Quality Risk Management (QRM) for Good Distribution Practice (GDP)

藥品優良運銷作業規範的品質風險管理

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Purpose of this talk

- To guide through the content of the Quality Risk Management (ICH Q9 document) from the Good Distribution Practice (GDP) perspective.

- Provide some considerations, possible interpretations and where appropriate examples

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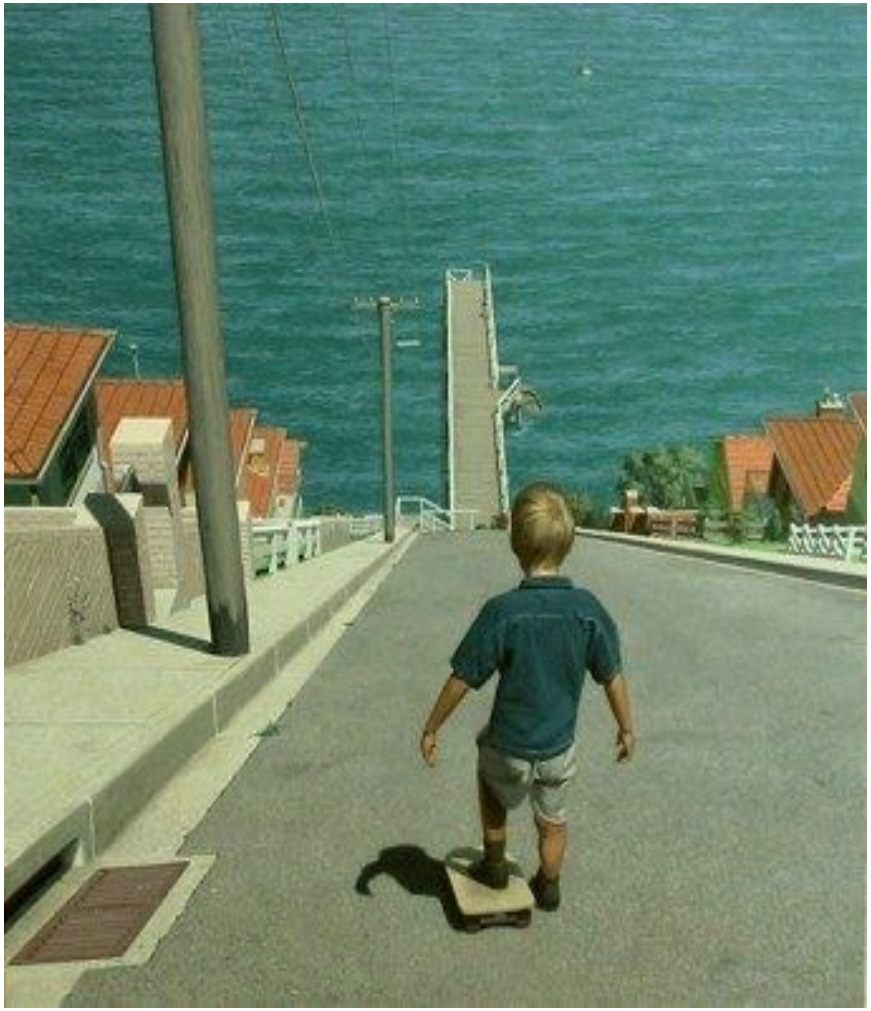
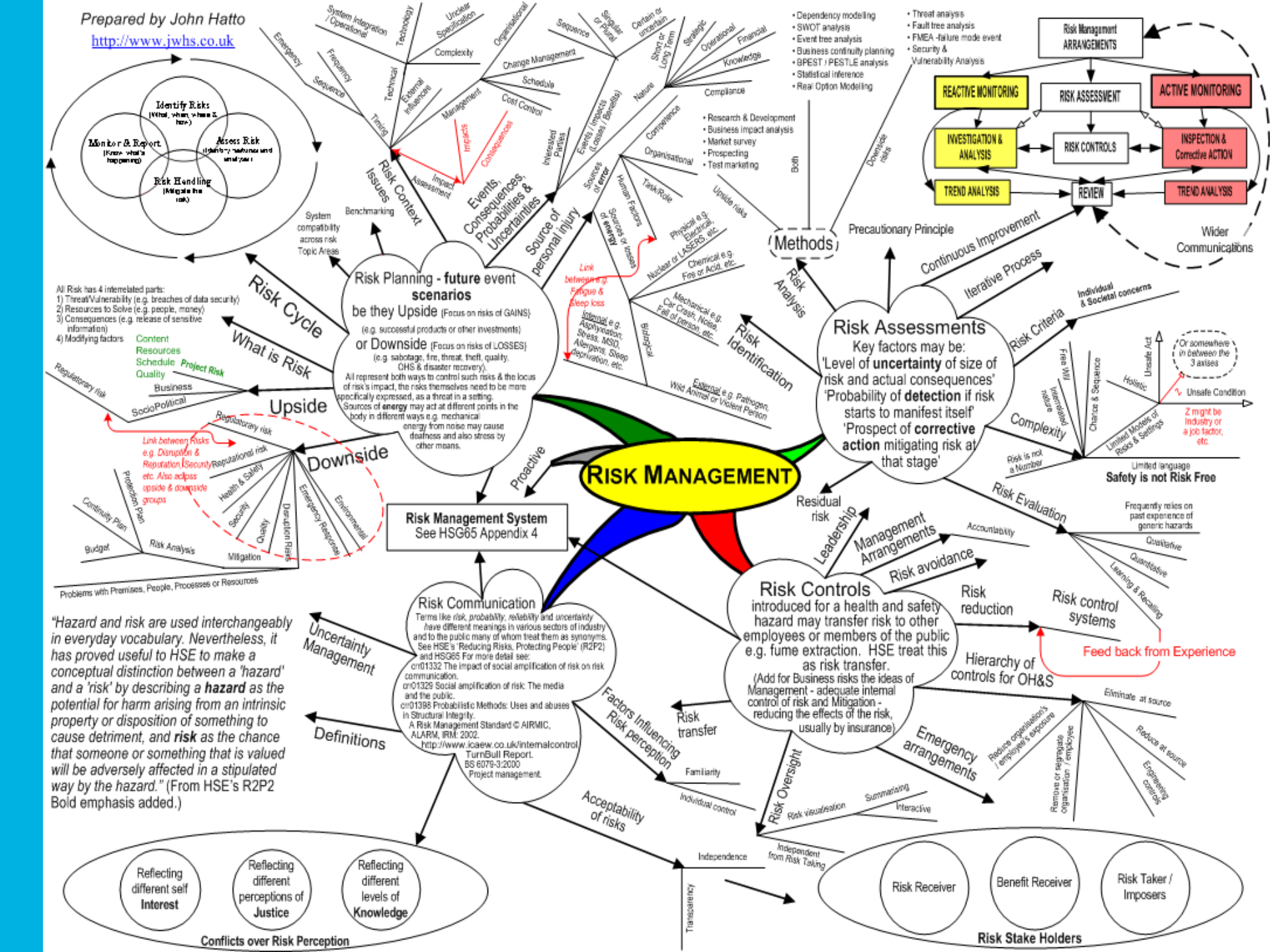
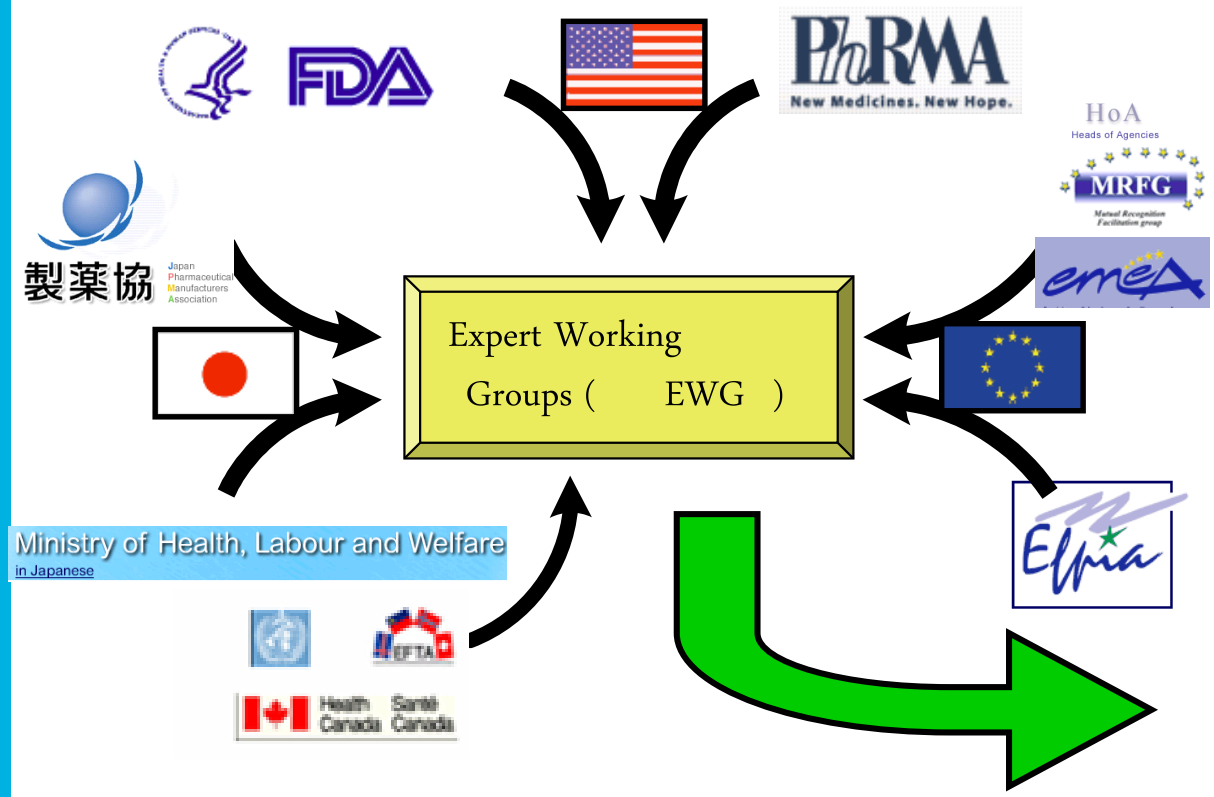
1. Introduction – Risk management 風險管理

What is Risk Management?




