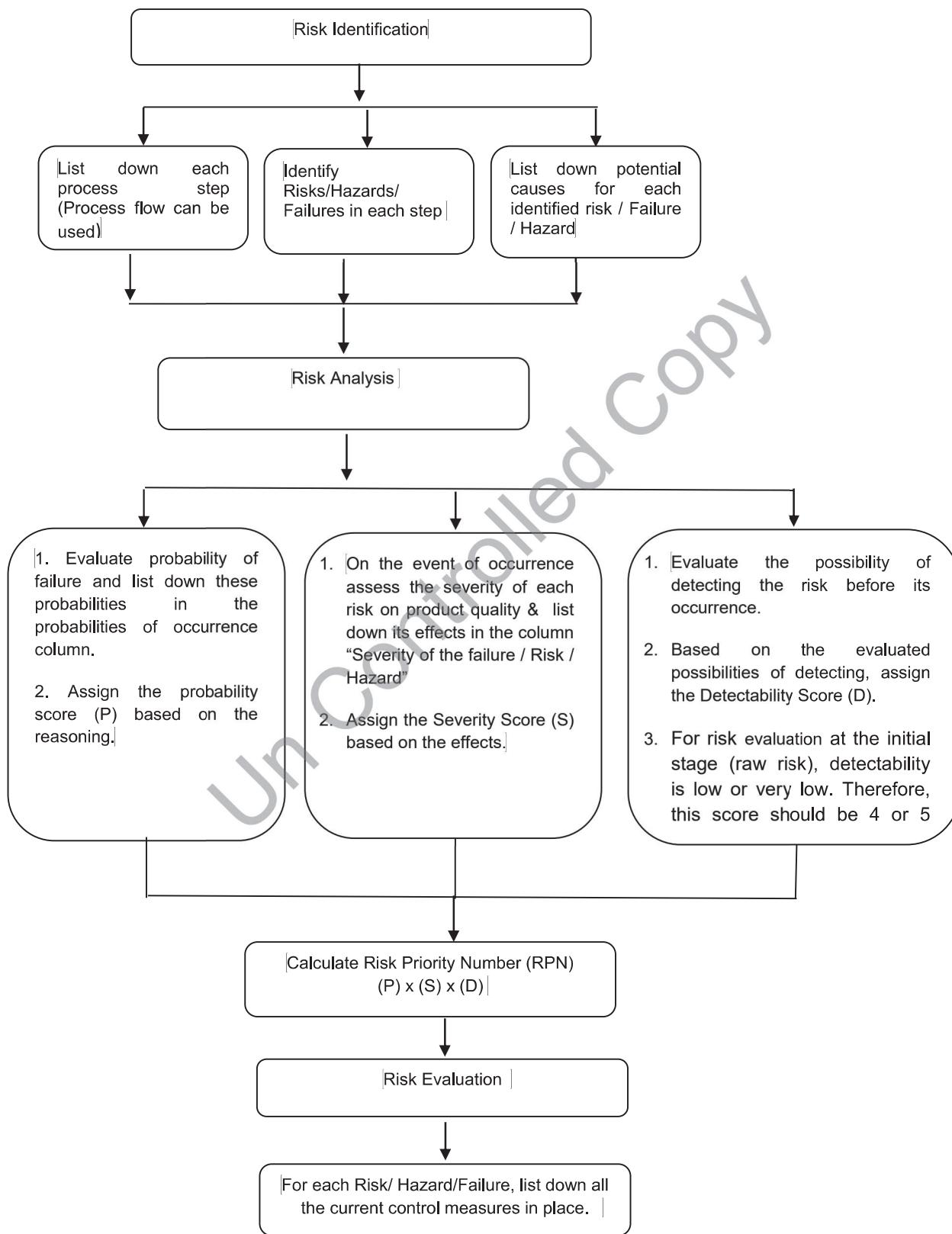
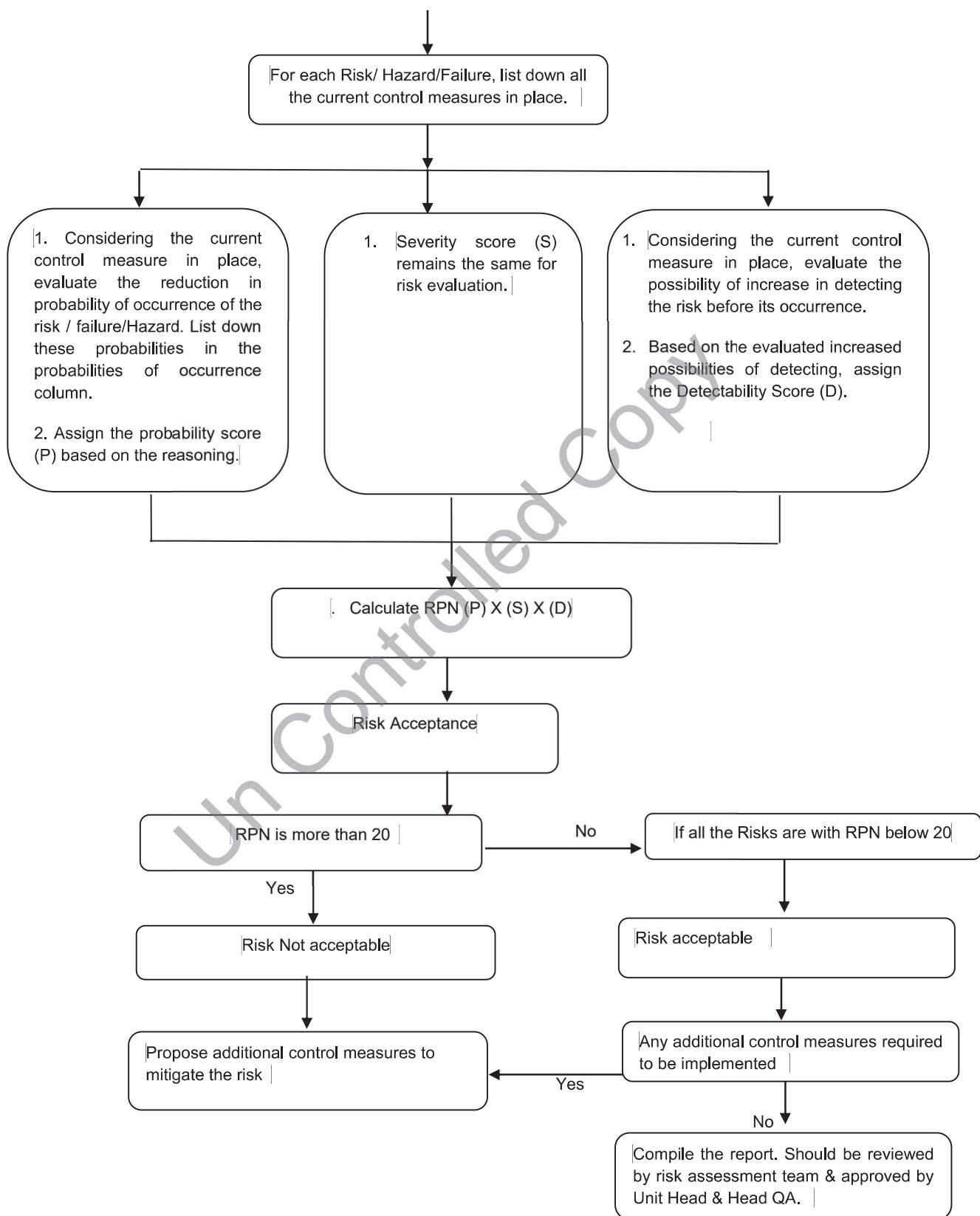
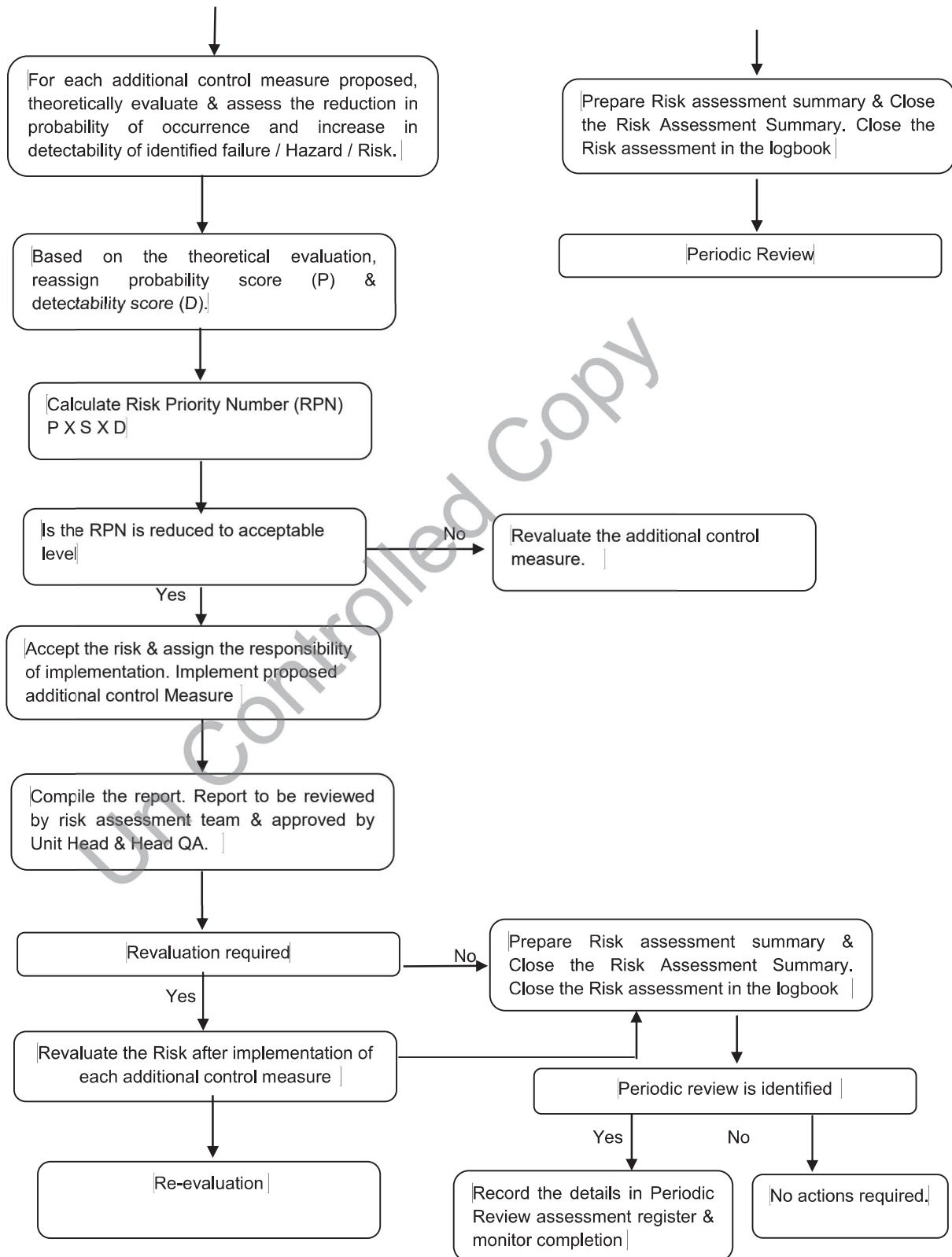


