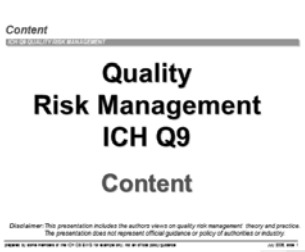
Links 相關連結

- **FDA**
  http://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0ahUKEwiKmsOc9b3OAhXTq5QKHfN-BXIQFggrMAI&url=http%3A%2F%2Fwww.pmda.go.jp%2Ffiles%2F000156539.ppt&usg=AFQjCNGiL_0owxFyo_Dclq40gFCYv4RnQg&sig2=QKprpe8ILku2LXbSVT8EHg
- **WHO**
  http://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwiQyueX9L3OAhWJW5QKHViFiCygQFggaMAA&url=http%3A%2F%2Fapps.who.int%2Fprequal%2Ftrainingresources%2Fpq_pres%2Fworkshop_China_November2009%2Fenglish%2F3-3_Risk_management.ppt&usg=AFQjCNGvMpef3GbU0OoG_-OsoedIKcYPGA&sig2=pqdhFRh4Mc4g2oOfOMYGBg
- **ICH**
  http://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwiQyueX9L3OAhWJW5QKHVFiCygQFggiMAE&url=http%3A%2F%2Fwww.fda.gov%2Fohrms%2Fdockets%2Fac%2F06%2Fslides%2F2006-4241s1_3.ppt&usg=AFQjCNGla8uuAjWkY9-94S--nmxe91Cnzg&sig2=Syx9B4fkLzurvdom0U3ajw



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Purpose of this talk 課程目的

- To guide through the content of the Quality Risk Management (ICH Q9 document).
- To provide some considerations, possible interpretations and where appropriate examples
- To practice risk assessment by using FMEA table

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Table of contents 課程大綱

I. ICH Q9 QRM 常用風險管理工具

1. Introduction
2. ICH Q9 – Quality Risk Management

II. 應用風險管理於GMP查核

1. Why we need risk assessment
2. Risk assessment tools
3. Case studies
4. Summary

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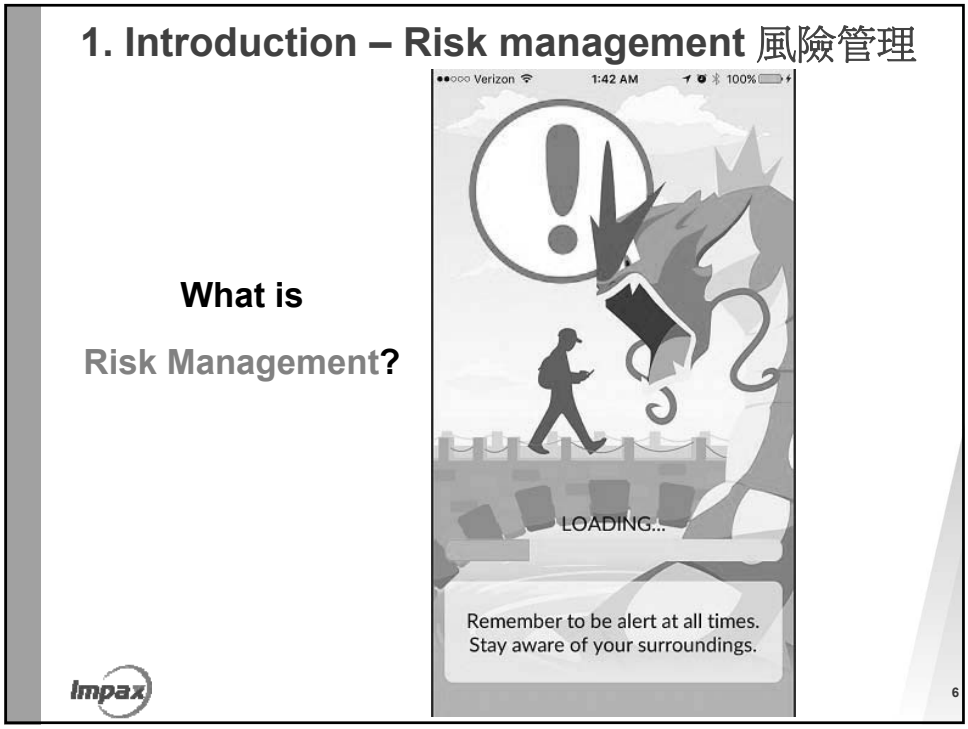

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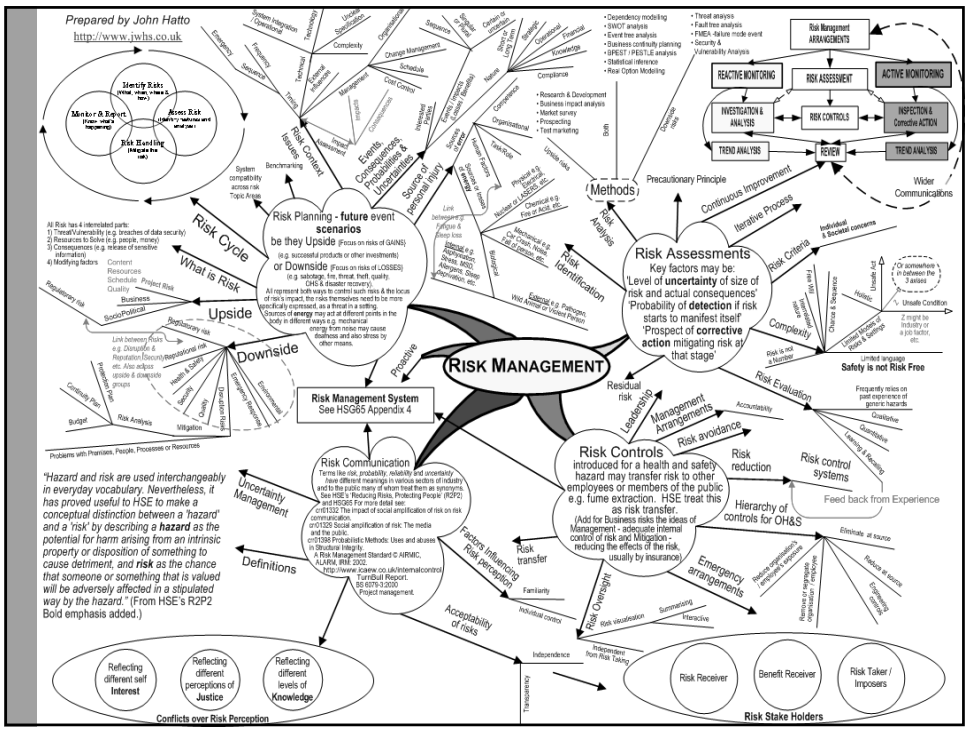