Prepared by John Hatto
http://www.jwhs.co.uk
RISK MANAGEMENT
Risk Management System
See HSG65 Appendix 4
Risk Planning - future event scenarios
be they Upside (Focus on risks of GAINS)
(e.g. successful products or other investments)
or Downside (Focus on risks of LOSSES)
(e.g. sabotage, fire, threat, theft, quality, OHS & disaster recovery).
All represent both ways to control such risks & the locus of risk's impact, the risks themselves need to be more specifically expressed, as a threat in a setting.
Sources of energy may act at different points in the body in different ways e.g. mechanical energy from noise may cause deafness and also stress by other means.
Risk Assessments
Key factors may be:
'Level of uncertainty of size of risk and actual consequences'
'Probability of detection if risk starts to manifest itself'
'Prospect of corrective action mitigating risk at that stage'
Risk Controls
introduced for a health and safety hazard may transfer risk to other employees or members of the public e.g. fume extraction. HSE treat this as risk transfer.
(Add for Business risks the ideas of Management - adequate internal control of risk and Mitigation - reducing the effects of the risk, usually by insurance)
Risk Communication
Terms like risk, probability, reliability and uncertainty have different meanings in various sectors of industry and to the public many of whom treat them as synonyms. See HSE's 'Reducing Risks, Protecting People' (R2P2) and HSG65 For more detail see:
cri01332 The impact of social amplification of risk on risk communication.
cri01329 Social amplification of risk: The media and the public.
cri01398 Probabilistic Methods: Uses and abuses in Structural Integrity.
A Risk Management Standard © AIRMIC, ALARM, IRM: 2002.
http://www.icaew.co.uk/internalcontrol
TurnBull Report.
BS 6079-3:2000 Project management.
Methods
Risk Cycle
What is Risk
Risk Context
Issues
Events, Consequences, Probabilities & Uncertainties
Source of personal injury
Risk Analysis
Risk Identification
Risk Evaluation
Proactive
Precautionary Principle
Continuous Improvement
Iterative Process
Wider Communications
Risk Management ARRANGEMENTS
REACTIVE MONITORING
RISK ASSESSMENT
ACTIVE MONITORING
INVESTIGATION & ANALYSIS
RISK CONTROLS
INSPECTION & Corrective ACTION
TREND ANALYSIS
REVIEW
TREND ANALYSIS
Identify Risks
Assess Risk
Risk Handling
Monitor & Report
Upside
Downside
Business
Socio/Political
Regulatory risk
Reputational risk
Health & Safety
Security
Quality
Disruption Risks
Emergency Response
Environmental
Budget
Risk Analysis
Mitigation
Continuity Plan
Protection Plan
Problems with Premises, People, Processes or Resources
Content
Resources
Schedule
Quality
Project Risk
All Risk has 4 interrelated parts:
1) Threat/Vulnerability (e.g. breaches of data security)
2) Resources to Solve (e.g. people, money)
3) Consequences (e.g. release of sensitive information)
4) Modifying factors
Residual risk
Leadership
Management Arrangements
Accountability
Risk avoidance
Risk reduction
Risk control systems
Feed back from Experience
Hierarchy of controls for OH&S
Eliminate at source
Reduce at source
Engineering controls
Remove or segregate organisation / employee
Reduce organisation's / employee's exposure
Emergency arrangements
Risk transfer
Risk Oversight
Risk visualisation
Summarising
Interactive
Factors Influencing Risk perception
Familiarity
Individual control
Acceptability of risks
Independence
Independent from Risk Taking
Transparency
Uncertainty Management
Definitions
Risk Criteria
Individual & Societal concerns
Complexity
Chance & Sequence
Holistic
Unsafe Act
Unsafe Condition
Or somewhere in between the 3 axises
Z might be Industry or a job factor, etc.
Limited Modes of Risks & Settings
Risk is not a Number
Limited language
Safety is not Risk Free
Frequently relies on past experience of generic hazards
Qualitative
Quantitative
Learning & Recalling
Risk Receiver
Benefit Receiver
Risk Taker / Imposers
Risk Stake Holders
Reflecting different self Interest
Reflecting different perceptions of Justice
Reflecting different levels of Knowledge
Conflicts over Risk Perception
"Hazard and risk are used interchangeably in everyday vocabulary. Nevertheless, it has proved useful to HSE to make a conceptual distinction between a 'hazard' and a 'risk' by describing a hazard as the potential for harm arising from an intrinsic property or disposition of something to cause detriment, and risk as the chance that someone or something that is valued will be adversely affected in a stipulated way by the hazard." (From HSE's R2P2 Bold emphasis added.)

1. Introduction – ICH



- *Guidelines on*
- Quality

  Chemical and pharmaceutical QA
- *Safety*

  In vitro and in-vivo pre-clinical studies
- *Efficacy*

  Clinical studies in human subject
- *Multidisciplinary*

  General topics

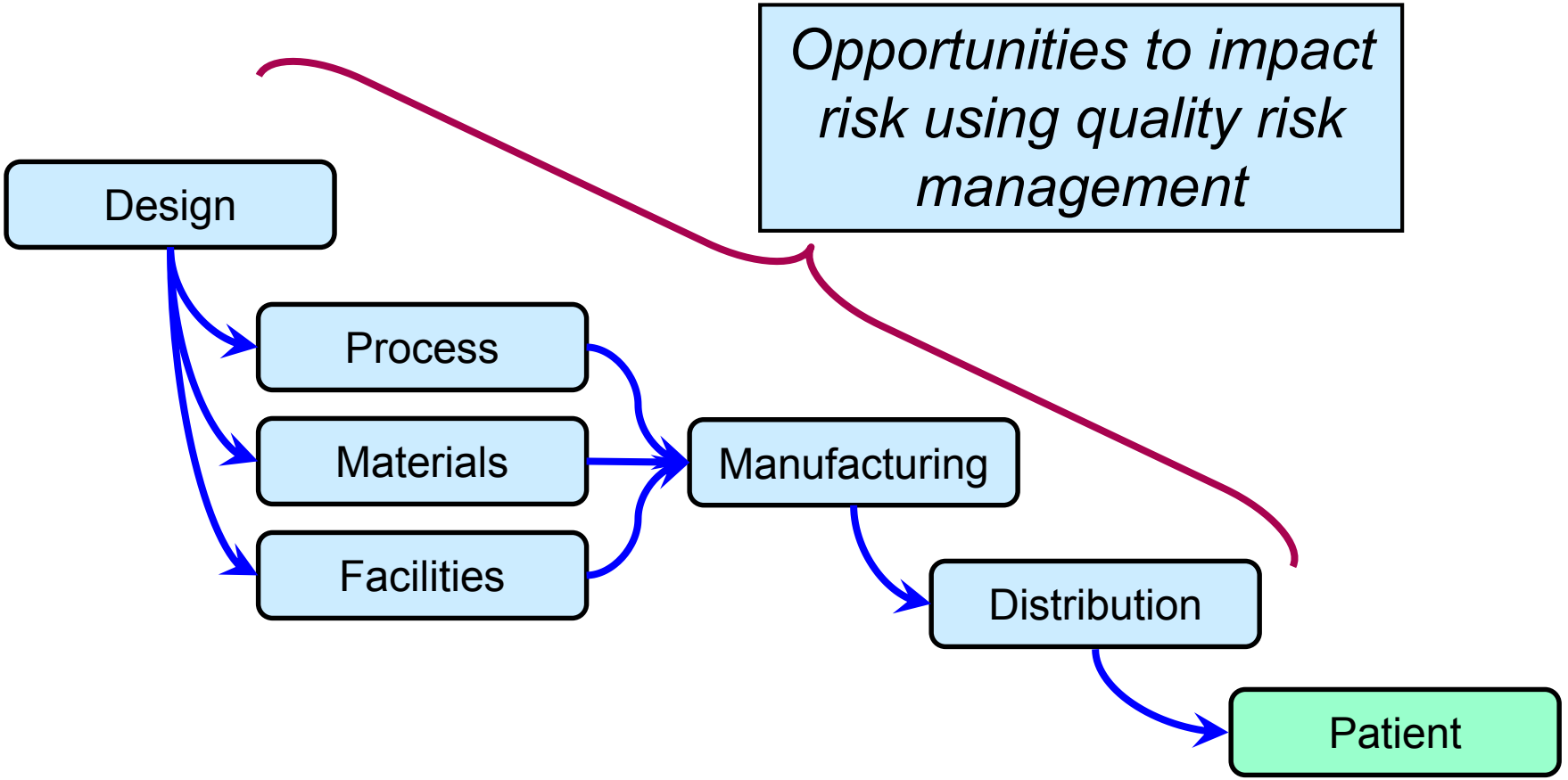
1. Introduction – ICH quality vision

"Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science." (ICH meeting Brussels , 2003)

1. Introduction – ICH guideline

- Q1 Stability
- Q2 Analytical Validation
- Q3 Impurities
- Q4 Pharmacopoeias
- Q5 Quality of Biotechnological Products
- Q6 Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- **Q9 Quality Risk Management**
- Q10 Pharmaceutical Quality Systems

1. Introduction – Link to patient risk



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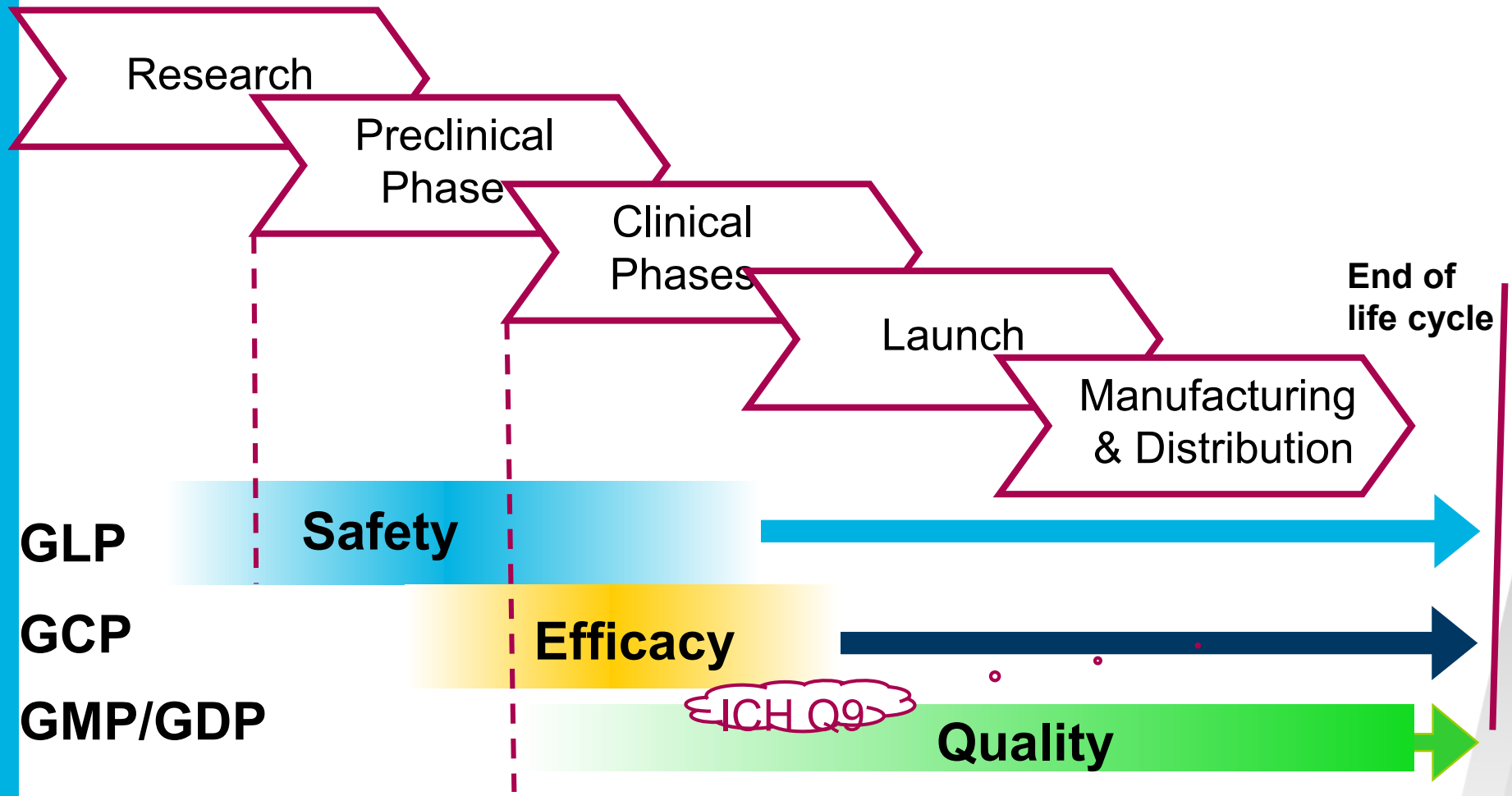


1. Introduction – Link to patient risk

- ICH Regulators:
  - **FDA: New paradigm with the 21st Century GMP initiative**
  - **EMEA: Revised EU directives**
  - **MHLW: Revised Japanese law (rPAL)**
- EU & Japan became involved at ICH GMP Workshop in July 2003: 5 year vision agreed:

  "***Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science***"
- Consequent ICH Expert Working Groups (EWG):
- **ICH Q8, on Pharmaceutical Development, doc. approved 2005**
- **ICH Q9, on Quality Risk Management, doc. approved 2005**
- **ICH Q10, on Quality Systems, topic accepted 2005**

1. Introduction – The new paradigm

1. Introduction – The new paradigm

Pharmaceutical Development (Q8)

Past:	Data transfer / Variable output
Present:	Knowledge transfer / Science based / consistent output