RISK ASSESSMENT FLOW CHART

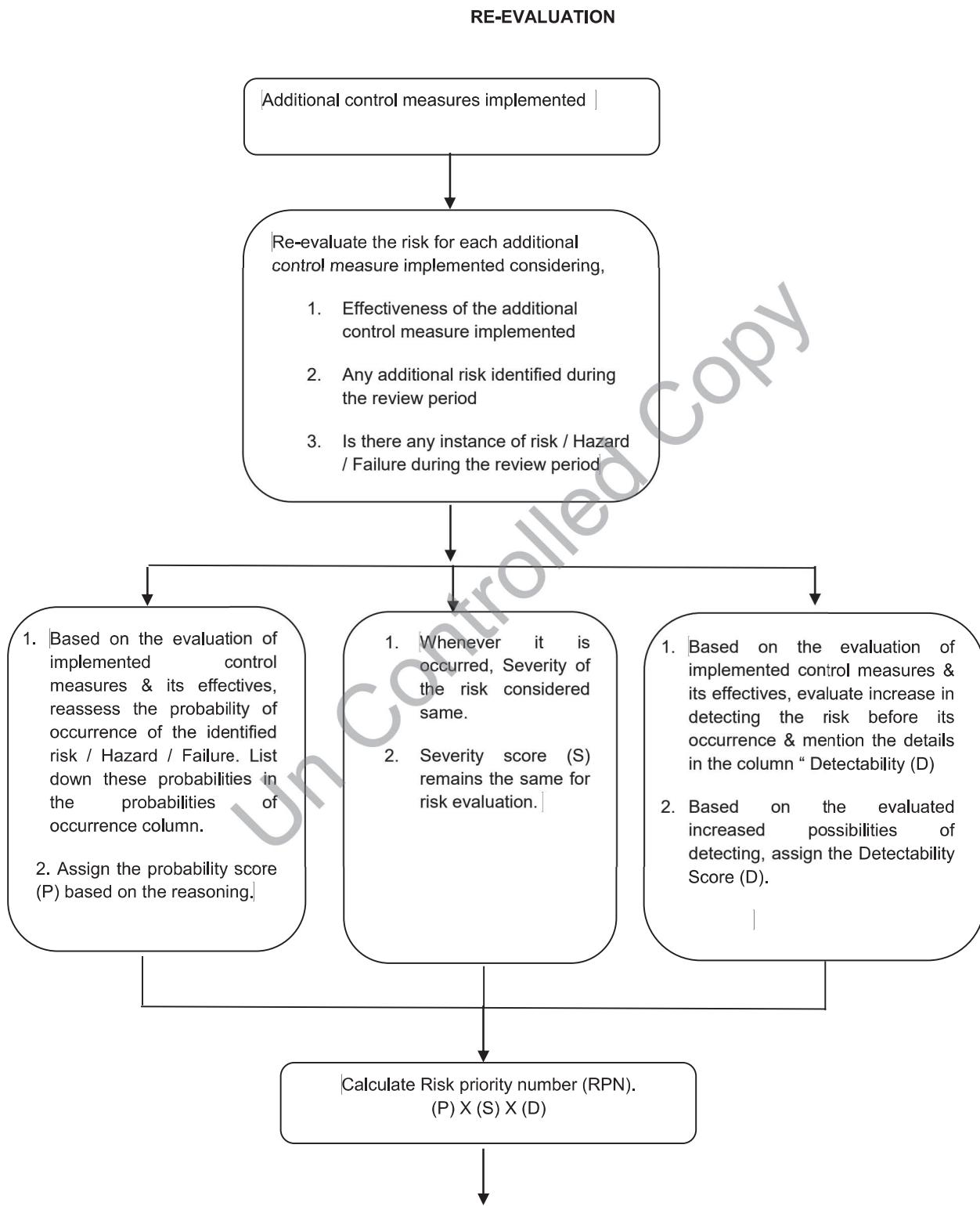


RISK ASSESSMENT FLOW CHART


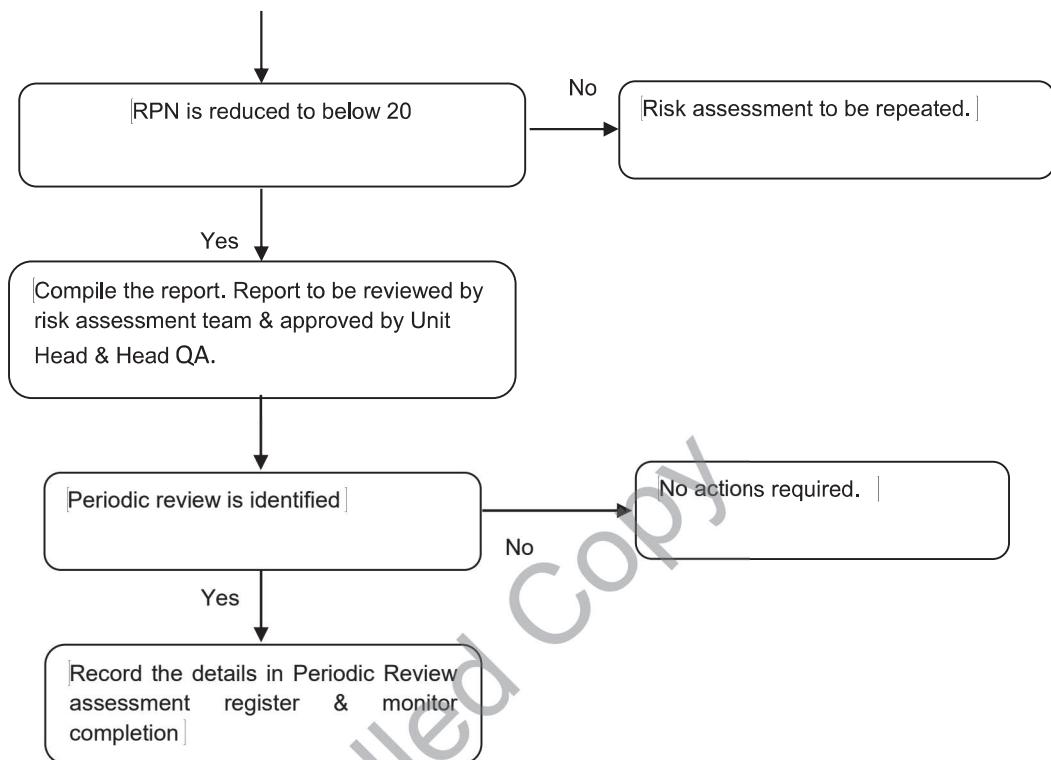
RISK ASSESSMENT FLOW CHART




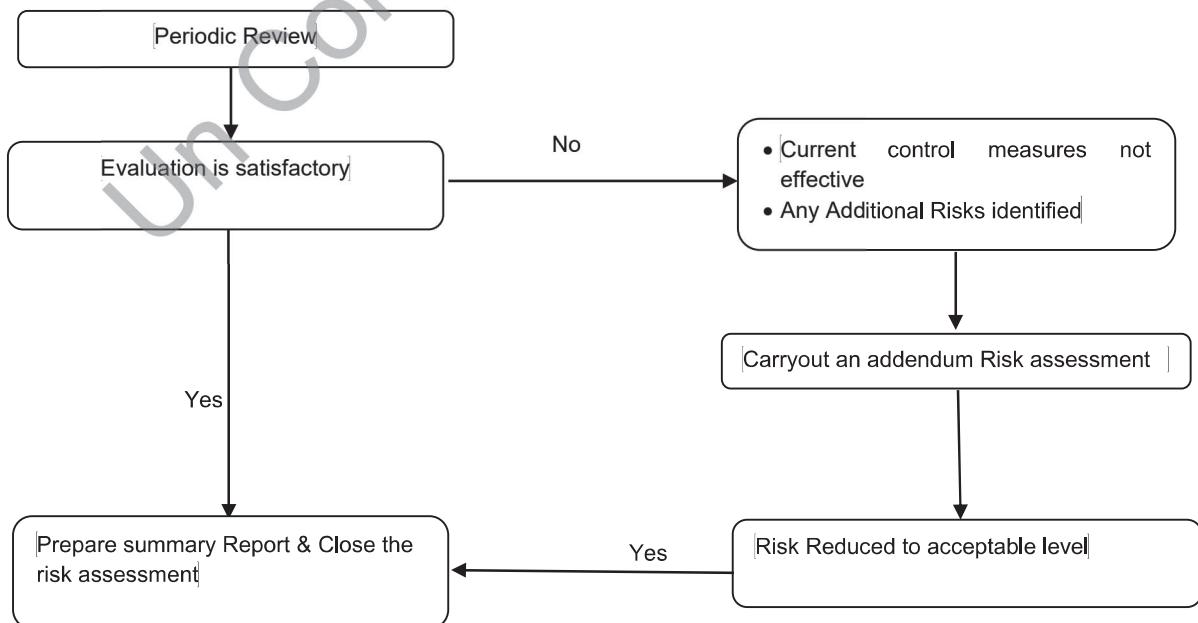
RISK ASSESSMENT FLOW CHART



RISK ASSESSMENT FLOW CHART



PERIODIC REVIEW





MICRO LABS

No.: QAP/MLCM/0043/ANX/0003-005

SELECTION OF RISK ASSESSMENT TEAM

Sl. No.	Example of Risk Assessment or Triggered by Changes	Applicable Department:										
		QA	QC	Micro biology	Production	Packaging	Engineering	HR	Stores	FG Stores	Safety	IT
1.	Changes Related to Equipment / Instrument	✓	\$	\$	\$	\$	✓	X	\$	X	✓	X
2.	Changes Related to Software / Hardware / Computerized System	✓	\$	\$	\$	\$	✓	X	\$	X	✓	X
3.	Deviation Related to Machine / System / Utility breakdown	✓	\$	\$	\$	\$	✓	X	\$	X	✓	X
4.	Deviation Related To Excursion of Temperature / %RH / ΔP	✓	\$	\$	\$	\$	✓	X	\$	X	✓	X
5.	Risk assessment of Existing System / Equipment / Utility	✓	\$	\$	\$	\$	✓	X	\$	X	✓	X
6.	Cross Contamination and Contamination / Mix ups	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓
7.	Change Related to Product / Material / Process / Vendor	✓	✓	✓	✓	✓	X	X	✓	✓	✓	In case of new products
8.	Changes Related to Facility / Utility	✓	✓	✓	✓	✓	\$	✓	X	\$	✓	In case of new products
9.	Deviation Related to Process	✓	✓	✓	✓	✓	\$	X	X	X	✓	In case of new products