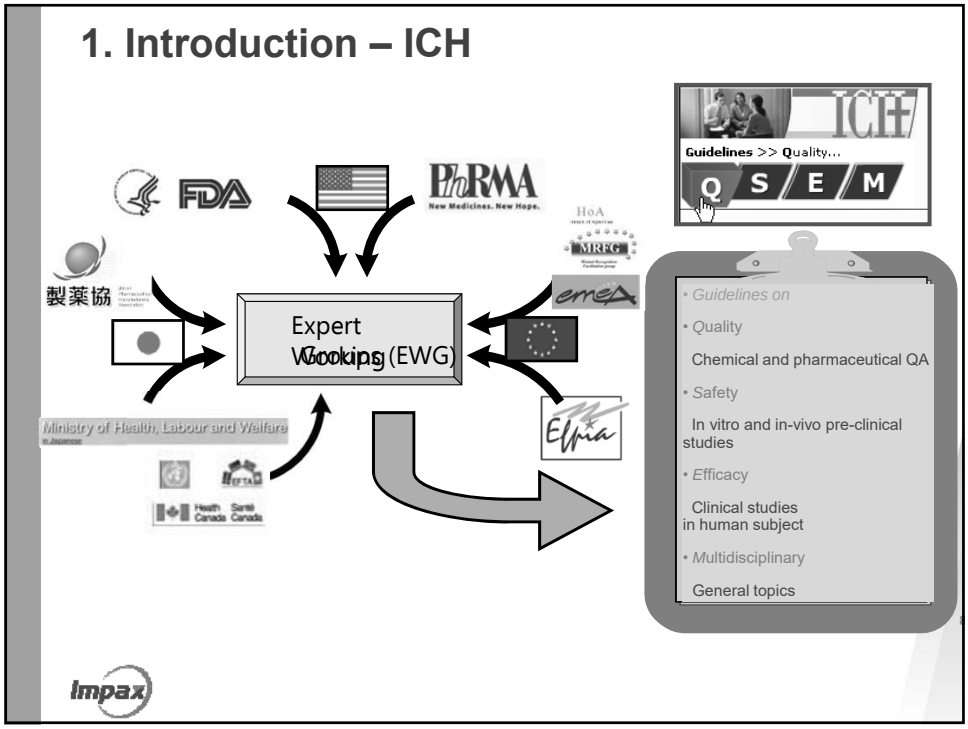

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1. Introduction – ICH quality vision

"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)

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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

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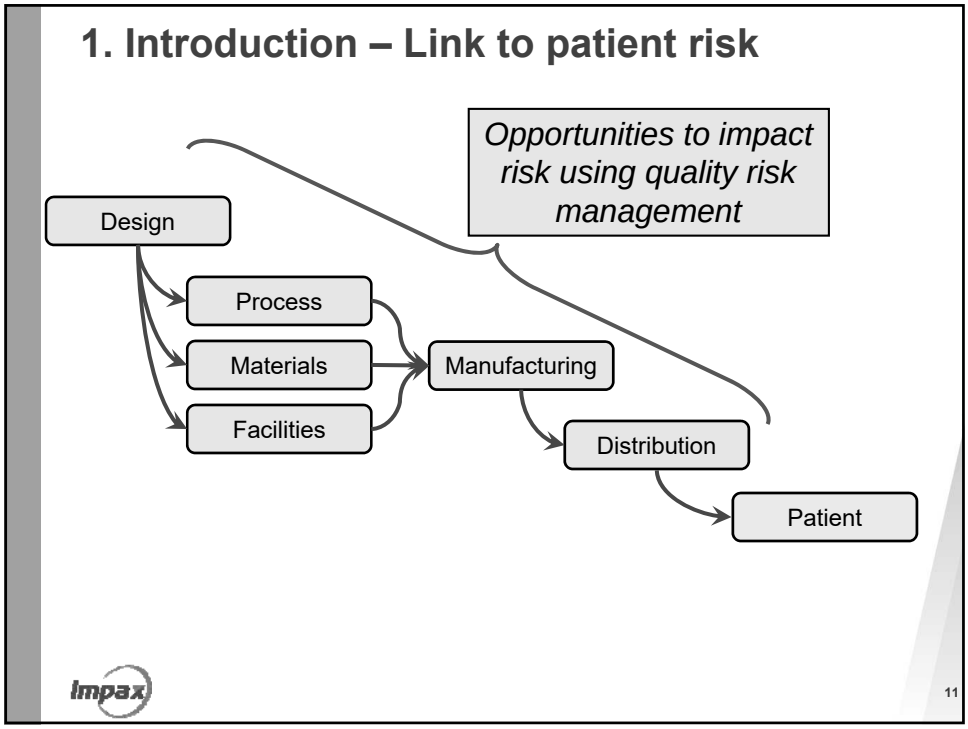