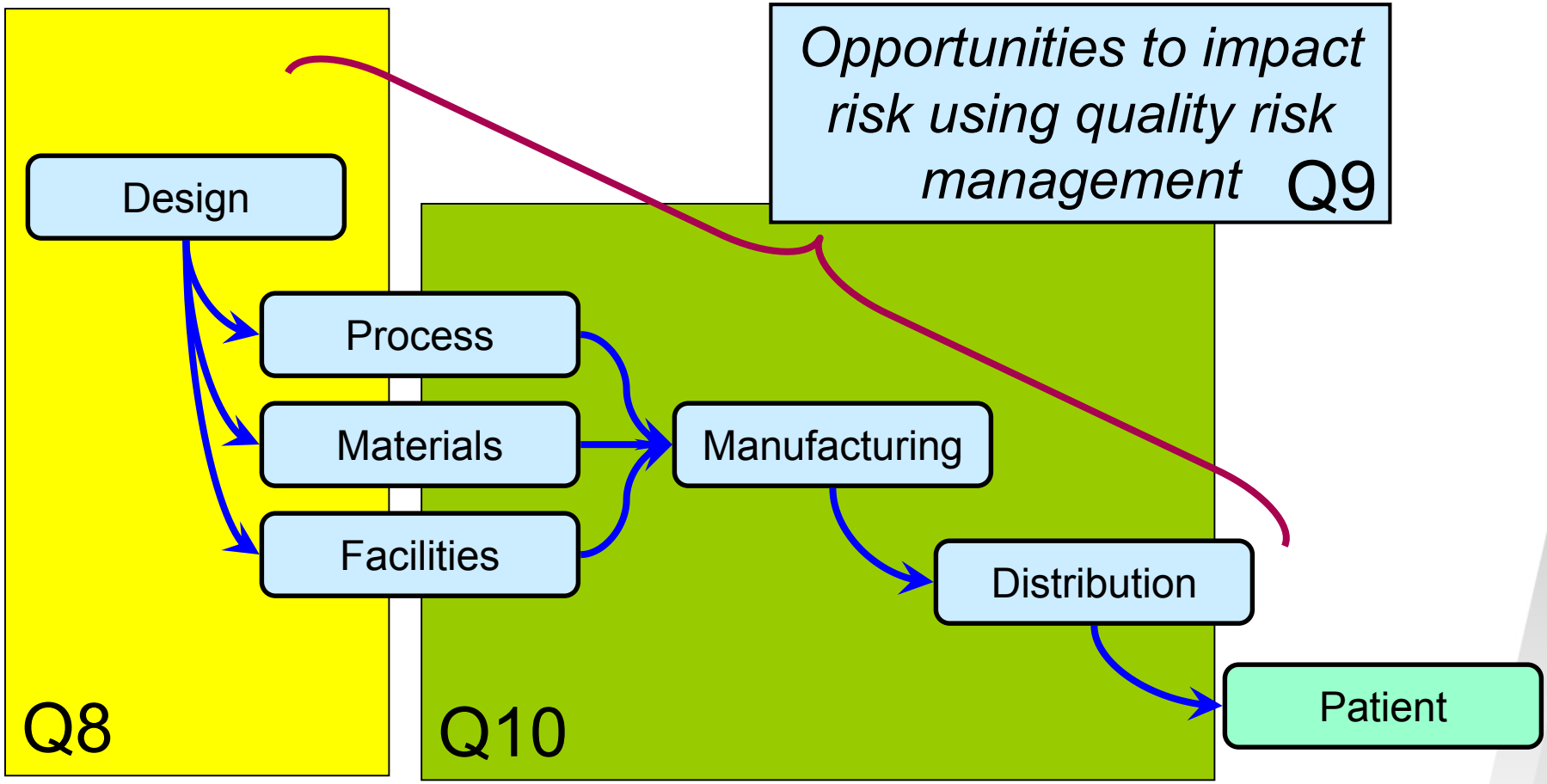
Quality Risk Management (Q9)

Past:	Used, however poorly defined
Present:	Opportunity to use structured process thinking

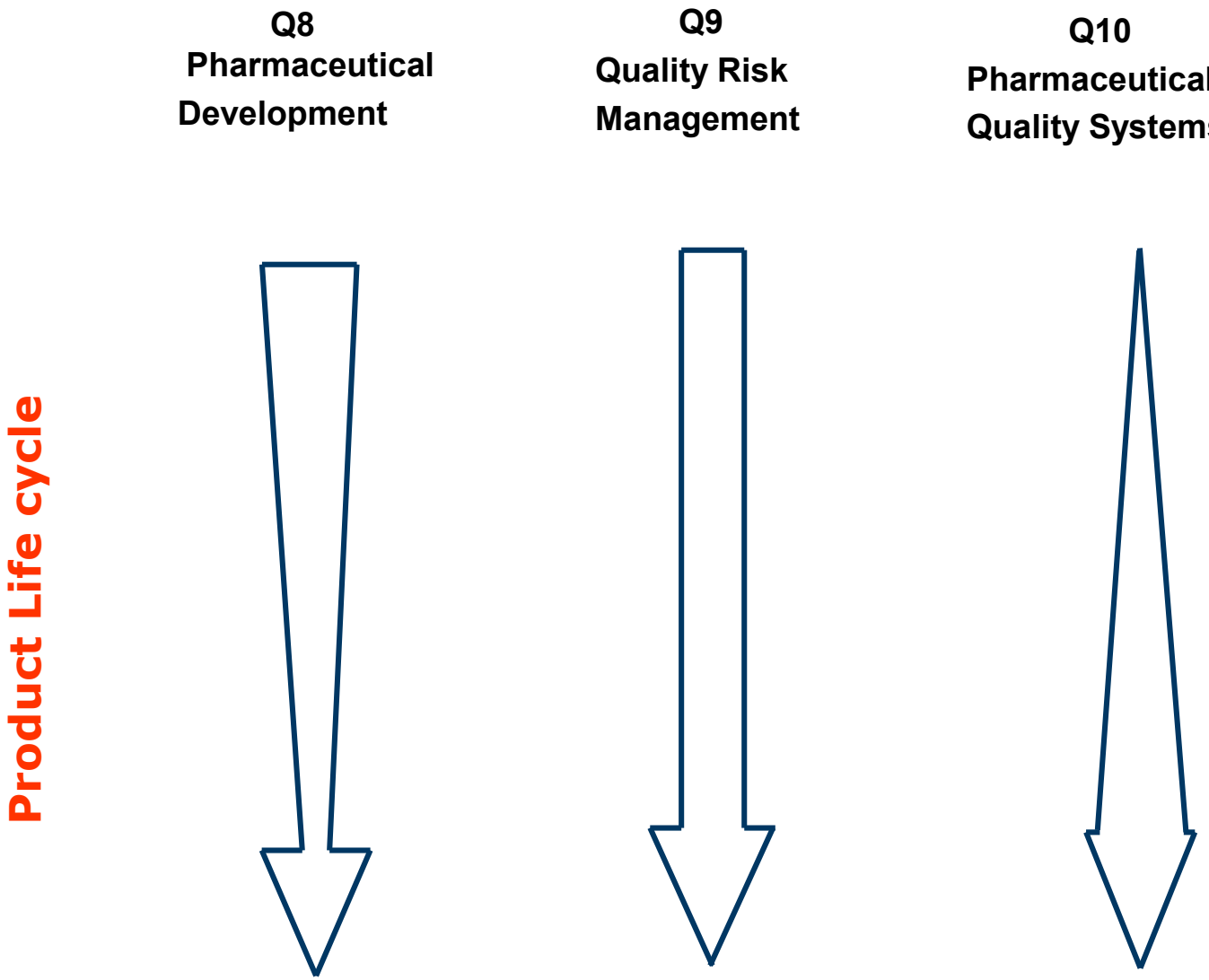
Pharmaceutical Quality Systems (Q10)

Past:	GMP checklist
Future:	Quality Systems across product life cycle

1. Introduction – ICH Q8, Q9, and Q10



1. Introduction – ICH Q8, Q9, and Q10



2. Why we need risk assessment (風險評估)?

23.11.2013 EN Official Journal of the European Union C 343/1

II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

EUROPEAN COMMISSION

Guidelines

of 5 November 2013

on Good Distribution Practice of medicinal products for human use

(Text with EEA relevance)

2. Why we need risk assessment?

CHAPTER 1 — QUALITY MANAGEMENT

1.1. **Principle**

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities ([1]). All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organisation's management and requires their leadership and active participation and should be supported by staff commitment.

2. Why we need risk assessment?

1.5. Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively.

Quality risk management 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 process should be commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found in guideline Q9 of the International Conference on Harmonisation ('ICH').

2. Why we need risk assessment?

9.1. **Principle**

It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft and to ensure that temperature conditions are maintained within acceptable limits during transport.

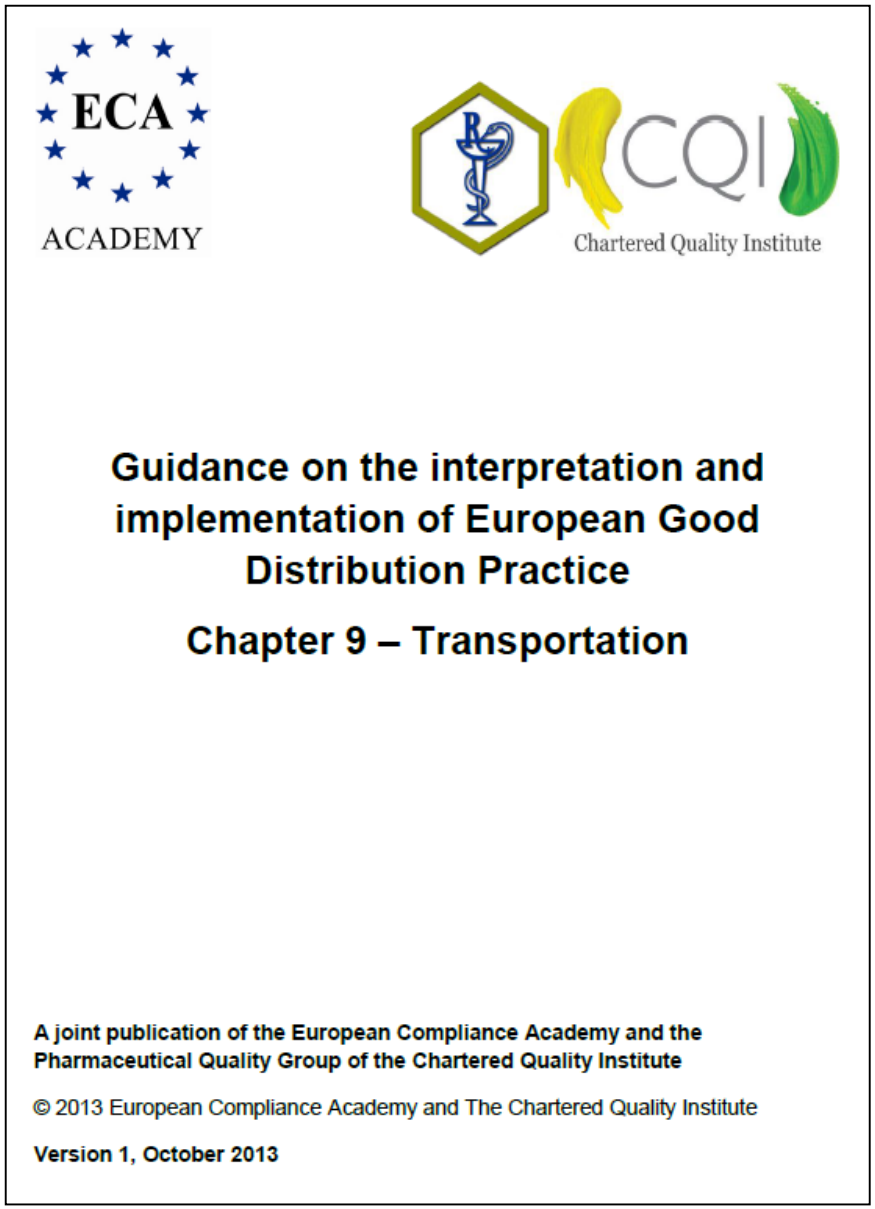
Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilised when planning transportation.

9.2.5

Risk assessment of delivery routes should be used to determine where temperature controls are required. Equipment used for temperature monitoring during transport within vehicles and/or containers, should be maintained and calibrated at regular intervals at least once a year.

See sections 9.3.2 and 9.4.4 for more detail.

2. Why we need risk assessment?



2. Why we need risk assessment?

Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.