10.	Malfunctioning of Software / Hardware in Qualified System	✓	\$	\$	\$	\$	✓	X	X	X	✓	In case of new products
11.	Risk Assessment of Existing Procedures (Operation / Cleaning / General / Preventive Maintenance etc)	✓	\$	\$	\$	\$	\$	\$	\$	\$	\$	X

Approved By: Satish Babu. V S

E-Sign/Date: 18/03/2024 10:02

Page 1 of 2



Sl. No.	Example of Risk Assessment or Triggered by Changes	Applicable Department										
		QA	QC	Micro biology	Production	Packaging	Engineering	HR	Stores	FG Stores	Safety	IT
12.	Campaign Batch Dispensing	✓	✓	✓	X	X	X	X	\$	X	X	X
13.	Different API source	✓	✓	✓	✓	X	X	✓	X	X	X	✓
14.	Change in Shipment Procedures	✓	X	X	X	X	X	X	✓	X	X	In case of new products
15.	Failure of Regulatory Commitment	✓	\$	\$	\$	\$	\$	\$	\$	\$	\$	X
16.	Introduction of New Facility / Equipment / System / Utility etc	✓	✓	✓	\$	\$	✓	X	\$	\$	✓	X
17.	Cleaning Validation	✓	✓	✓	✓	X	X	X	X	X	X	X
18.	Complaint Management	✓	✓	✓	✓	✓	✓	X	✓	✓	X	X
19.	Training and education	✓	\$	\$	\$	\$	\$	\$	\$	✓	X	X
20.	Production (Manufacturing and Packing)	✓	✓	✓	✓	✓	✓	X	✓	✓	X	X
21.	Material Management (Receipt, Storage, handling and dispensing of material)	✓	✓	✓	X	X	X	✓	X	X	X	In case of new products
22.	Laboratory control and stability Testing	✓	✓	✓	X	X	X	X	X	X	X	X
23.	Cleaning, sanitation and hygiene	✓	✓	✓	\$	\$	\$	\$	\$	X	X	X

✓ - Applicable

X - Not Applicable

\$ - Applicable in case the triggered changes are related to the respective department.