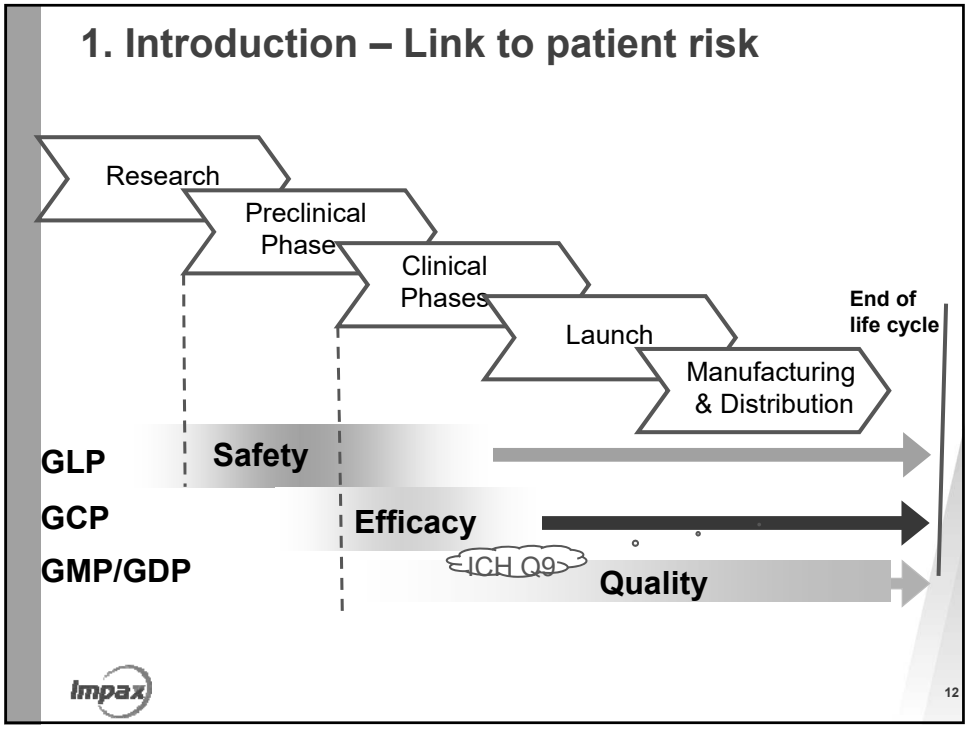

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1. Introduction – Link to patient risk

- 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**

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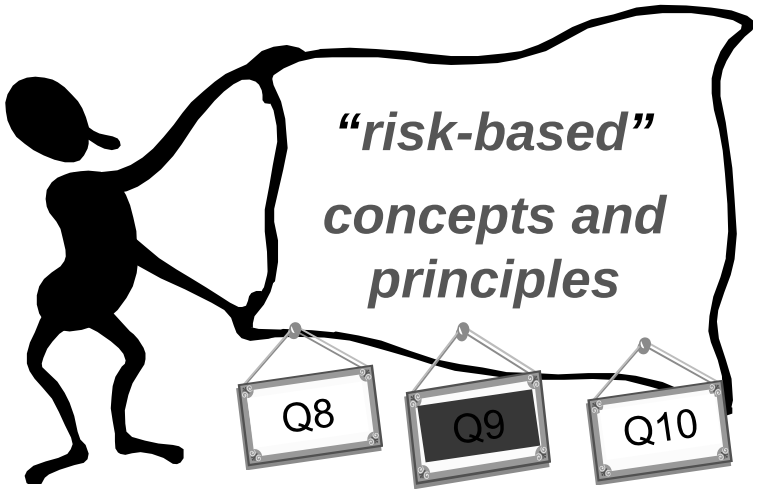
1. Introduction – The new paradigm



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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

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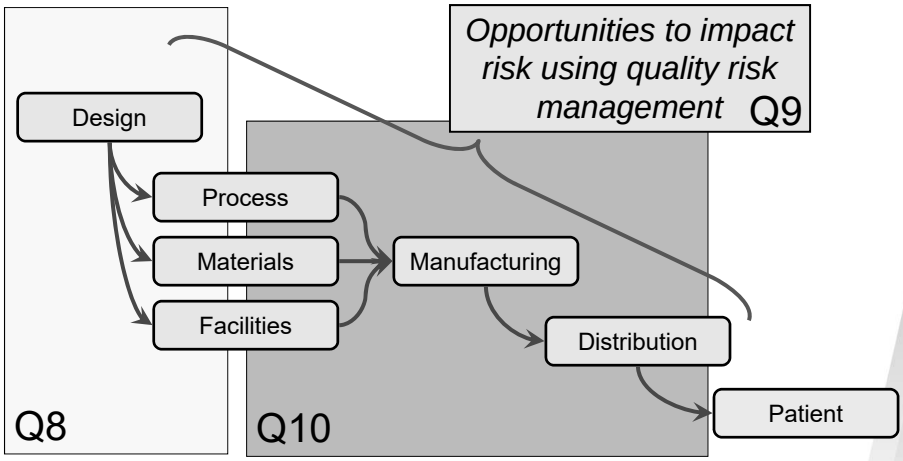
1. Introduction – ICH Q8, Q9, and Q10



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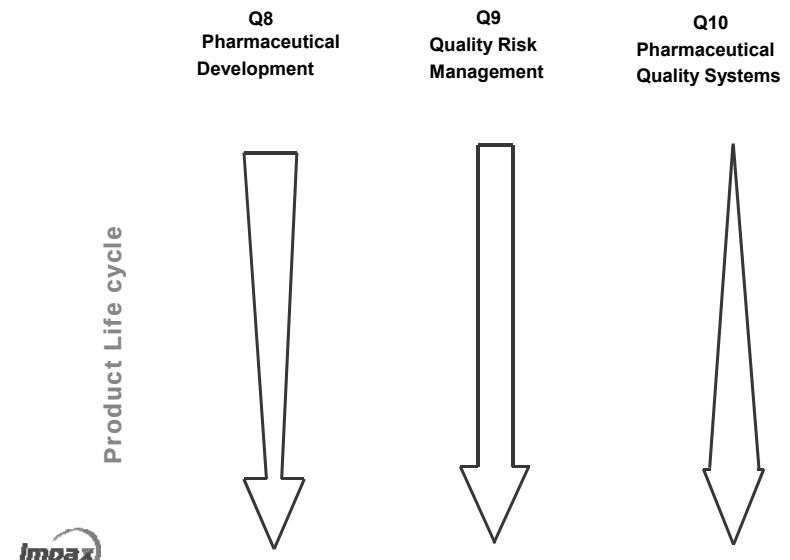
1. Introduction – ICH Q8, Q9, and Q10



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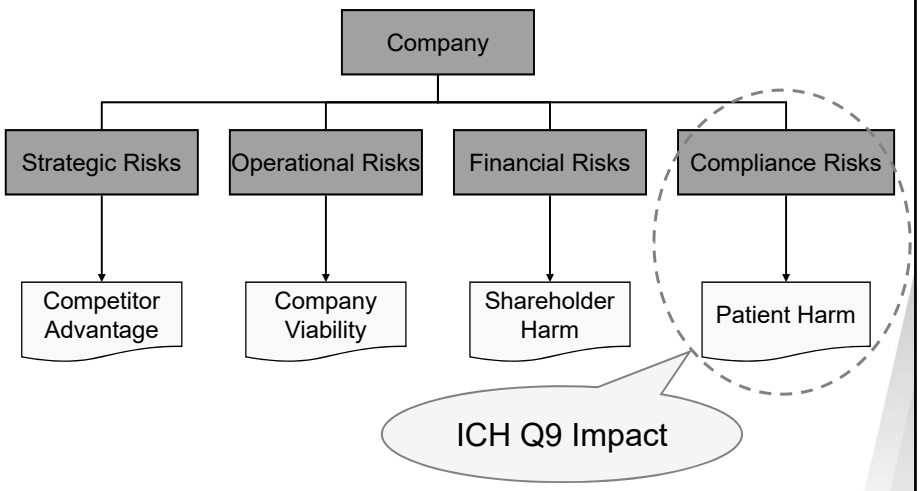
1. Introduction – Risk management is Universal