The distribution network for medicinal products is often complex, involving many different parties. In addition to the challenges associated with this complexity, there is also a growing threat from criminal activities seeking to introduce falsified medicines into the legal supply chain. The European regulators recognised several years ago that there was a need to update the content of the 1994 GDP guideline to take into account advancements in practices and changes in legislation since it was issued. A consultation draft was issued in mid 2011 and, following the receipt of many comments from interested parties, a final revised version was issued in March 2013 with an effective date of 8 September 2013.

The new guideline has a much stronger focus on the quality system with clear responsibilities and processes and the application of risk management principles. More detailed guidance is given on most elements. New chapters relating to transportation and specific provisions for brokers have been added.

3. ICH Q9 – Quality Risk Management (品質風險管理)

3. ICH Q9 - Scope

This 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 lifecycle
of drug substances, drug (medicinal) products,
biological and biotechnological products

3. ICH Q9 – Scope 範圍

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

Including the selection and use of

- **Raw materials**
- **Solvents**
- **Excipients**
- **Packaging and labelling materials**
- **Components**

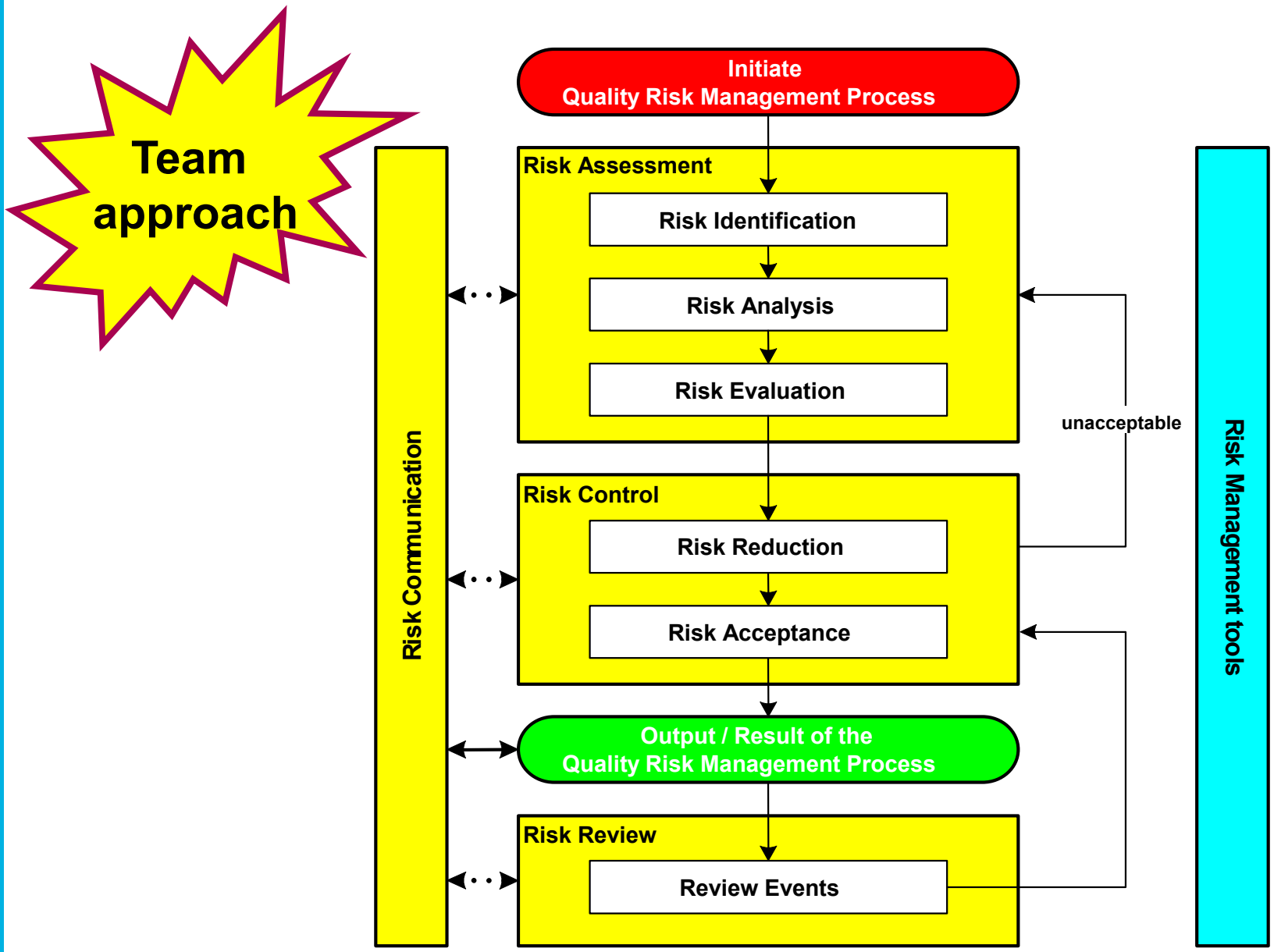
3. ICH Q9 – Principles 原則

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

3. ICH Q9 – General process 基本流程



3. ICH Q9 – Responsibilities 責任

Decision makers:
People
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

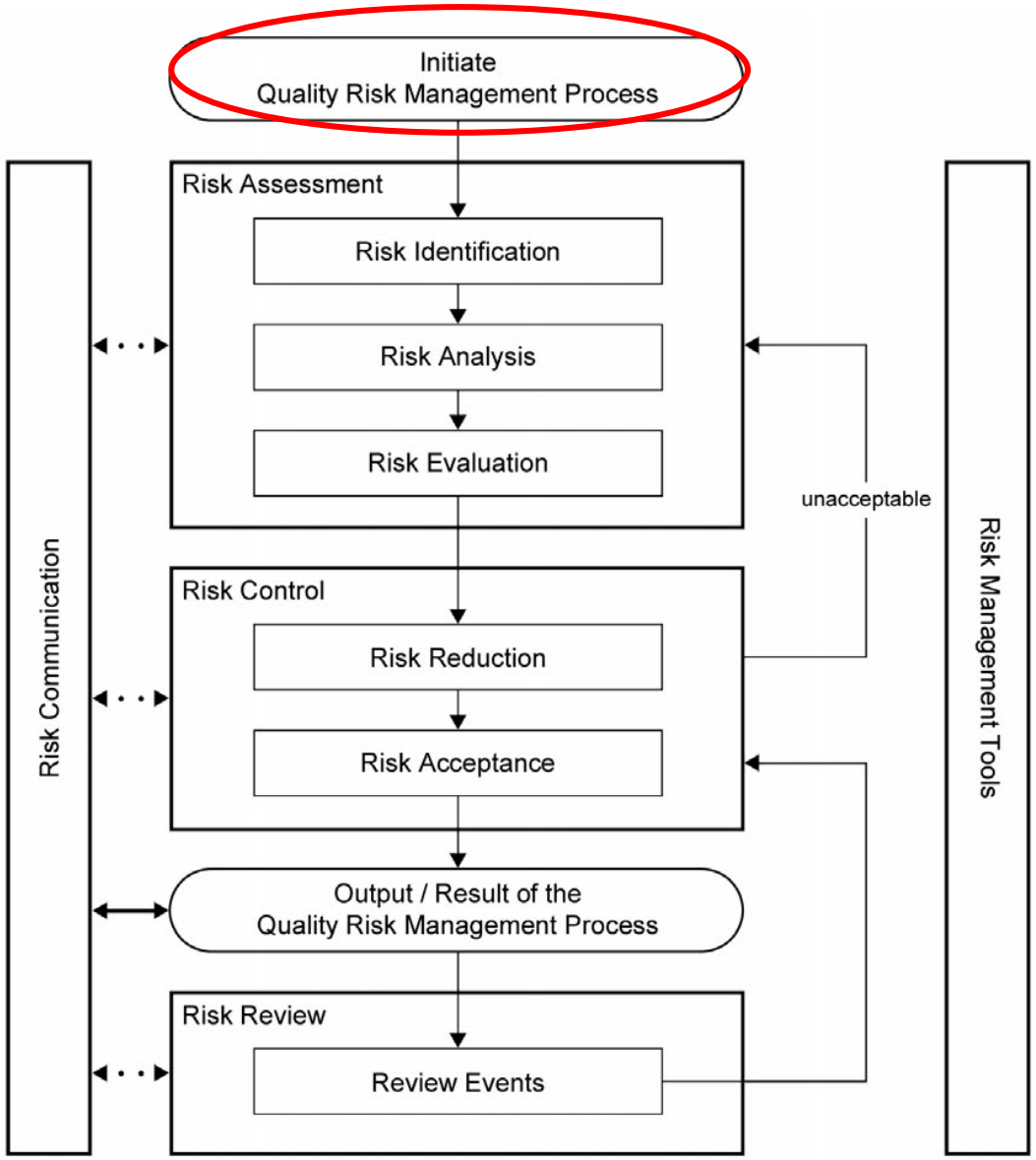
Management responsibility

3. ICH Q9 – Responsibilities

Team approach

- Usually, but not always, undertaken by interdisciplinary teams from areas appropriate to the risk being considered e.g.
  - **Quality unit**
  - **Development**
  - **Engineering / Statistics**
  - **Regulatory affairs**
  - **Production operations**
  - **Business, Sales and Marketing**
  - **Legal**
  - **Medical / Clinical**
  - **&… Individuals knowledgeable of the QRM processes**

3. ICH Q9 – Initiation 起始

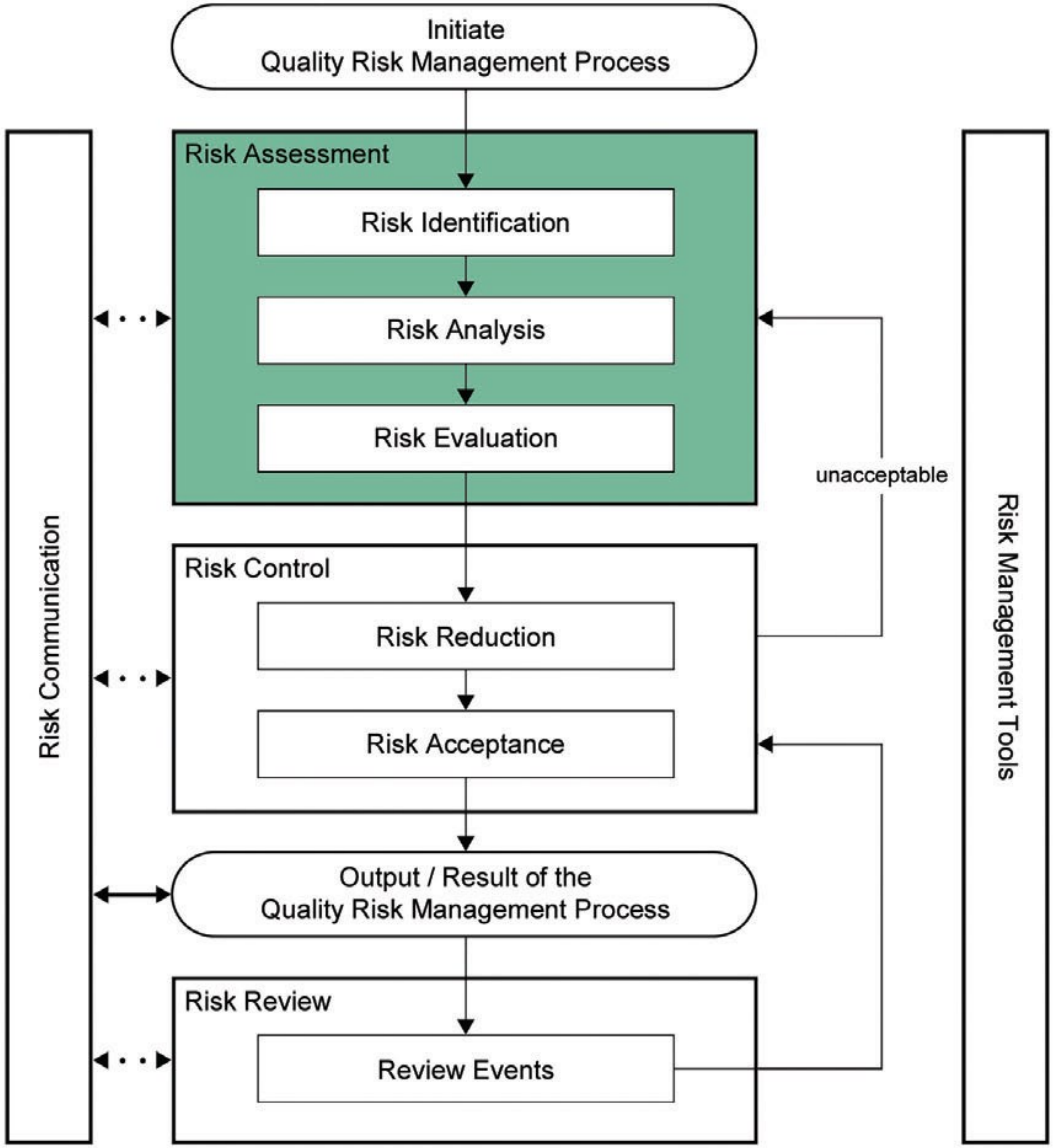


3. ICH Q9 – Initiation

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**

3. ICH Q9 – Risk Assessment 風險評估

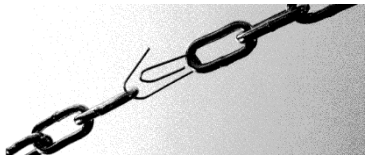


3. ICH Q9 – Risk Assessment 風險評估

- *Risk Identification*
  What might go wrong?
- *Risk Analysis*
  What is the likelihood (probability) it will go wrong?
- *Risk Evaluation*
  What are the consequences (severity)?