Note: 1. The examples listed above is not limited, any other activities which triggers the requirement of risk assessment shall also be considered and in such case selection of risk assessment team shall be done by Head of Site QA.

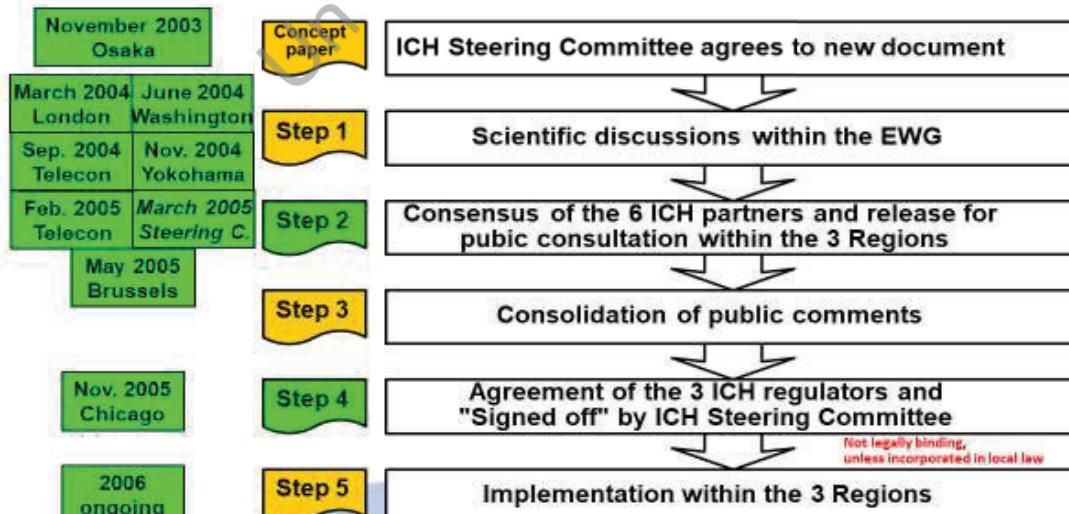
2. The final decision on selection of the Risk assessment team shall be done by Head of Site QA based on the nature of the risk identified.



Training Module – Risk Assessment

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ICH Q9 Milestones



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Quality Risk Management - ICH Q9

Contents



1. Introduction
2. Definitions
3. Scope
4. Principles of Quality Risk Management
5. General Quality Risk Management Process
6. Risk Management Methods and Tools
7. Potential application of QRM

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1. Introduction



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT Q9

Current Step 4 version
dated 9 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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1. Introduction



**Quality Risk Management
Quality Risk Assessment
Quality Systems
Hazard/Harm
Severity/ Probability
Product Life Cycle
GMP Compliance**



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1. Introduction



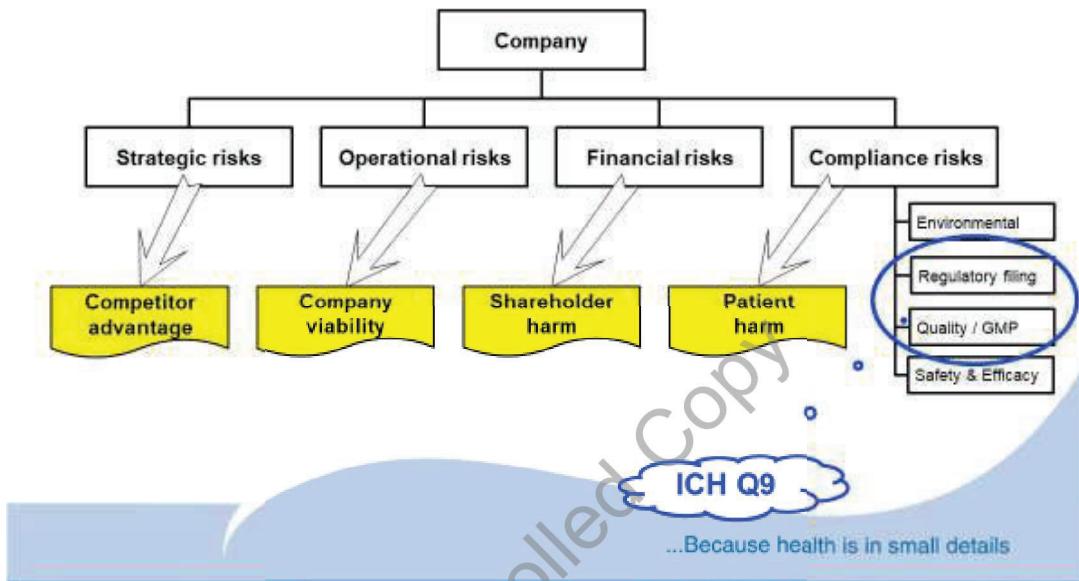
- Risk management principles are effectively utilised in the many areas of the businesses.
- Applicable in Finance, insurance, occupational safety, public health, pharmaceuticals, pharmacovigilance and by agencies regulating these industries.
- Quality Risk Management is valuable component of an effective quality system applicable to Pharma industry.
- Protection of the patient by managing the risk to quality should be considered of prime importance.

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1. Introduction

Managing risks in a company



2. Definitions

Quality

Degree to which a set of inherent Properties of a product, system or process fulfills requirements

Hazard

Potential source of harm

Harm

Damage to health, including the damage that can occur from loss of product quality or availability

Probability

Frequency of “occurrences” driven by the number of trials or Degree of belief

Severity

A measure of the possible consequences of a hazard

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2. Definitions

Risk

combination of the probability of occurrence of harm and the severity of that harm

Risk Assessment

Systematic process of organizing information, identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards



Systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle

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3. Scope

ICH Q9 guideline provides principles & examples of tools

of quality risk management that can be applied to different aspects of pharmaceutical quality.

These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the product lifecycle



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3. Scope

- Drug substances,
- Drug (medicinal) products,
- Biological and biotechnological products

Including the selection and use of

- > Raw materials
- > Solvents
- > Excipients
- > Packaging and labelling materials
- > Other Components

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4. Principles of Quality Risk Management

Two primary principles:

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

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5. General Quality Risk Management Process



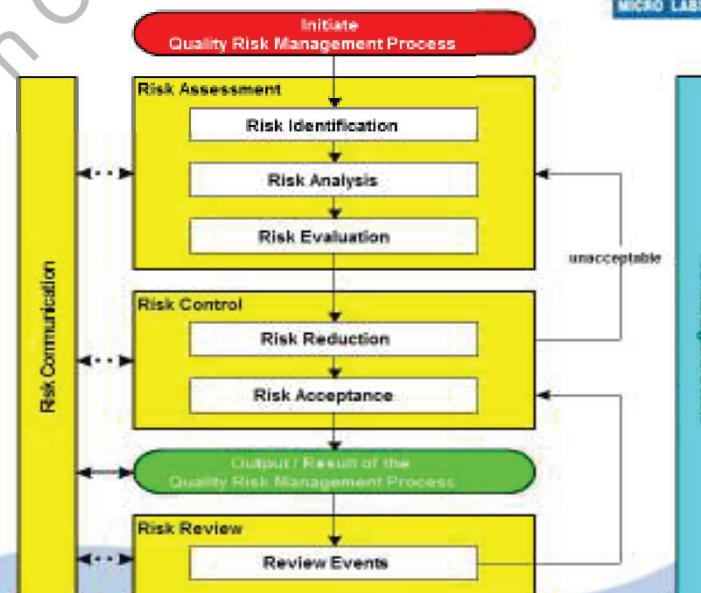
**Systematic processes
designed to
coordinate, facilitate and improve
science-based decision making
with respect to risk to quality**