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

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2. 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

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2. 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**

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2. 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

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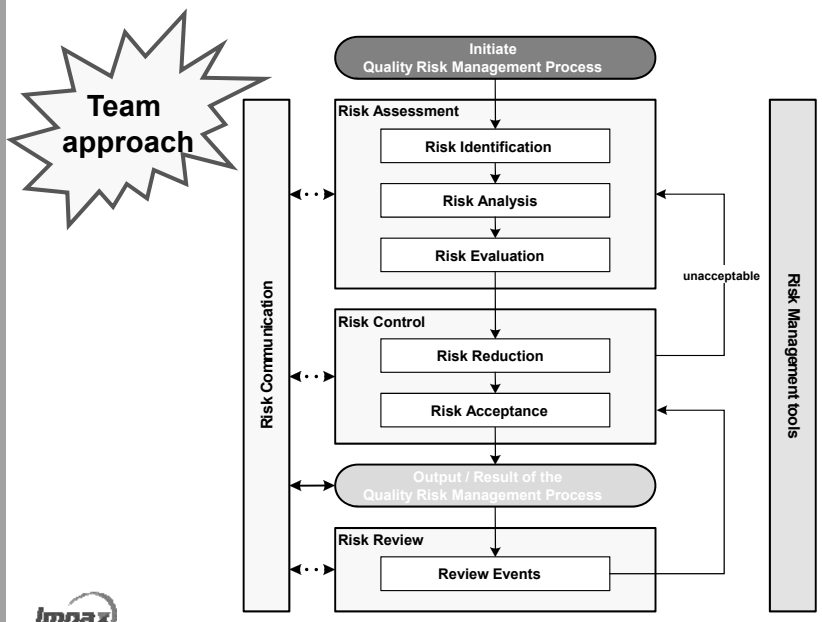
2. ICH Q9 – General process 基本流程



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2. 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

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2. 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**

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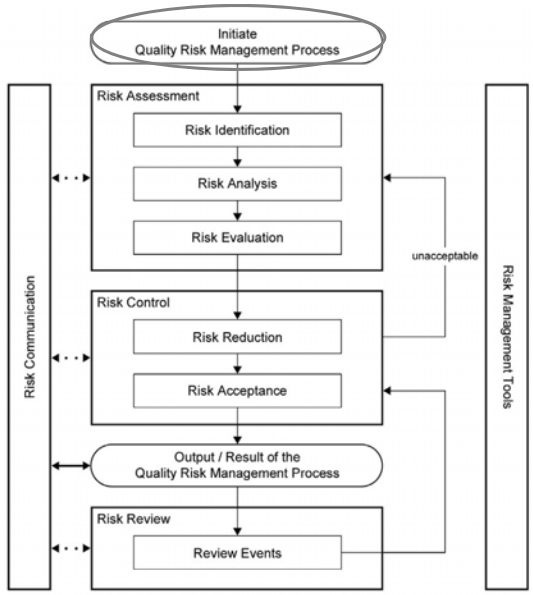
2. ICH Q9 – Initiation 起始



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2. 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**

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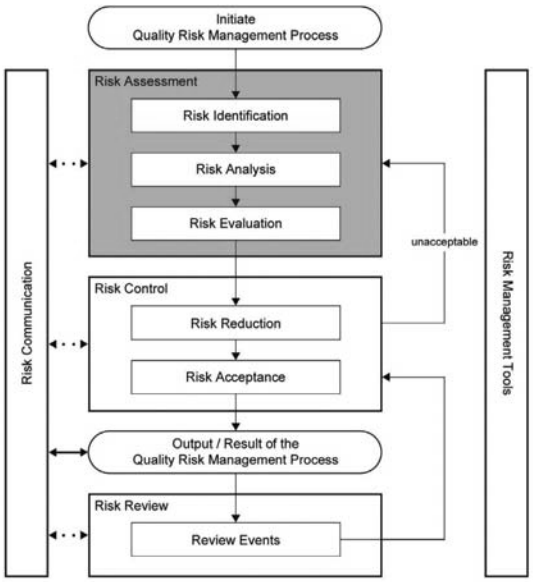
2. ICH Q9 – Risk Assessment 風險評估



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2. ICH Q9 – Risk Assessment 風險評估

3 fundamental questions

- *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!

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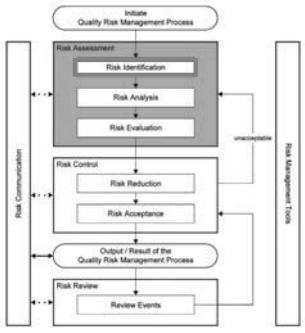
2. ICH Q9 – Risk Assessment

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**



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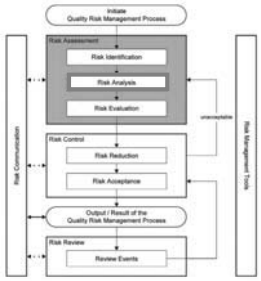
2. ICH Q9 – Risk Assessment

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)



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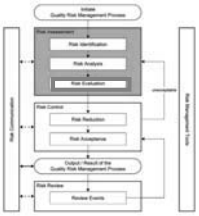
2. ICH Q9 – Risk Assessment

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)?