Note: People often use terms
"Risk analysis", "Risk assessment" and
"Risk management" interchangeably
which is incorrect!

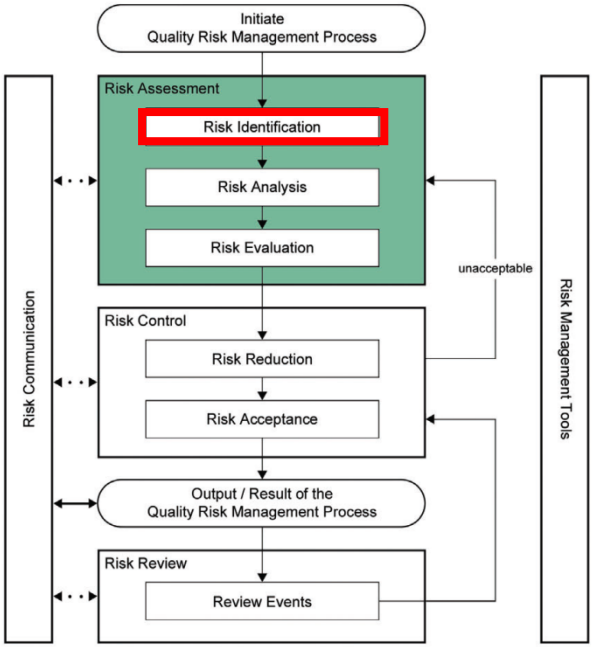
3. ICH Q9 – Risk Assessment



Risk Assessment: Risk Identification 風險辨識

"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**

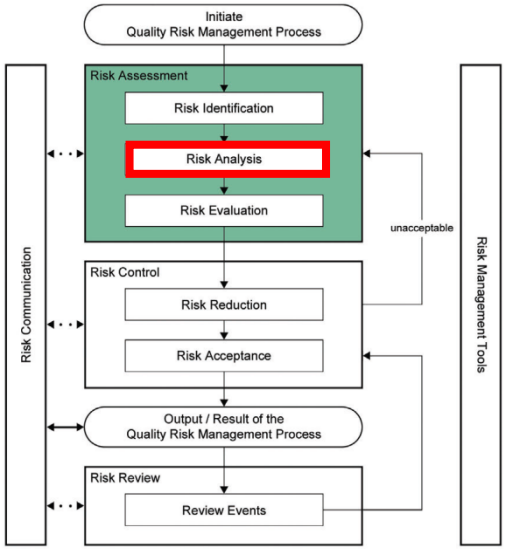


3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Analysis 風險分析

"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 (used in some tools)

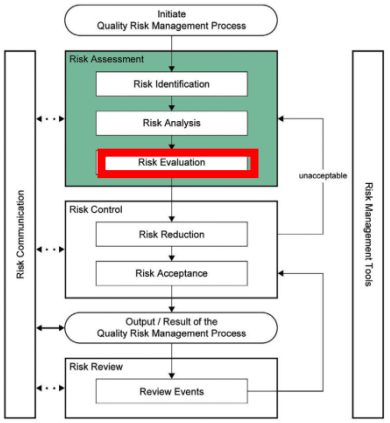


3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation 風險評價

"What is the risk?"

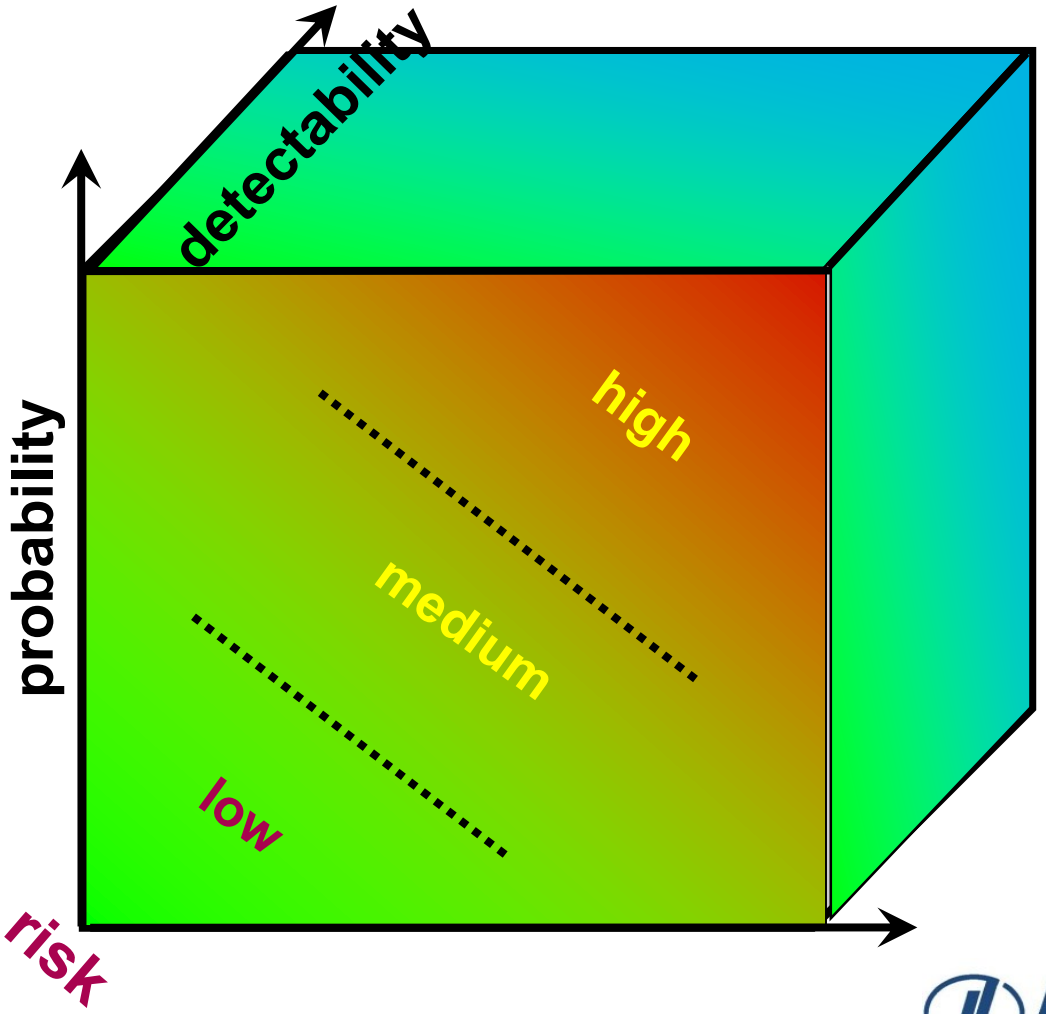
- Compare the identified and analysed risk against given risk criteria
- Consider the strength of evidence for all three of the fundamental questions
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?



3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

Parameters for evaluating risks

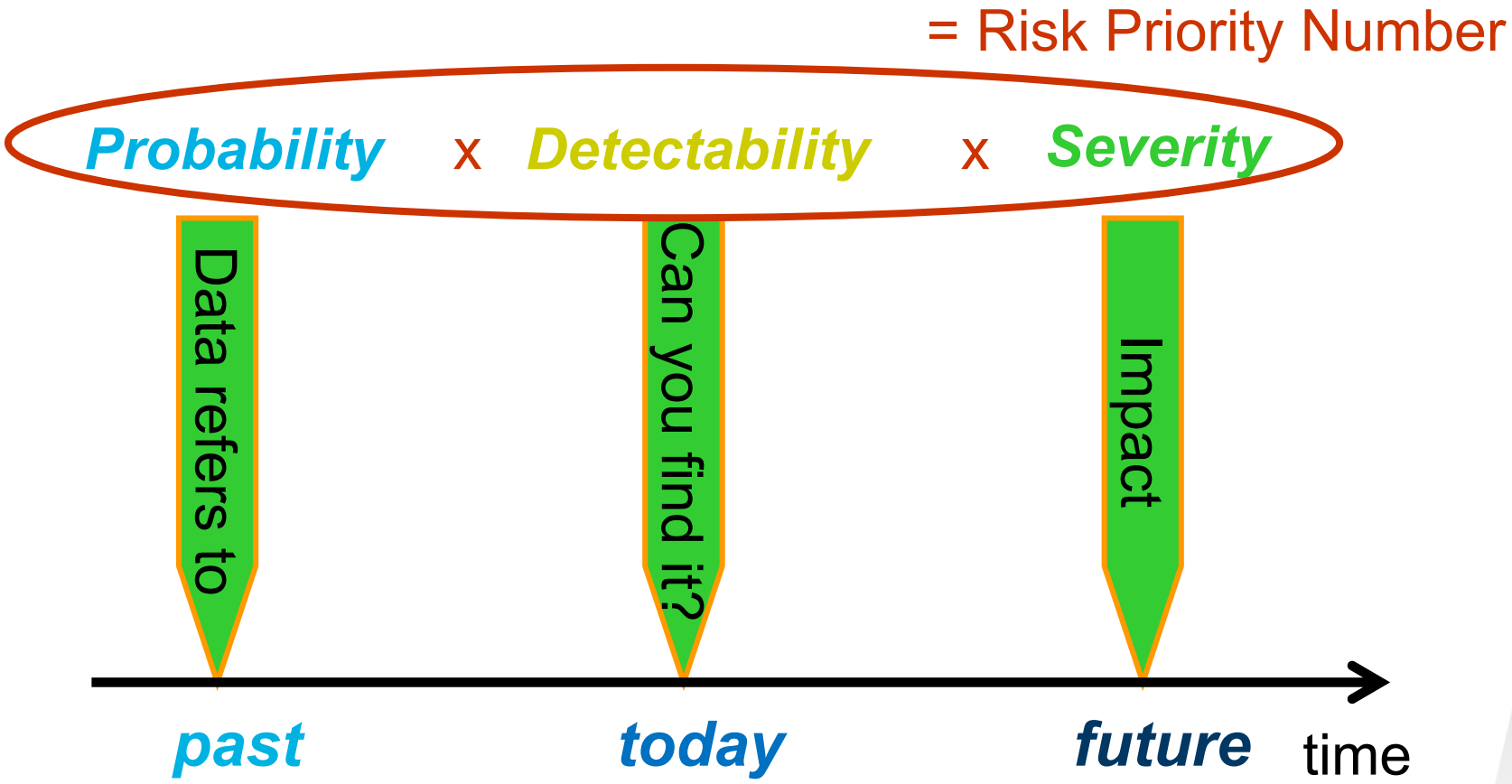


IMPAX LABORATORIES (TAIWAN), INC.