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5. General Quality Risk Management Process

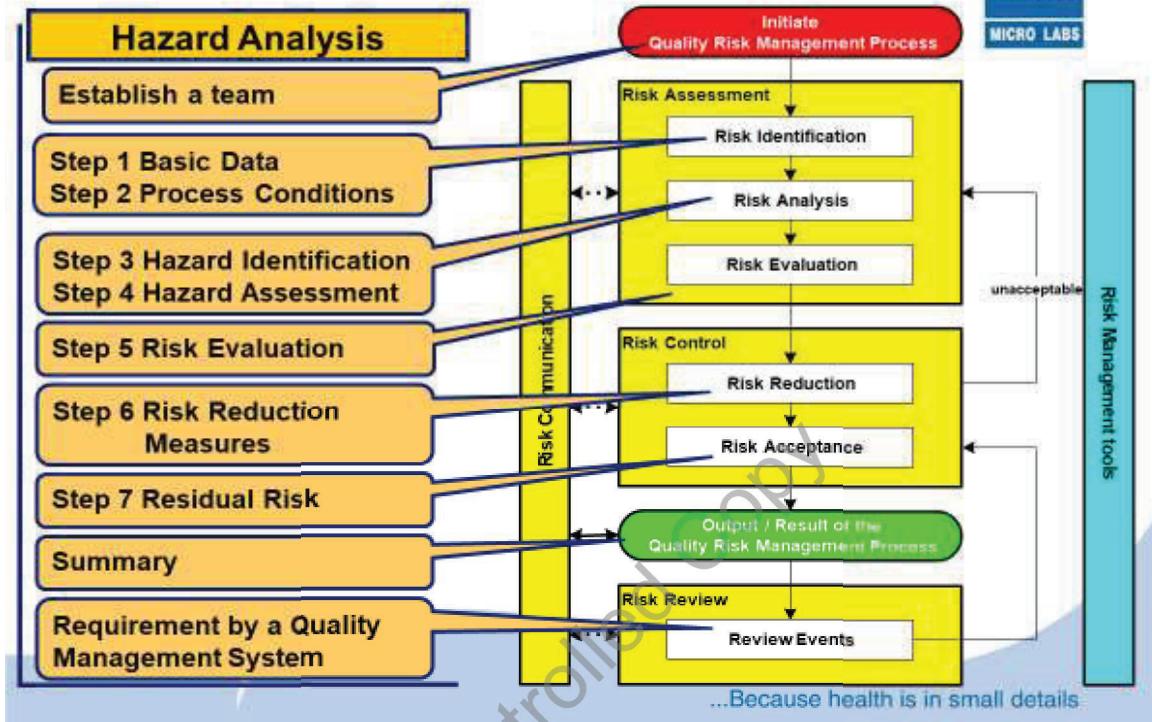


Team approach



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5. General Quality Risk Management Process



5. General Quality Risk Management Process

Decision makers:
Person(s)
with competence and authority
to make a decision

- Ensuring that ongoing Quality Risk Management processes operate
- Coordinating quality risk management process across various functions and departments
- Supporting the team approach

Management responsibility

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5. General Quality Risk Management Process



Team approach

- Usually, but not always, undertaken by interdisciplinary teams from areas appropriate to the risk being considered e.g.
 - > Quality Assurance
 - > Quality Control
 - > Production operations
 - > Packing operations
 - > Warehouse management
 - > Engineering/EHS
 - > RA and R&D
 - > Business, Sales and Marketing
 - > Legal
 - > Medical / Clinical
 - > &... Individuals knowledgeable of the QRM processes

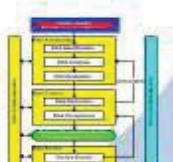
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5. General Quality Risk Management Process



When to initiate and plan a QRM Process

- First define the question which should be answered (e.g. a problem and/or risk question)
 - > including pertinent assumptions identifying the potential for risk
- Then assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk
 - > Identify a leader and necessary resources
 - > Specify a timeline, deliverables and appropriate level of decision making for the QRM process



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5. General Quality Risk Management Process

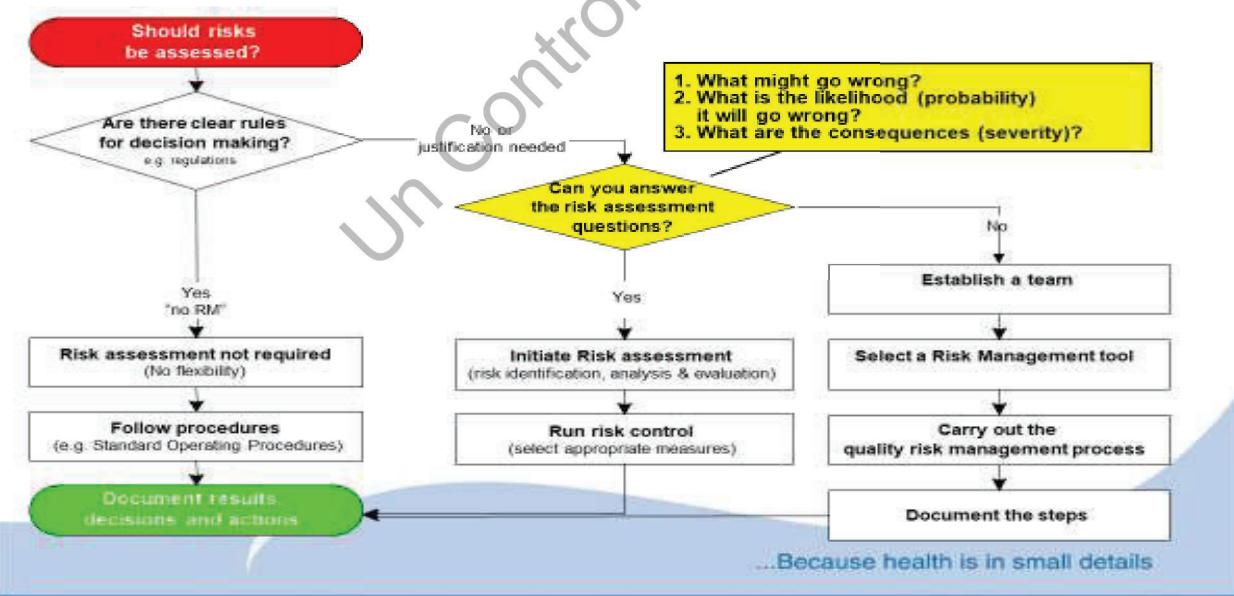


How to determine Scale??

- Estimation of risk applicable to complex process with multiple process with many risk elements
- Expressed using numerical probability

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When to apply Quality Risk Management?



5. General Quality Risk Management Process

Risk Assessment

- ***Risk Identification***

What might go wrong?

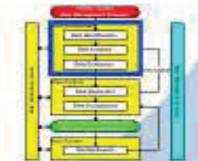
- ***Risk Analysis***

What is the likelihood (probability) it will go wrong?

- ***Risk Evaluation***

What are the consequences (severity)?

3 fundamental questions



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5. General Quality Risk Management Process

Risk Assessment: Risk Identification



"What might go wrong?"

- **A systematic use of information to identify hazards referring to the risk question or problem**
 - > historical data
 - > theoretical analysis
 - > informed opinions
 - > concerns of stakeholders
 - > Vendor assessment



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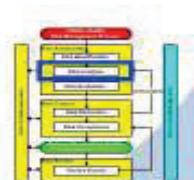
5. General Quality Risk Management Process



Risk Assessment: Risk Analysis

“What is the likelihood it will go wrong?”

- The estimation of the risk associated with the identified hazards.
- A qualitative or quantitative process of linking the likelihood of occurrence and severity of harm
- Consider detectability if applicable
- Trend and use statistics (e.g. extrapolation)
- Comparing between different sets of data
- Data must be reliable and accessible



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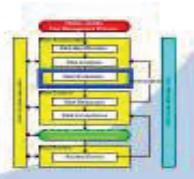
5. General Quality Risk Management Process



Risk Assessment: Risk Evaluation

“What is the risk?”