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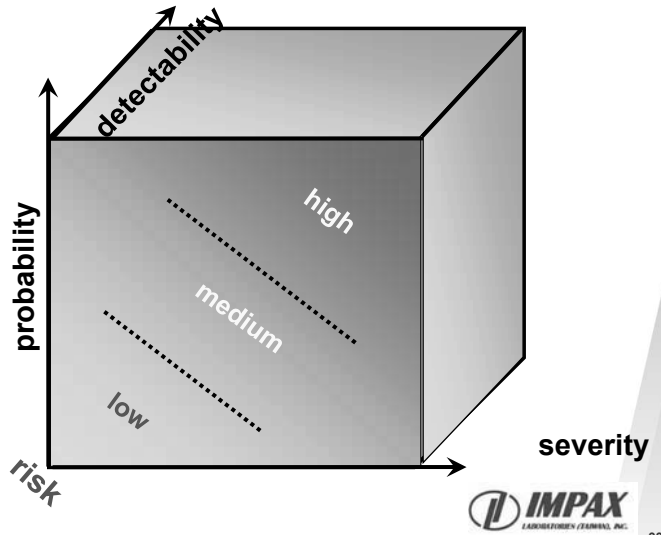
2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

Parameters for evaluating risks



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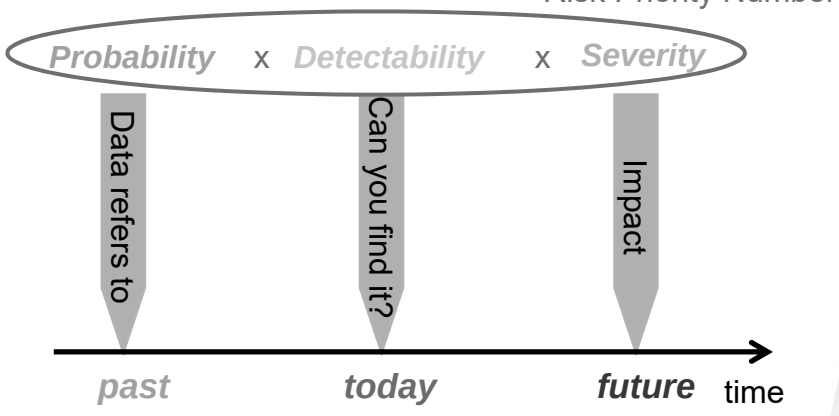
2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

A picture of the life cycle

= Risk Priority Number



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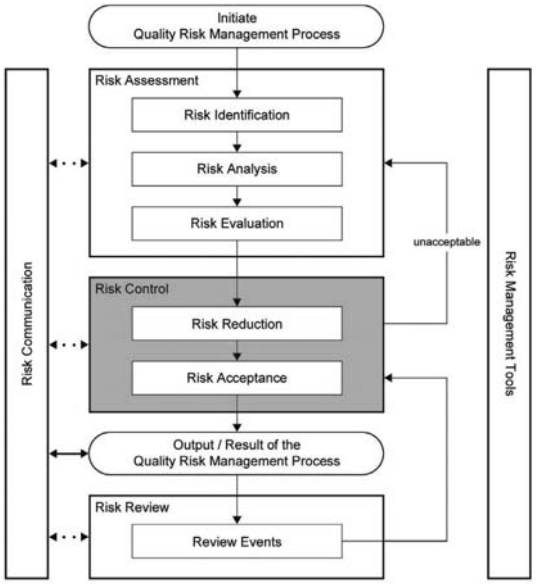
2. ICH Q9 – Risk Control 風險控制



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2. 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?**

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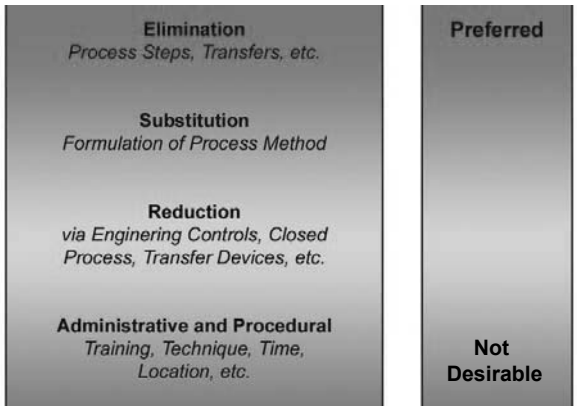
2. ICH Q9 – Risk Control

Risk Control: Risk Reduction 風險降低



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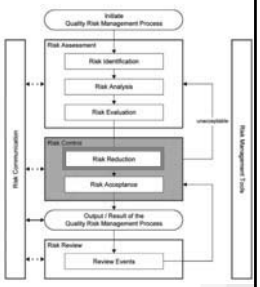
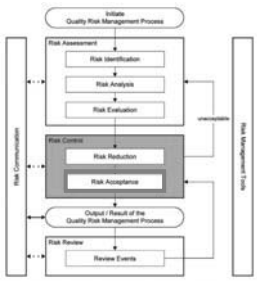


2. ICH Q9 – Risk Control

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**



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2. 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**

2. 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

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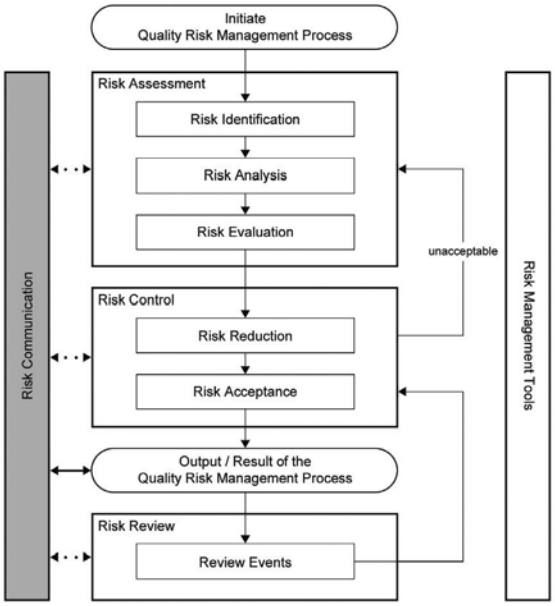
2. ICH Q9 – Risk Communication 風險溝通



2. 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

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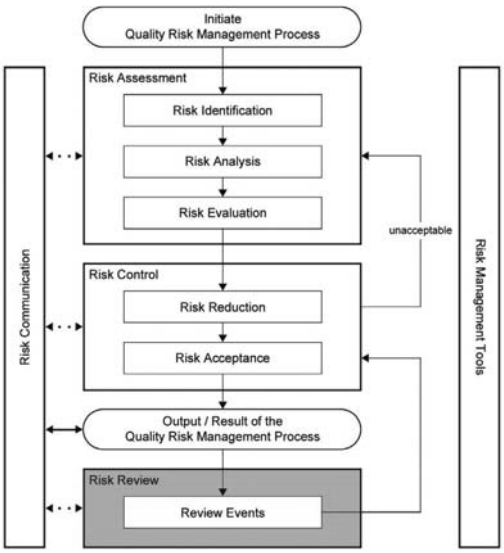
2. ICH Q9 – Risk Communication