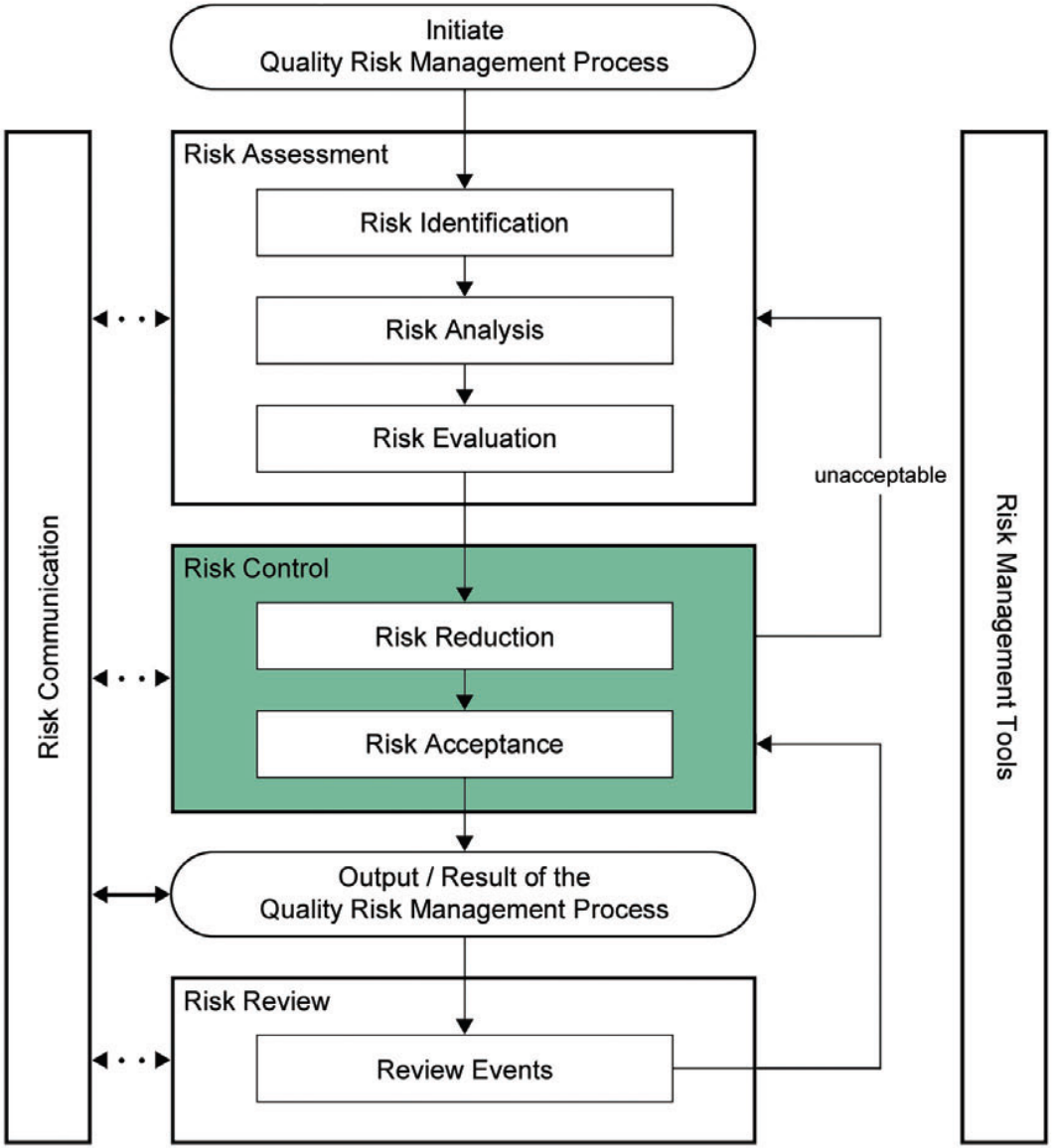
3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

A picture of the life cycle



3. ICH Q9 – Risk Control 風險控制



3. ICH Q9 – Risk Control

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?**

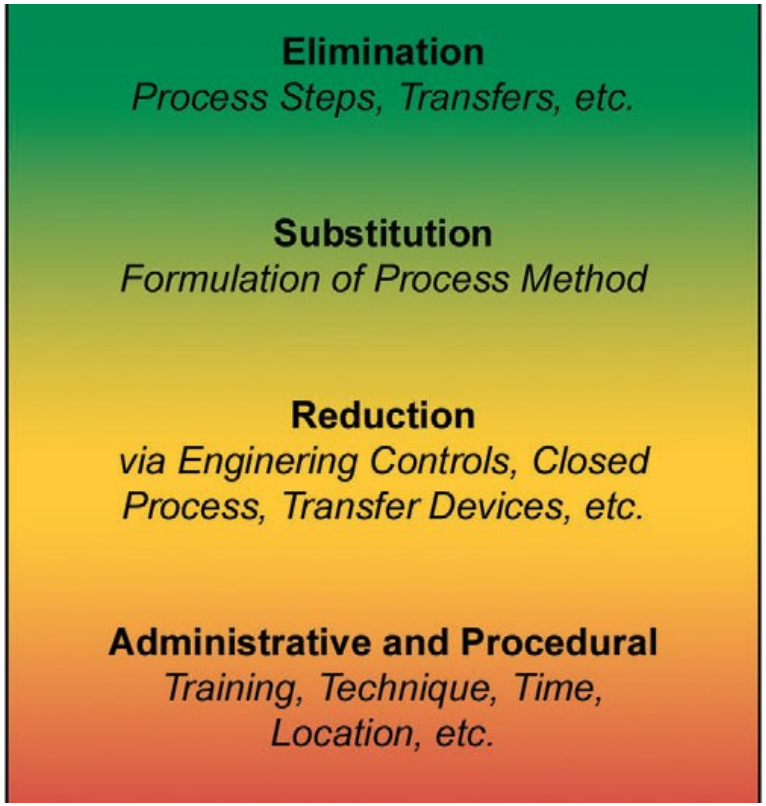
3. ICH Q9 – Risk Control

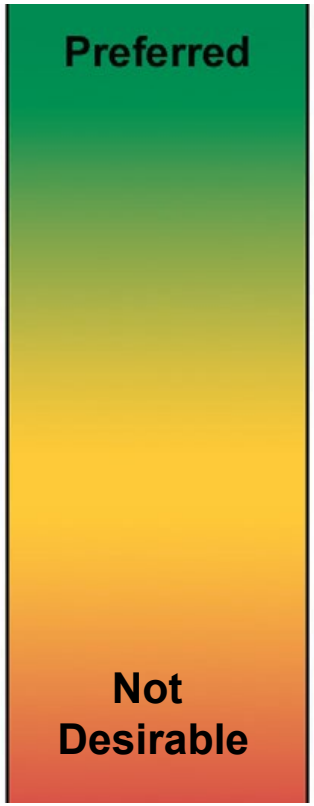
Risk Control: Residual Risk

- 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

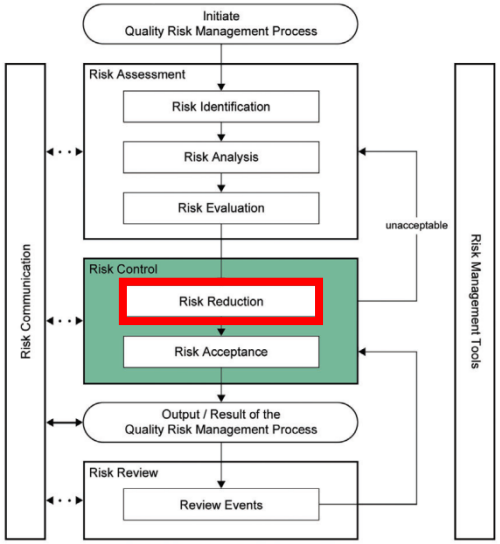
3. ICH Q9 – Risk Control

Risk Control: Risk Reduction 風險降低





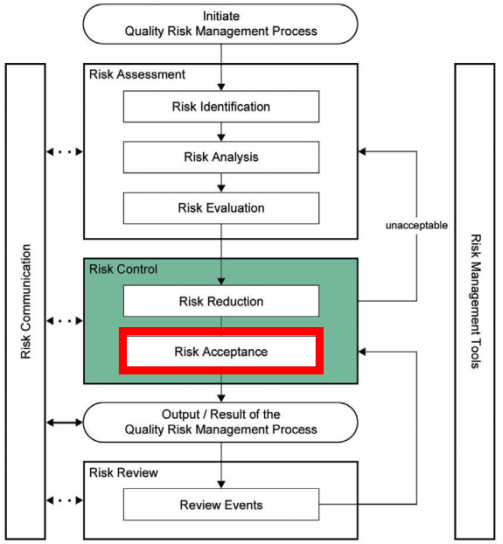
ISPE Risk-MaPP Volume 7



3. ICH Q9 – Risk Control

Risk Control: Risk Acceptance 風險接受

- **Decision to**
  - > **Accept the residual risk**
  - > **Passively accept non specified residual risks**
- **May require support by (senior) management**
  - > **Applies to both industry and competent authorities**
- **Will always be made on a case-by-case basis**



3. ICH Q9 – Risk Control

Risk Control: Risk Acceptance風險接受

- Discuss the appropriate balance between benefits, risks, and resources
- Focus on the patients' interests and good science/data
- Risk acceptance **is not**
  - **Inappropriately interpreting data and information**
  - **Hiding risks from management / competent authorities**

3. ICH Q9 – Risk Control

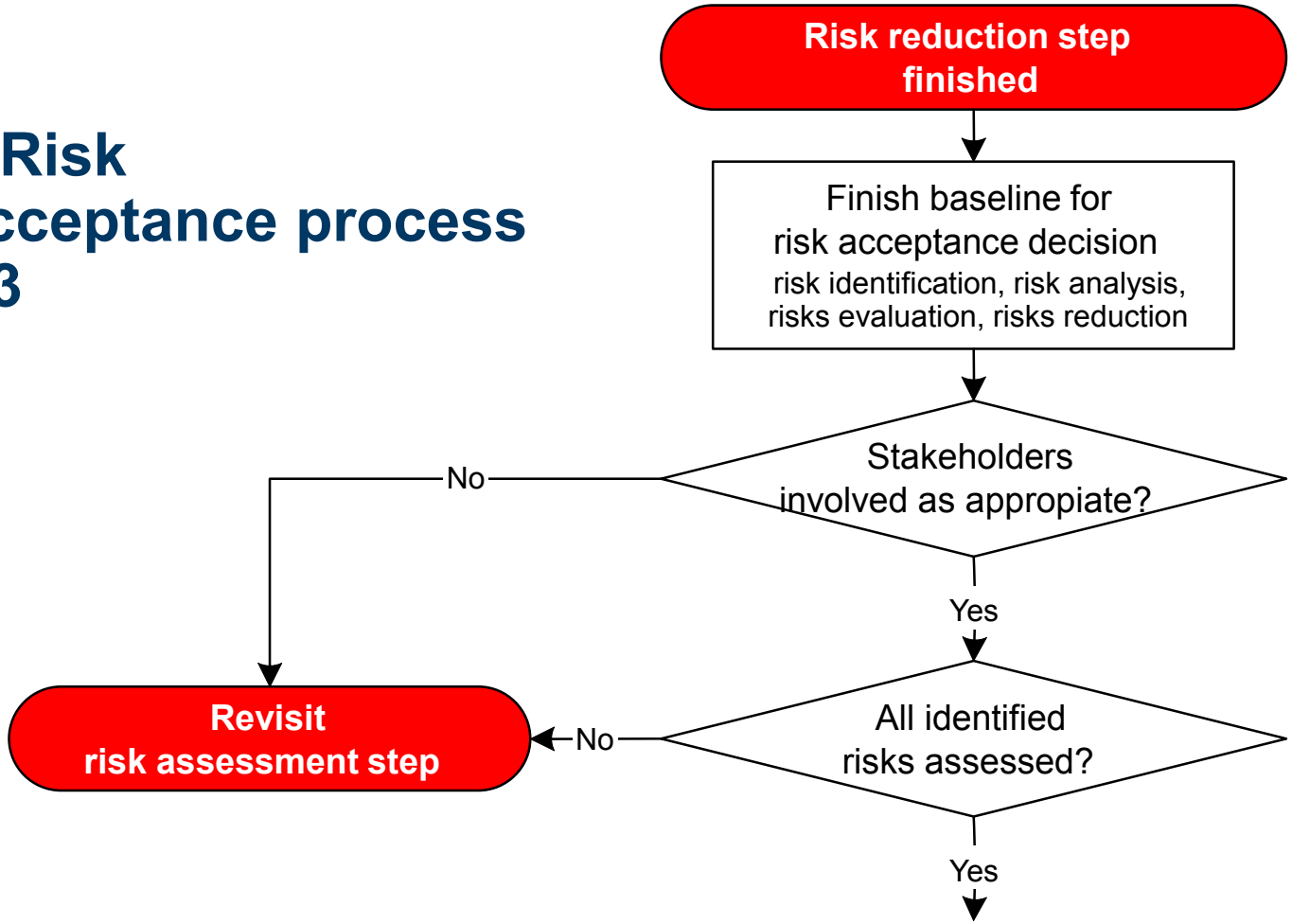
Risk Control: Risk Acceptance 風險接受

Who has to accept risk?