- Compare the identified and analysed risk against given risk criteria
- Consider the strength of evidence for all three of the fundamental questions
 - > What might go wrong?
 - > What is the likelihood (probability) it will go wrong?
 - > What are the consequences (severity)?



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5. General Quality Risk Management Process

Risk Assessment: Risk Evaluation



Numerical assessment of risk assigned to a process/steps in a process (FMEA)

= Risk Priority Number

Probability x **Detectability** x **Severity**

- Frequency of "occurrences" driven by the number of trials
- Degree of belief

Data refers to

Ability to discover /determine the presence of hazard

Can you find it?

Measure of possible consequences of hazard

Impact

past

today

future

time

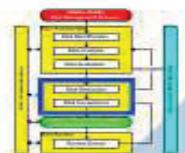
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5. General Quality Risk Management Process



Risk Control: Decision-making activity

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance between benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?



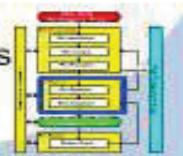
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5. General Quality Risk Management Process

Risk Control: Residual Risk



- **The residual risk consists of e.g.**
 - > Hazards that have been assessed and risks that have been accepted
 - > Hazards which have been identified but the risks have not been correctly assessed
 - > Hazards that have not yet been identified
 - > Hazards which are not yet linked to the patient risk
- **Is the risk reduced to an acceptable level?**
 - > Fulfil all legal and internal obligations
 - > Consider current scientific knowledge & techniques



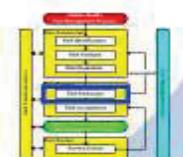
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5. General Quality Risk Management Process



Risk Control: Risk Reduction

- **Mitigation or avoidance of quality risk**
- **Elimination of risks, where appropriate**
- **Focus actions on severity and/or probability of harm; don't forget detectability**
- **It might be appropriate to revisit the risk assessment during the life cycle for new risks or increased significance of existing risks**



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5. General Quality Risk Management Process

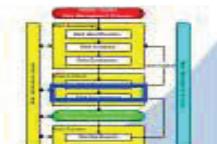


Risk Control: Risk Acceptance

- **Decision to**
 - > **Accept the residual risk**
 - > **Passively accept non specified residual risks**

Who has to accept risk ?

- > **All stakeholder involved in QRA**
- > **Impacted group or department**

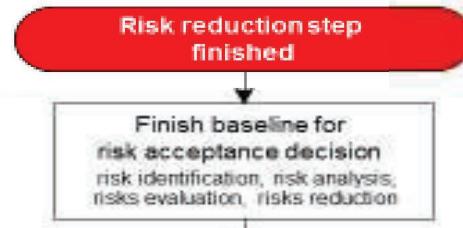


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5. General Quality Risk Management Process

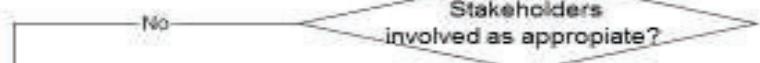


A Risk Acceptance process 1/3



Finish baseline for risk acceptance decision
risk identification, risk analysis, risks evaluation, risks reduction

Stakeholders involved as appropriate?

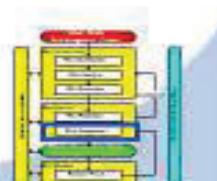


Revisit risk assessment step

All identified risks assessed?

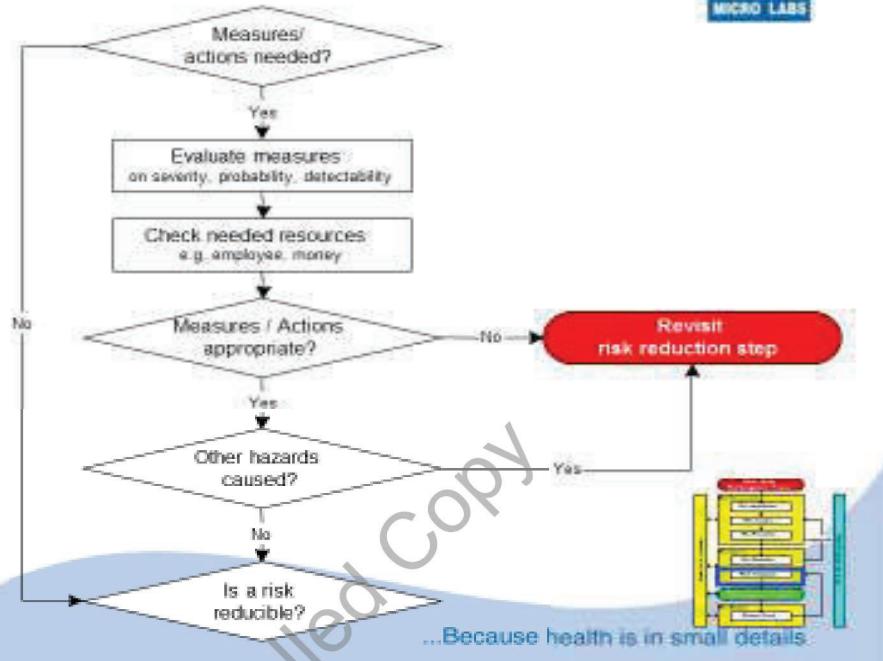
Yes

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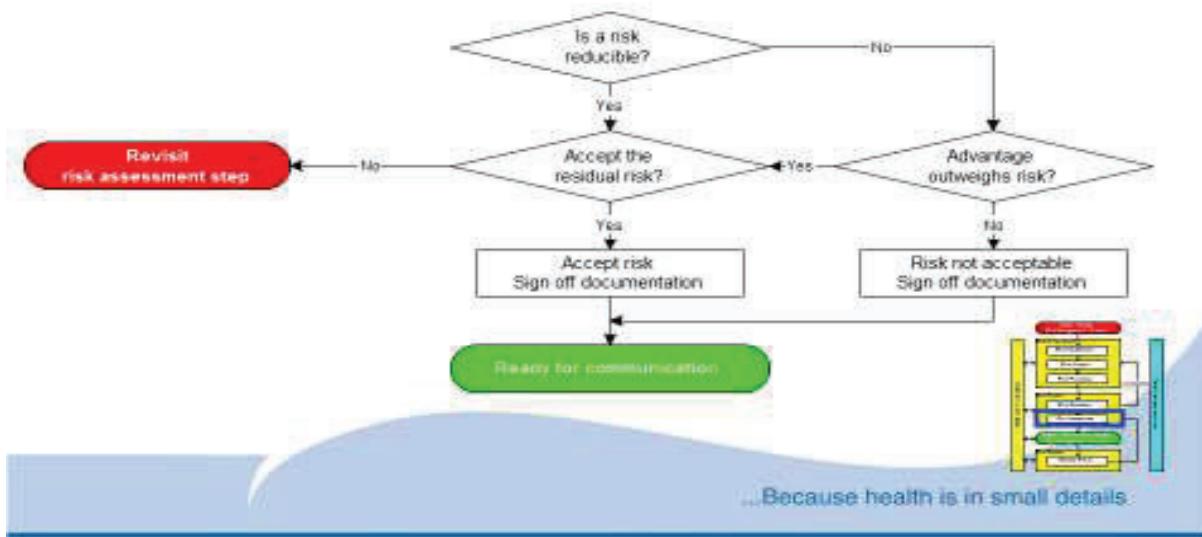
5. General Quality Risk Management Process

A Risk Acceptance process 2/3



5. General Quality Risk Management Process

A Risk Acceptance process 3/3



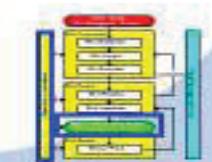


5. General Quality Risk Management Process

Risk Communication

- Exchange or **sharing of information**, as appropriate
- Communicate at **any stage** of the QRM process
- Communication need **not be carried out** for each and every individual risk acceptance
- Increase transparency