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

2. ICH Q9 – Risk Review 風險評審



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2. 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

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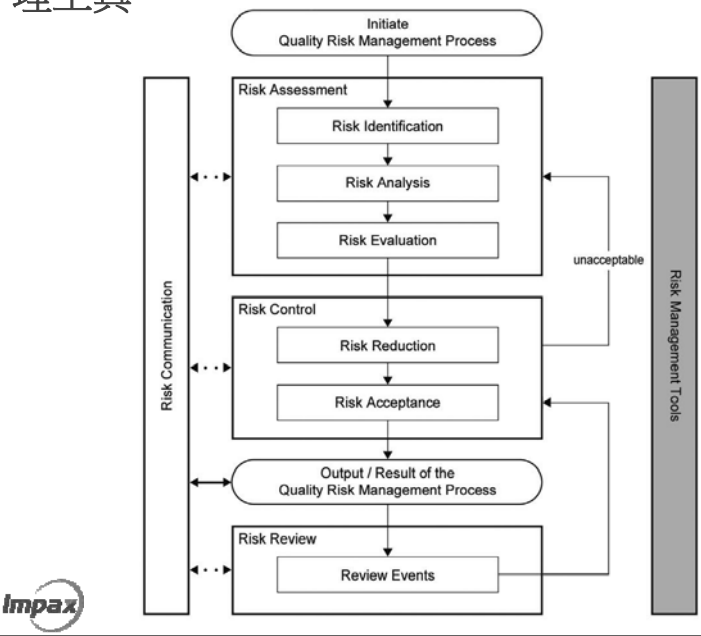
2. ICH Q9 – Risk Management Tools 風險管理工具



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2. ICH Q9 – Risk Management Tools

One method
"all inclusive"?

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2. 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

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2. 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**

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2. 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

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

- PIC/S issued a draft guidance on Data Integrity (10Aug2016). The guidance is quite detailed and mentions Quality Culture, management review, data criticality, **risk management** and more.


PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 2)
10 August 2016

DRAFT PIC/S GUIDANCE

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS

DRAFT

Editor: PIC/S Secretariat
e-mail: info@picscheme.org
web site: http://www.picscheme.org

PI 041-1 (Draft 2) 1 of 41 10 August 2016

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

- EMA released 23 questions and answers on data integrity. The stakeholder advice includes measures that ensure data integrity and minimize risks at all stages of the data lifecycle in pharmaceutical quality systems.

Data integrity (NEW August 2016)

Back to top

Expand all items in this list

- Data integrity
- 1. How can data risk be assessed?
- 2. How can data criticality be assessed?
- 3. What does 'Data Lifecycle' refer to?
- 4. Why is 'Data lifecycle' management important to ensure effective data integrity measures?
- 5. What should be considered when reviewing the 'Data lifecycle'?
- 6. 'Data lifecycle': What risks should be considered when assessing the generating and recording of data?
- 7. 'Data lifecycle': What risks should be considered when assessing the processing data into usable information?
- 8. 'Data lifecycle': What risks should be considered when checking the completeness and accuracy of reported data and processed information?
- 9. 'Data lifecycle': What risks should be considered when data (or results) are used to make a decision?

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

- EMA released 23 questions and answers on data integrity.

Data integrity

1. How can data risk be assessed?

Data risk assessment should consider the vulnerability of data to involuntary or deliberate amendment, deletion or recreation. Control measures which prevent unauthorised activity and increase visibility / detectability can be used as risk mitigating actions.

Examples of factors which can increase risk of data integrity failure include complex, inconsistent processes with open-ended and subjective outcomes. Simple tasks which are consistent, well-defined and objective lead to reduced risk.

Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT system functionality or complexity. Factors to consider include:

- Process complexity
- Process consistency, degree of automation /human interface
- Subjectivity of outcome / result
- Is the process open-ended or well defined

This ensures that manual interfaces with IT systems are considered in the risk assessment process. Computerised system validation in isolation may not result in low data integrity risk, in particular when the user is able to influence the reporting of data from the validated system.

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

On 01Mar2015, the EU will have new GMP regulations that address cross contamination. Chapters 3 and 5 of Volume 4 of the EudraLex have been updated.

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

[a] In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

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

On 01Mar2015, the EU will have new GMP regulations that address cross contamination. Chapters 3 and 5 of Volume 4 of the EudraLex have been updated.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a

1. Why we need risk assessment?

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)

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1. 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.

1. 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').

1. 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.

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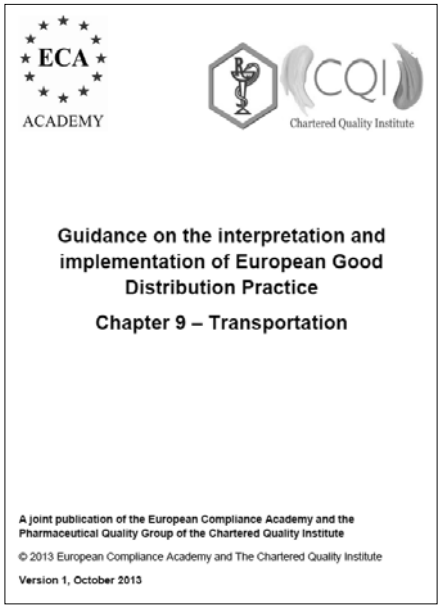
1. Why we need risk assessment?


ECA ACADEMY

Chartered Quality Institute

Guidance on the interpretation and implementation of European Good Distribution Practice

Chapter 9 – Transportation

A joint publication of the European Compliance Academy and the Pharmaceutical Quality Group of the Chartered Quality Institute

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Version 1, October 2013

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1. 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.