- Decision Maker(s)
  - Person(s) with the competence and authority to make appropriate and timely quality risk management decisions
- Stakeholder
  - Any individual, group or organization that can …be affected by a risk
  - Decision makers might also be stakeholders
  - The primary stakeholders are the patient, healthcare professional, regulatory authority, and industry
  - The secondary stakeholders are patient associations, public opinions, politicians

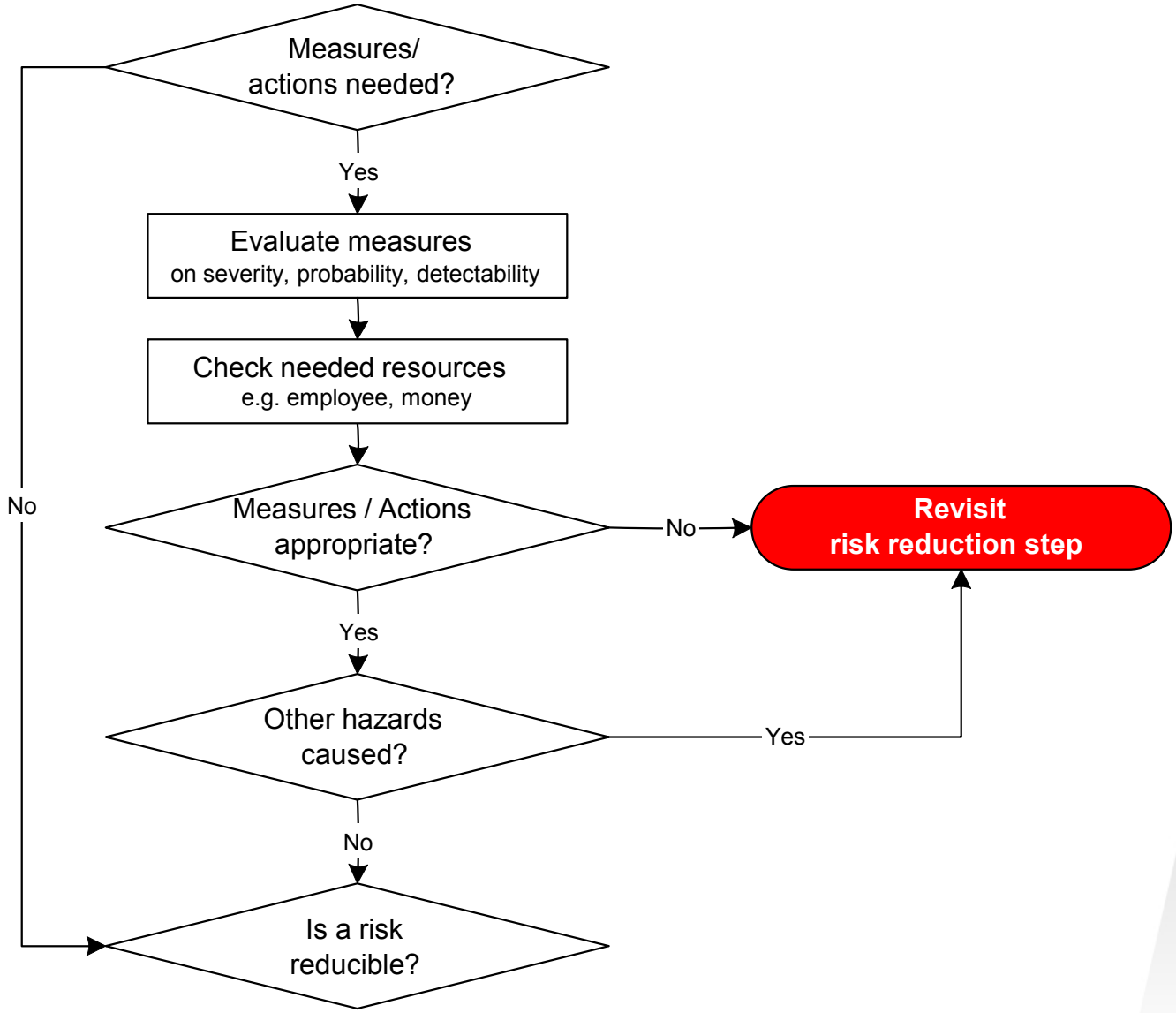
3. ICH Q9 – Risk Control 風險控制

A Risk Acceptance process 1/3



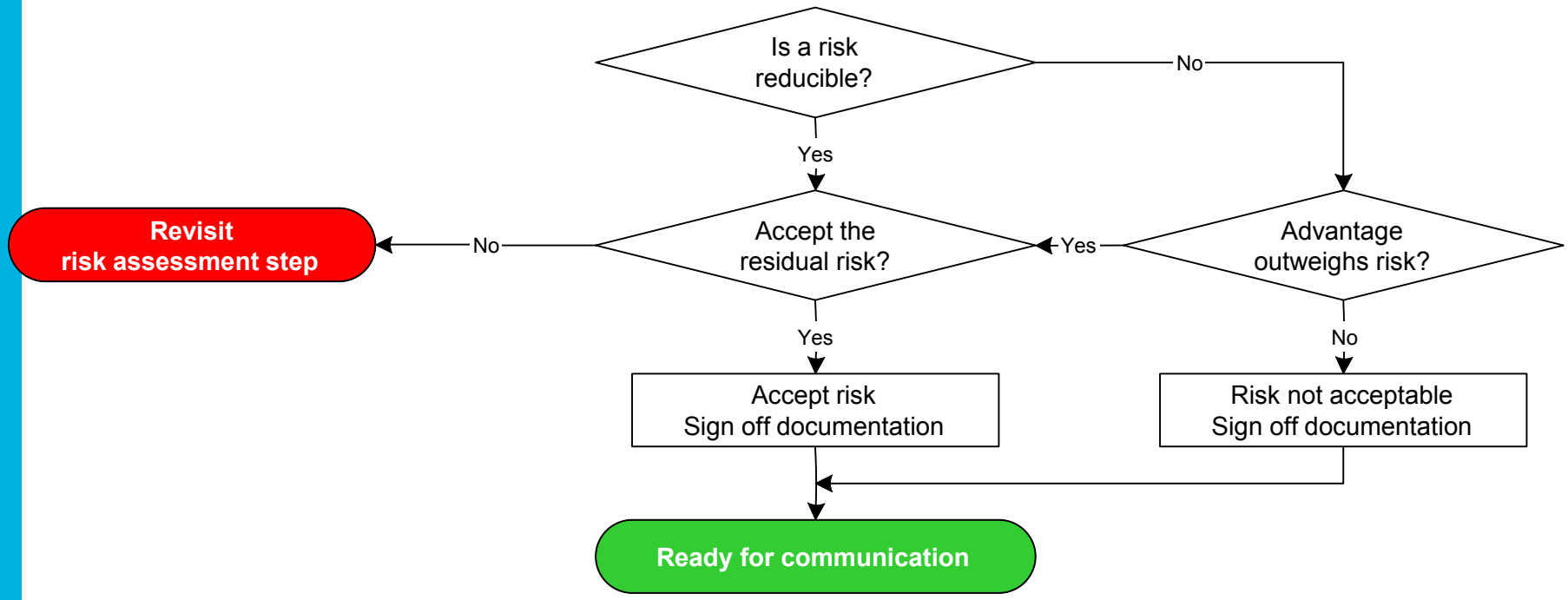
3. ICH Q9 – Risk Control 風險控制

A Risk Acceptance process 2/3

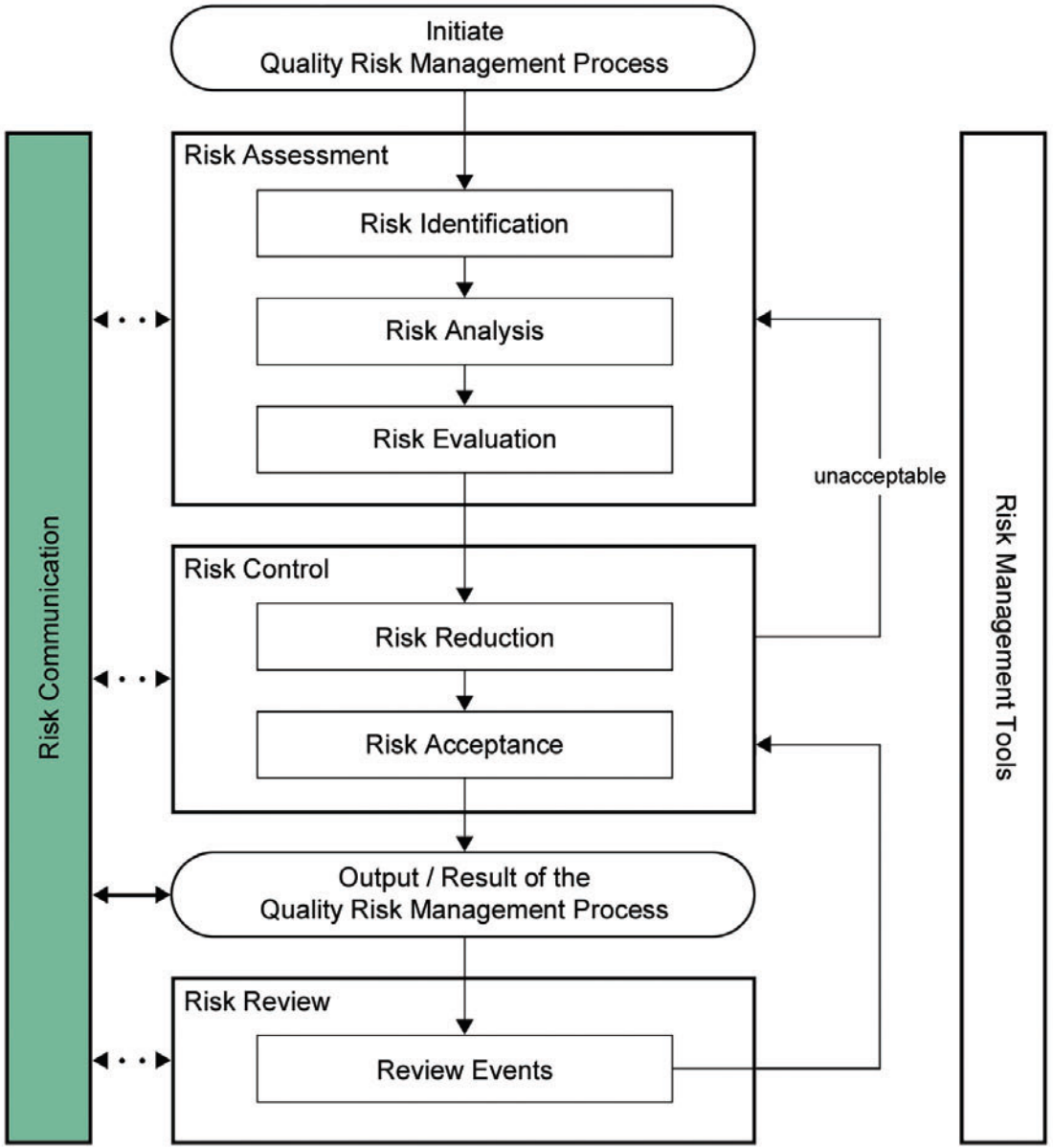


3. ICH Q9 – Risk Control 風險控制

A Risk Acceptance process 3/3



3. ICH Q9 – Risk Communication 風險溝通



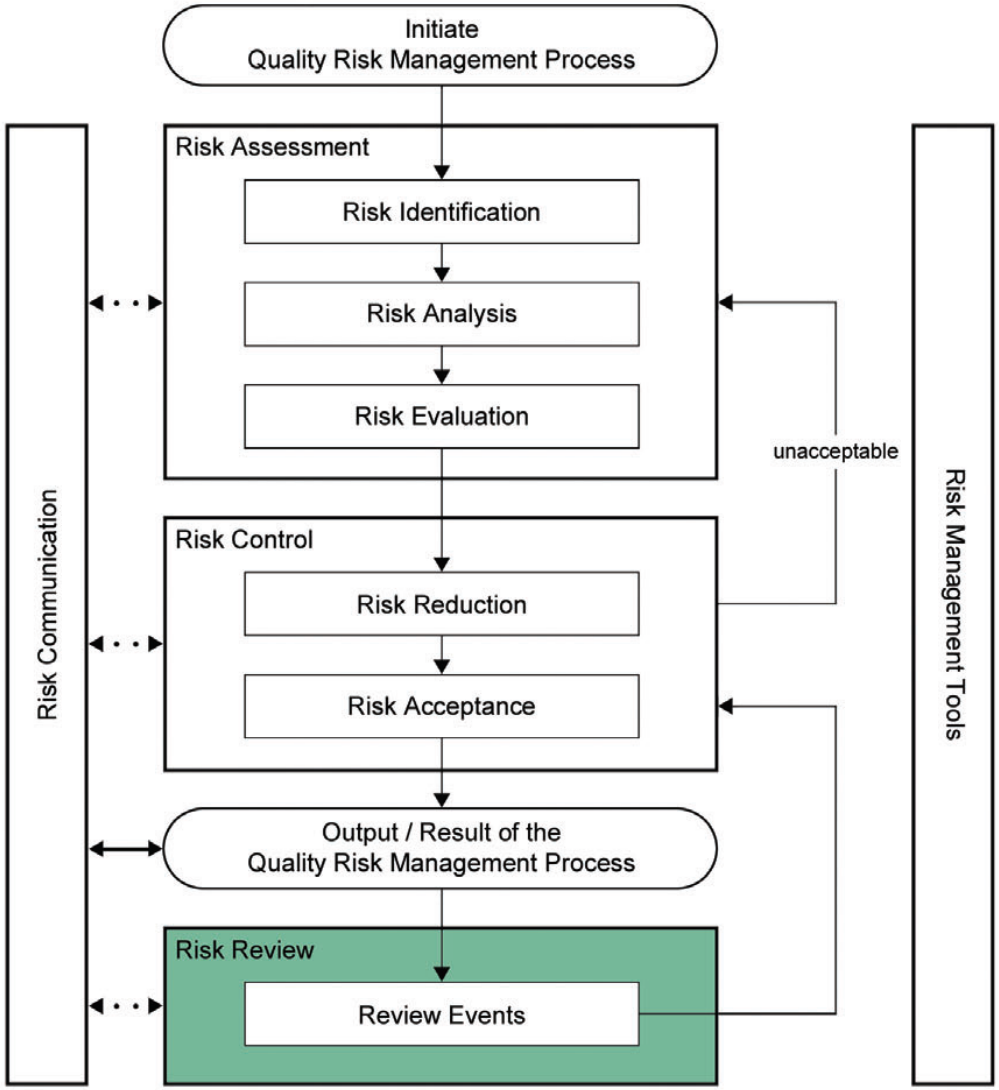
3. ICH Q9 – Risk Communication

- Bi-directional sharing of information about risk and risk management between the decision makers and others
- Communicate at any stage of the QRM process
- Communicate and document the output/result of the QRM process appropriately
- Communication need not be carried out for each and every individual risk acceptance
- Use existing channels as specified in regulations, guidance and SOP's

3. ICH Q9 – Risk Communication

- Exchange or sharing of information, as appropriate
- Sometimes formal sometimes informal