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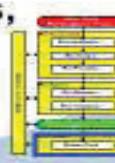


5. General Quality Risk Management Process

Risk review: Review Events

- **Review** the output / results of the QRM process
- Take into account **new knowledge and experience**
- Utilise for planned or unplanned **events**
- Implement a mechanism to **review or monitor events**
- **Reconsideration** of risk acceptance decisions, as appropriate

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6. Risk Management Methods and Tools



- Supports science-based decisions
- Variety of tools listed in the guideline
- No single tool is appropriate for all cases
- Specific risks do not always require the same tool
- Using a tool the level of detail of an investigation will vary according to the risk from case to case
- Different companies, consultancies and competent authorities may promote use of different tools based on their culture and experiences

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6. Risk Management Methods and Tools



Overview: Some Basic tools and their Potential Applications

Risk Management	Description / Attributes	Tool Potential Applications
Basic Tools		
Diagram Analysis Flowcharts Check Sheets Process Mapping Cause/Effect Diagrams	Simple techniques that are commonly used to gather/organize data, structure risk management processes, and facilitate decision making.	Compilation of observations, trends, or other experimental information to support a variety of less complex deviations, complaints, defects, or other circumstances.
Risk Ranking and Filtering	• Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores.	• Prioritize operating areas / sites for audit/assessment. • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.

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6. Risk Management Methods and Tools

Overview: Some Advanced tools and their Potential Applications



Risk Management	Description / Attributes	Tool Potential Applications
Fault Tree Analysis (FTA)	<ul style="list-style-type: none"> Method used to identify all root causes of an assumed failure or problem. Used to evaluate system/sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains. Relies heavily on full process understanding to identify causal factors. 	<ul style="list-style-type: none"> Investigate product complaints, deviations or any non-compliances.
Hazard Operability Analysis (HAZOP)	<ul style="list-style-type: none"> Tool assumes that risk events are caused by deviations from the design and operating intentions Uses a systematic technique to help identify potential deviations from normal use or design intentions. 	<ul style="list-style-type: none"> Assessment of manufacturing processes, facilities, and equipment Commonly used to evaluate process safety hazards.
Hazards Analysis and Critical Control Points (HACCP)	<ul style="list-style-type: none"> Identify process controls that prevent hazard conditions from occurring Bottom-up approach that considers how to prevent hazards from occurring Emphasizes strength of preventive controls rather than ability to detect Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment Tool ensures that critical process parameters will be met 	<ul style="list-style-type: none"> Preventive tool Assessment of process validation Assessment of the efficacy of CPPs and the ability to consistently execute them for any process Can be applied during PQR risk assessment <p>...Because health is in small details</p>

6. Risk Management Methods and Tools

Overview: Some Advanced tools and their Potential Applications



Risk Management	Description / Attributes	Tool Potential Applications
Failure Mode Effects Analysis (FMEA)	<ul style="list-style-type: none"> Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance. Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures. Highly dependent upon strong understanding of product, process and/or facility under evaluation. Output is a relative "risk score" for each failure mode. 	Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.
Failure Mode, Effects and Criticality Analysis (FMECA)	<ul style="list-style-type: none"> FMEA & links severity, probability & detectability to criticality 	Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.
Preliminary Hazard Analysis (PHA)	<ul style="list-style-type: none"> Analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that can cause harm. In estimating their probability of occurrence for a given activity, facility, product or system 	<ul style="list-style-type: none"> Analyzing existing systems Evaluate the types of hazards for the general product type, then the product class and finally the specific product Early in the development: information on design, operating procedures For product, process and facility design <p>...Because health is in small details</p>

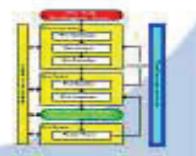
6. Risk Management Methods and Tools

Overview: Some tools and their key words

- **Failure Mode Effects Analysis (FMEA)**
 - > Break down large complex processes into manageable steps
- **Failure Mode, Effects and Criticality Analysis (FMECA)**
 - > FMEA & links severity, probability & detectability to criticality
- **Fault Tree Analysis (FTA)**
 - > Tree of failure modes combinations with logical operators
- **Hazard Analysis and Critical Control Points (HACCP)**
 - > Systematic, proactive, and preventive method on criticality
- **Hazard Operability Analysis (HAZOP)**
 - > Brainstorming technique
- **Preliminary Hazard Analysis (PHA)**
 - > Possibilities that the risk event happens
- **Risk ranking and filtering**
 - > Compare and prioritize risks with factors for each risk



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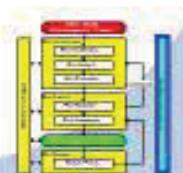
6. Risk Management Methods and Tools



• Supporting statistical tools

- > Acceptance Control Charts
- > Control Charts (for example)
 - > Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
 - > Cumulative Sum Charts; "CuSum" (see ISO 7871)
 - > Shewhart Control Charts (see ISO 8258)
- > Design of Experiments (DOE)
 - > Pareto Charts
- > Process Capability Analysis
- > Histograms

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7. Potential Application for QRM



This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators.

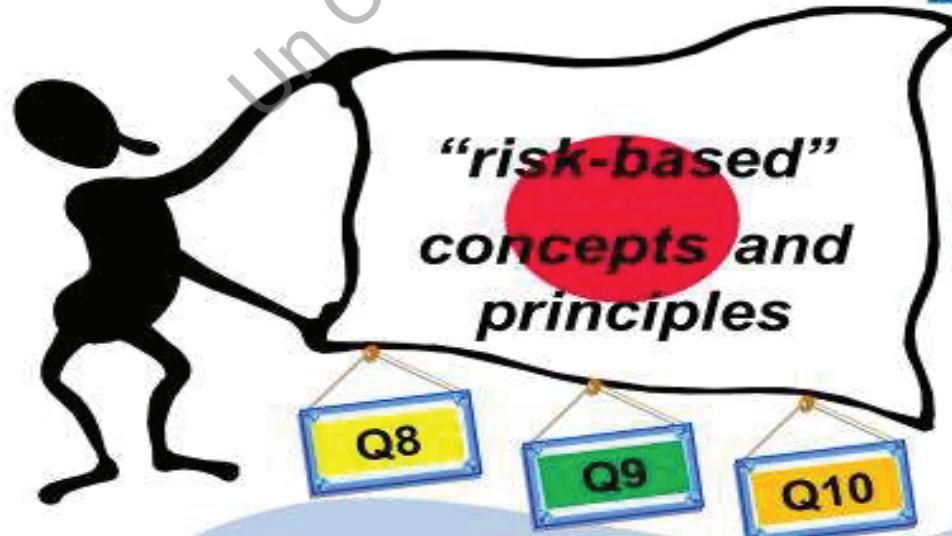
However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management.

This Annex is not intended to create any new expectations beyond the current regulatory requirements.