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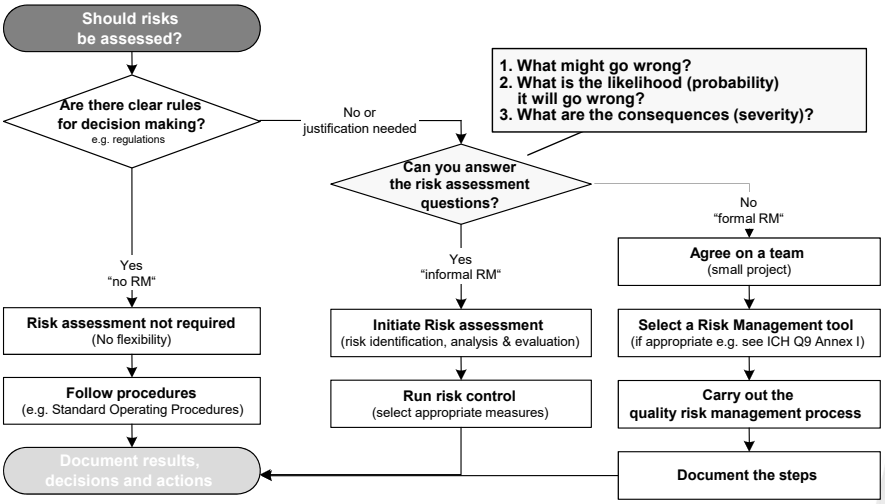
2. Risk Assessment Tools

- When to apply Risk Assessment / QRM?



Based on K. Connelly, AstraZeneca, 2005

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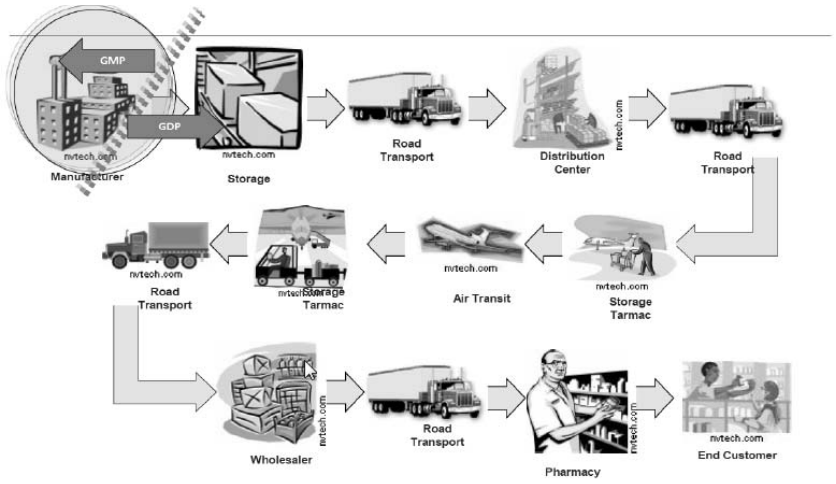
2. Risk Assessment Tools – Process map

Transportation QRM



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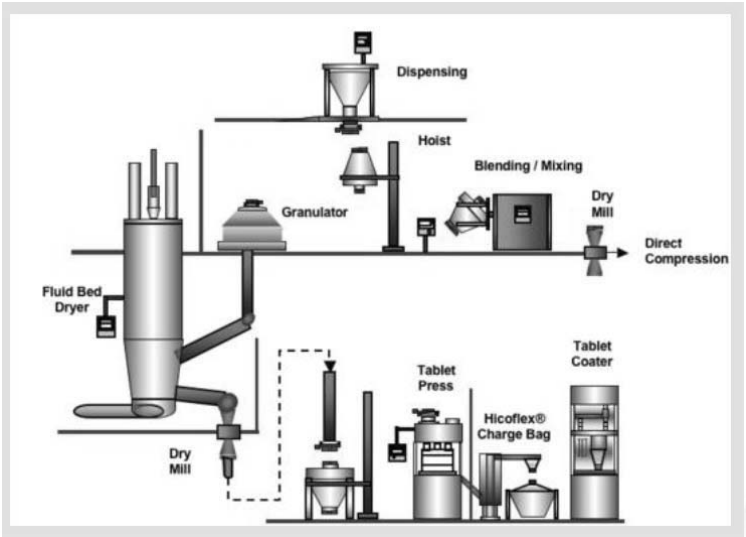
2. Risk Assessment Tools – Process map

Cross Contamination QRM



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2. Risk Assessment Tools – FMEA 失效模式

- Identify each way the process can fail
- Identify the possible consequences of each failure mode
- Assign numerical rankings

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2. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Severity 嚴重性**

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

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2. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Probability** 發生率

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

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2. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Detectability** 可偵測性

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

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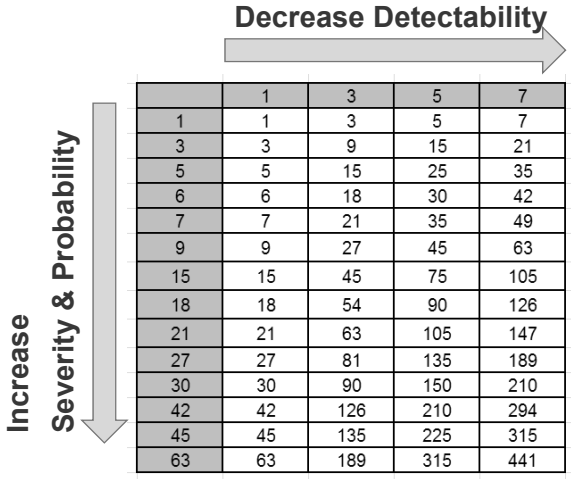
2. Risk Assessment Tools – FMEA

Risk Evaluation Score
(Severity X Probability X Detectability = RPN)



	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
15	15	45	75	105
18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

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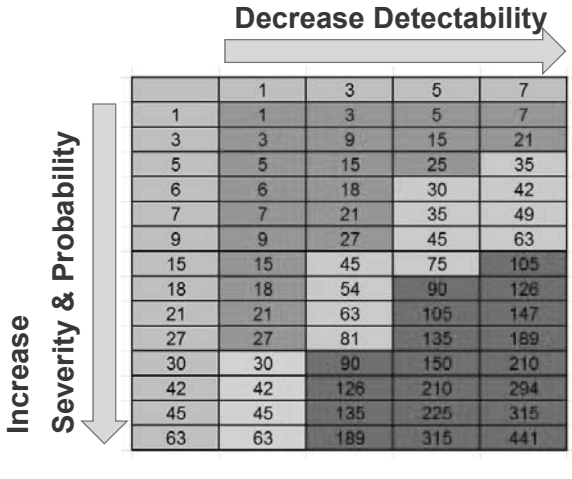
2. Risk Assessment Tools – FMEA

Risk Evaluation – Risk Acceptance?



	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
15	15	45	75	105
18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

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2. Risk Assessment Tools – FMEA

How to design a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk sources (phenomena and root cause)

Based on the historical data (e.g. deviations), interview, experience, and etc.