  - **Improve ways of thinking and communicating**
- Increase transparency

3. ICH Q9 – Risk Review 風險評審

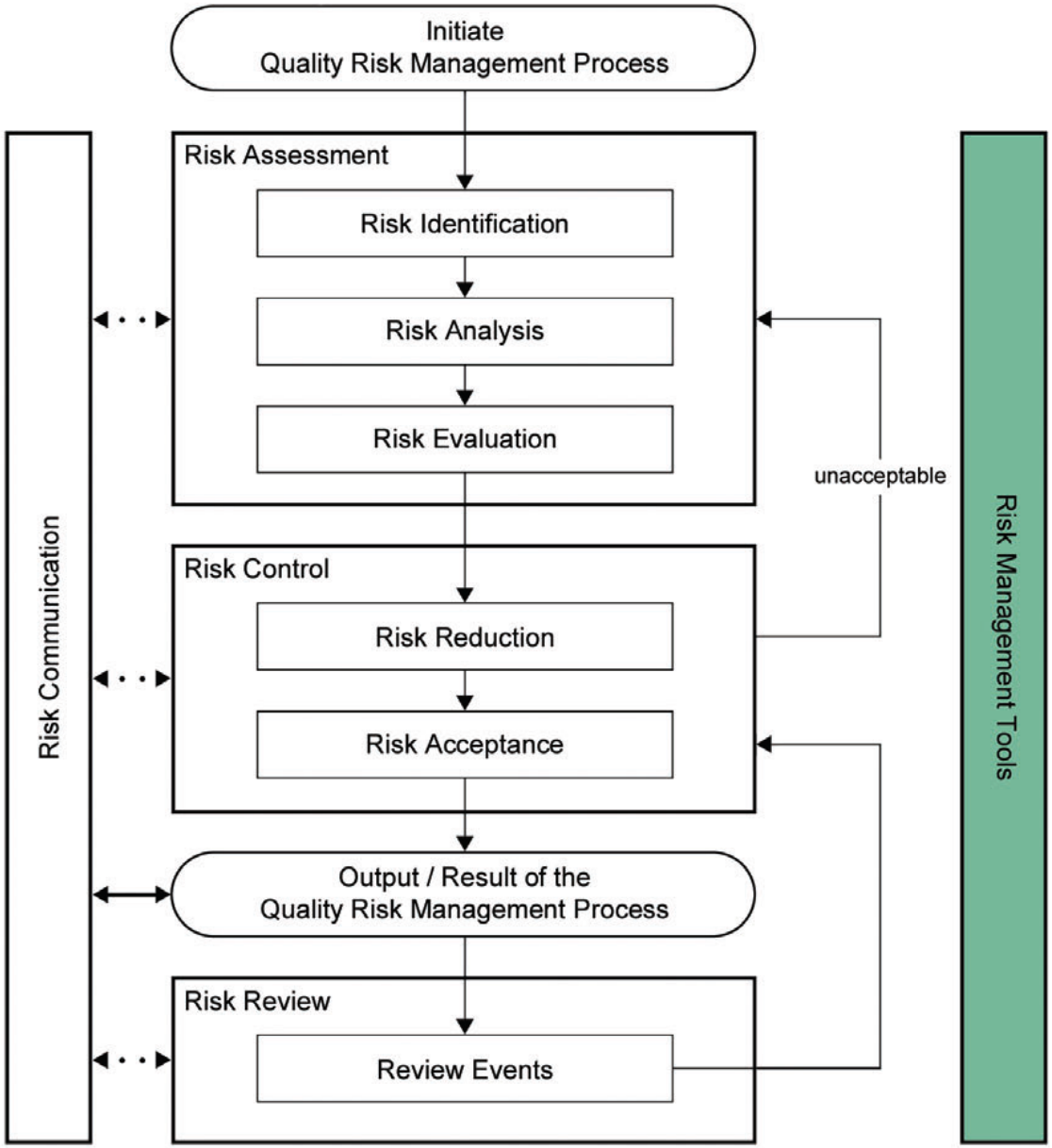


3. ICH Q9 – Risk Review 風險評審

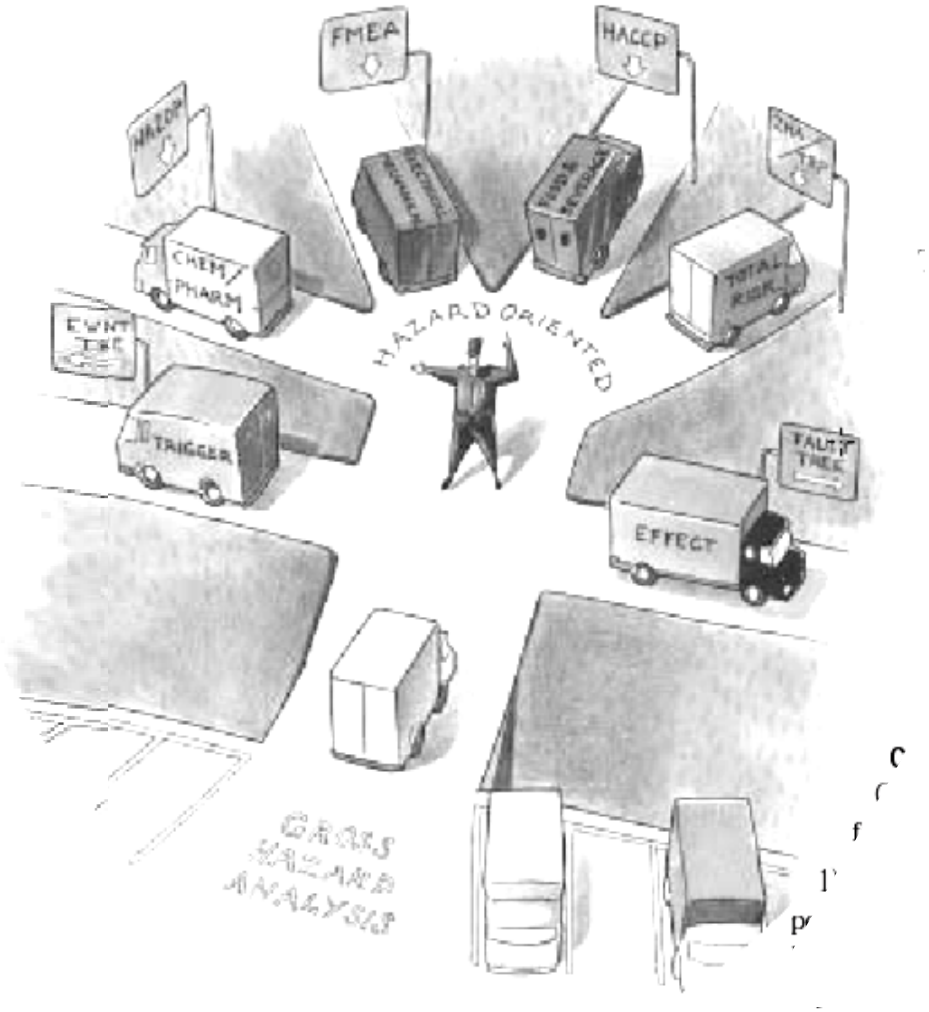
Risk review: Review Events

- 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

3. ICH Q9 – Risk Management Tools 風險管理工具



3. ICH Q9 – Risk Management Tools



One method "all inclusive"?

3. ICH Q9 – Risk Management Tools

- Supports science-based decisions
- A great variety are listed but other existing or new ones might also be used
- 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

3. ICH Q9 – Risk Management Tools

- Supports a scientific and practical approach to decision-making

- Accomplishing steps of the QRM process
  - **Provides documented, transparent and reproducible methods**
  - **Assessing current knowledge**
  - **Assessing probability, severity and sometimes detectability**

3. ICH Q9 – Risk Management Tools

- Adapt the tools for use in specific areas
- Combined use of tools may provide flexibility
- The degree of rigor and formality of QRM
  - **Should be commensurate with the complexity and / or criticality of the issue to be addressed and reflect available knowledge**
- Informal ways
  - **empirical methods and / or internal procedures**

3. ICH Q9 – Risk Management Tools

- 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