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7. Potential Application for QRM

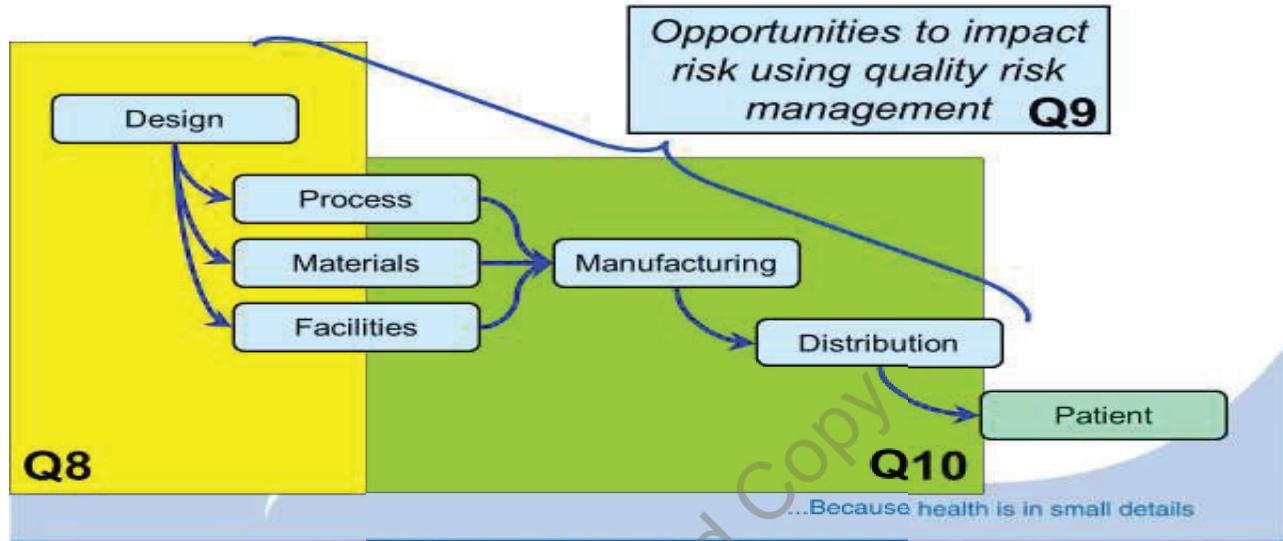


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7. Potential Application for QRM



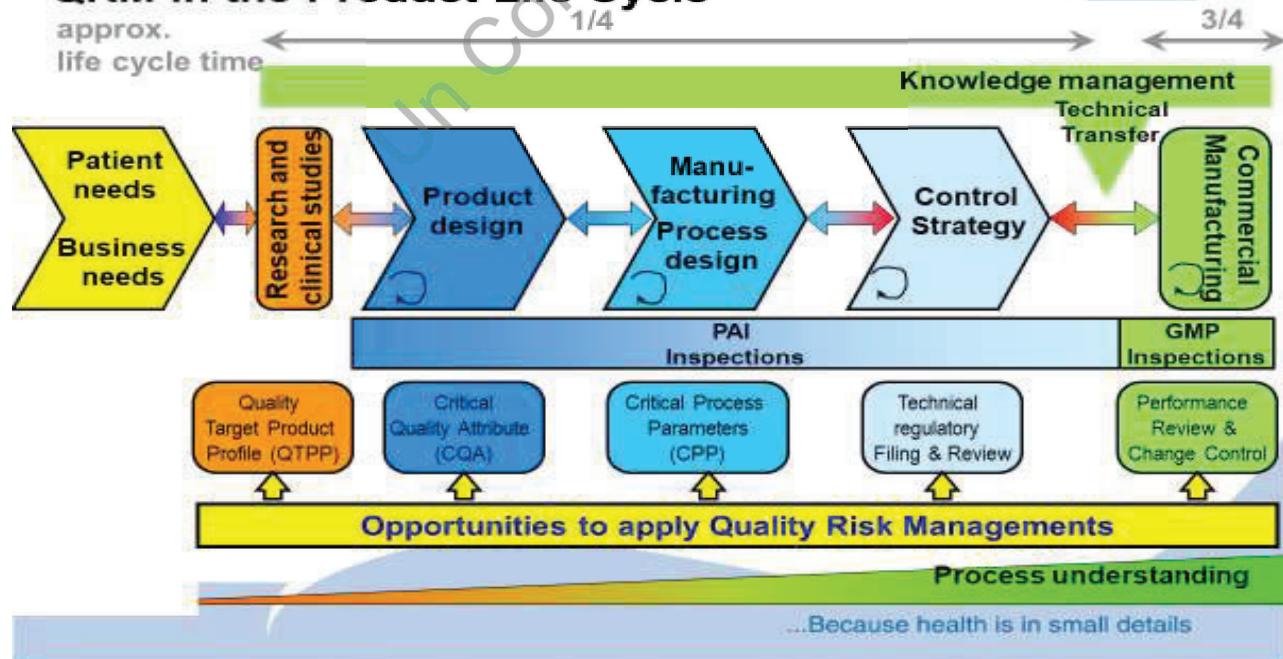
ICH Q9 Link back to patient risk



7. Potential Application for QRM



QRM in the Product Life Cycle



7. Potential Application for QRM



Quality risk management as part of

- **Integrated quality management**

- > Documentation
- > Training and education
- > Quality defects
- > Auditing / Inspection
- > Periodic review
- > Change management / change control
- > Continual improvement



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7. Potential Application for QRM



Quality risk management as part of

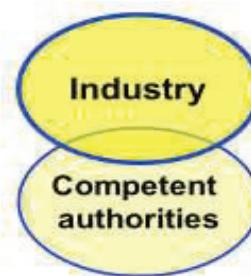
- **Regulatory operations**

- > Inspection and assessment activities



- **Industry operations**

- > Development
- > Facilities, equipment and utilities
- > Materials management
- > Production
- > Laboratory control and stability testing
- > Packaging and labelling



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MHRA Observations



- Risk assessments did not fully describe the nature of the activities being assessed and did not capture all the risks associated with the event.
- Risk Assessment related to manual capping of plugged containers. This risk assessment did not consider the potential impact on the product of performing the activity in the Grade C zone rather than the Grade A zone which was normally used for this activity. The risk of variation in capping pressure due to use of manual capping rather than automated capping was also not considered.
- Deviation relating to corrupted BFS Integrity Testing electronic records. No appropriate risk assessment for the loss of original raw data was carried out.
- The cross-contamination risk assessment was too high level and did not identify all significant risks such as difficult to clean areas on equipment or change parts.

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Key Messages

- **QRM is an iterative process and not a one off activity**
- **QRM used by company can provide regulators with greater assurance of a company's product and process understanding and the ability to assure quality of manufactured products**
 - > Facilitate the awareness of risks
 - > Risk does not go away
 - > Risk can be predicted, prevented and controlled
- **QRM processes should**
 - > Focus on what is important to establish the manufacturing process and controls and maintain them over the life cycle
 - > Be integrated in Pharmaceutical Quality System elements

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Key Messages

- **Regulators should use QRM methods appropriately to reach rational and justified regulatory decisions e.g.**
 - > Risk based regulatory decisions
(suspected quality defects etc.)
 - > Assessment of regulatory filing
 - > Planning and conducting of inspections
 - > Prioritisation of inspection findings

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Quality Risk Management **is NOT**

- **Hiding risks**
- **Writing half the truth (e.g. in an investigation report)**
- **A means of removing industry's obligation to comply with regulatory requirements**

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Reference

- **ICH Harmonized Tripartite Guideline**

Quality Risk Management – Q9

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MICRO LABS LIMITED, _____*

COMMUNICATION OF RISK ASSESSMENT OUTCOME TO CONTRACT GIVER / MA HOLDER / REGULATORY DEPARTMENT

From: Site QA		To: Contract Giver / MA Holder / Regulatory Department
Risk assessment No:		
1.0	Risk Assessment carried out for:	
2.0	Risk Identified:	
3.0	Details of Product Impacted:	
4.0	Name of the Customer / Contract Giver (if CGs product is impacted):	
5.0	Impact on product:	
6.0	Immediate actions Proposed:	

QAP/MLCM/0043/FMT/0016-000

Approved By: Satish Babu. V S

E-Sign/Date: 18/03/2024 10:02

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COMMUNICATION OF RISK ASSESSMENT OUTCOME TO CONTRACT GIVER / MA HOLDER / REGULATORY DEPARTMENT

7.0	Actions Proposed:
	Date of notification: _____ Notified by (Site QA) _____ Signature / Date _____
8.0	Review by Contract Giver / MA Holder / Regulatory Department:
9.0	Final closure by Site QA: (Implementation of proposed actions / recommendations given by Contract Giver / MA Holder / Regulatory Department) Reference QMS Document no. (if any) Sign/date : _____

QAP/MLCM/0043/FMT/0016-000

Approved By: Satish Babu. V S

E-Sign/Date: 18/03/2024 10:02

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