2. Risk Assessment Tools – FMEA

How to create a FMEA table

Temperature

Vibration

Humidity

Process

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2. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Severity

2. Risk Assessment Tools – FMEA

Example 1, Drum appearance: Severity = 1

Example 2, API Degradation: Severity = 3

Example 3, Low toxic impurity: Severity = 6

Example 4, High toxic impurity: Severity = 9

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

2. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Probability

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2. Risk Assessment Tools – FMEA

Example 1, Temp controlled: Probability = 1

Example 2, Softbox during Spring: Probability = 3

Example 3, Softbox during Summer : Probability = 5

Example 4, N/A during Summer: Probability = 7

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

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2. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Detectability

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2. Risk Assessment Tools – FMEA

Example 1, Temp logger: Detectability = 1

Example 2, QA and Operator checking: Detectability = 3

Example 3, Operator checking: Detectability = 5

Example 4, N/A: Detectability = 7

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

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2. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk Control: implement control actions to reduce risk (**Risk Reduction**)

2. Risk Assessment Tools – FMEA

How to create a FMEA table

Elimination *Process Steps, Transfers, etc.*	**Do not ship via this route**
Substitution *Formulation of Process Method*	**Change to a better packaging material**
Reduction *via Enginering Controls, Closed Process, Transfer Devices, etc.*	**Request VUN in the airport**
Administrative and Procedural *Training, Technique, Time, Location, etc.*	**Revise SOP for personnel training**

2. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
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18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Control: reduce risk level to acceptable level (**Risk acceptance**)

3. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS									

3. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6								

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

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3. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1						

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

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3. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1	Temperature monitored by RMS	Automatic	1			

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

3. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1	Temperature monitored by RMS	Automatic	1	6	Not required	N/A

Risk Evaluation Score:
Severity X Probability X Detectability = RPN
6 X 1 X 1 = 6

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

3. Case Study II – Warehouse Humidity

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												

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3. Case Study II – Warehouse Humidity

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Humidity	High excursion	Environmental effect (sunny and raining day)	Impurity, AS		N/A		Humidity monitored by RMS	automatic	1	42		

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

3. Case Study III – Warehouse Vibration

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Vibration	Bulk product breakage	Dropping or bumping of the drum	Appearance	1	Bubble wrap application in the inner drum	1	1. Monitored by packaing operator at packaging site 2. Packaging site QA sampling	Manual	3	3	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

3. Case Study IV – Warehouse Process

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Process	Drum or lid cracking	Improper packaging (piling) of the drums leads to drum or lid cracking	Appearance	1	SOP for equipment safety operation process	3	1. Checked by packaing personnel at warehouse personnel 2. Checked by QA at packaging site	Manual	3	9	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

3. Case Study V – Apron Temperature

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
ULD Area Apron in TPE Airport												
Temperature	High excursoin during Summer	Seasonal environmental effect	Impurity, AS	3	1. Night freight during the period of Apr to Oct 2. VUN requested. The time at the apron is controlled in 1-3 hours 3. Insulated packaging to control temperatre variation	5	TT4 monitoring	Automatic	1	15	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

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3. Case Study VI – Your term

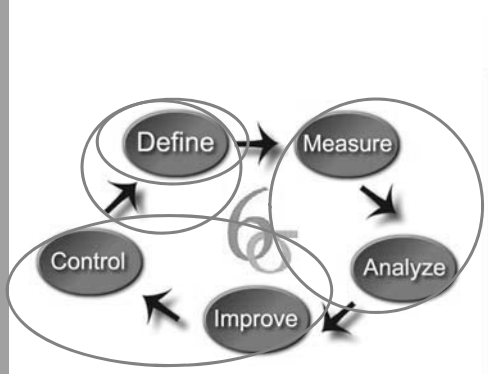
Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

Impax

4. Summary



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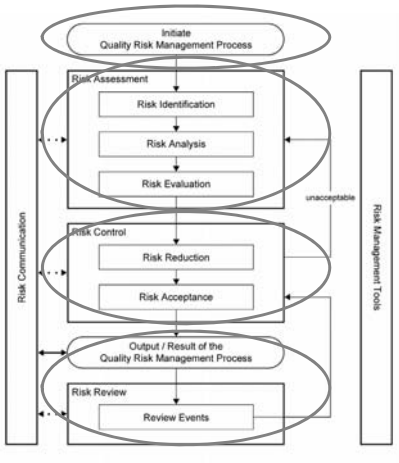
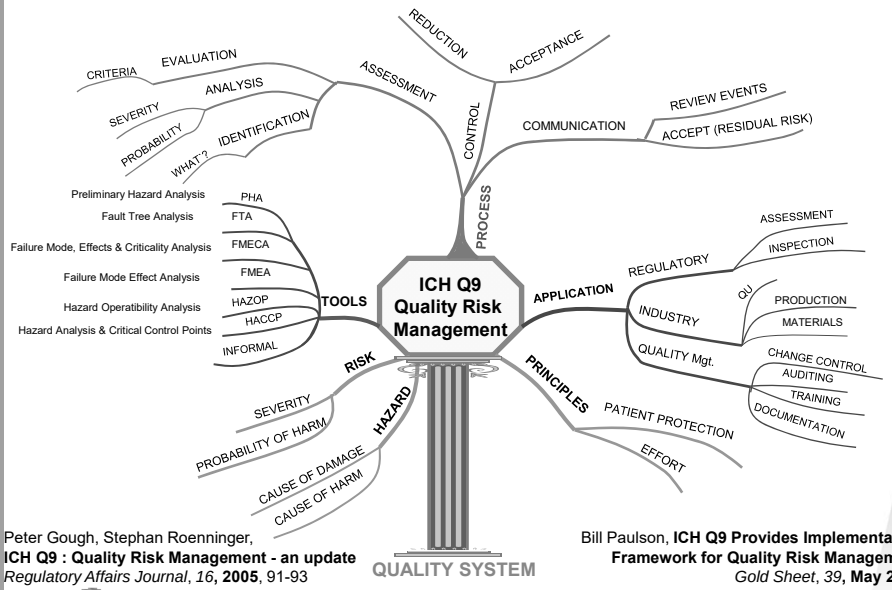


ICH Q9

4. Summary



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Gold Sheet, *39*, **May 2005**

Disclaimer: The ICH Q9 briefing pack is offered as a supplementary explanation of the material in ICH Q9. It was prepared by some members of the ICH Q9 EWG for example only. It has not gone through any ICH formal process. It does not represent an official policy/guidance.

Thank you for your attention

Questions?

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