Application of Quality Risk Assessment on Drug Storage

藥品儲存之品質風險評估應用

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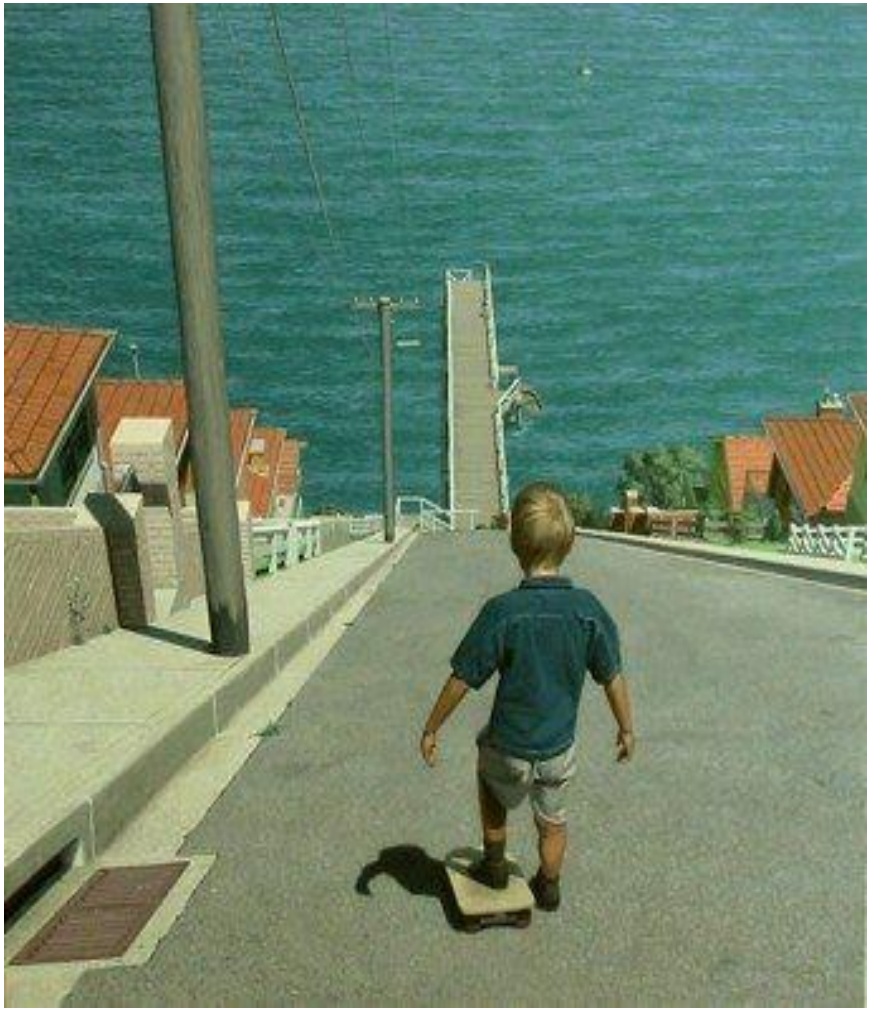
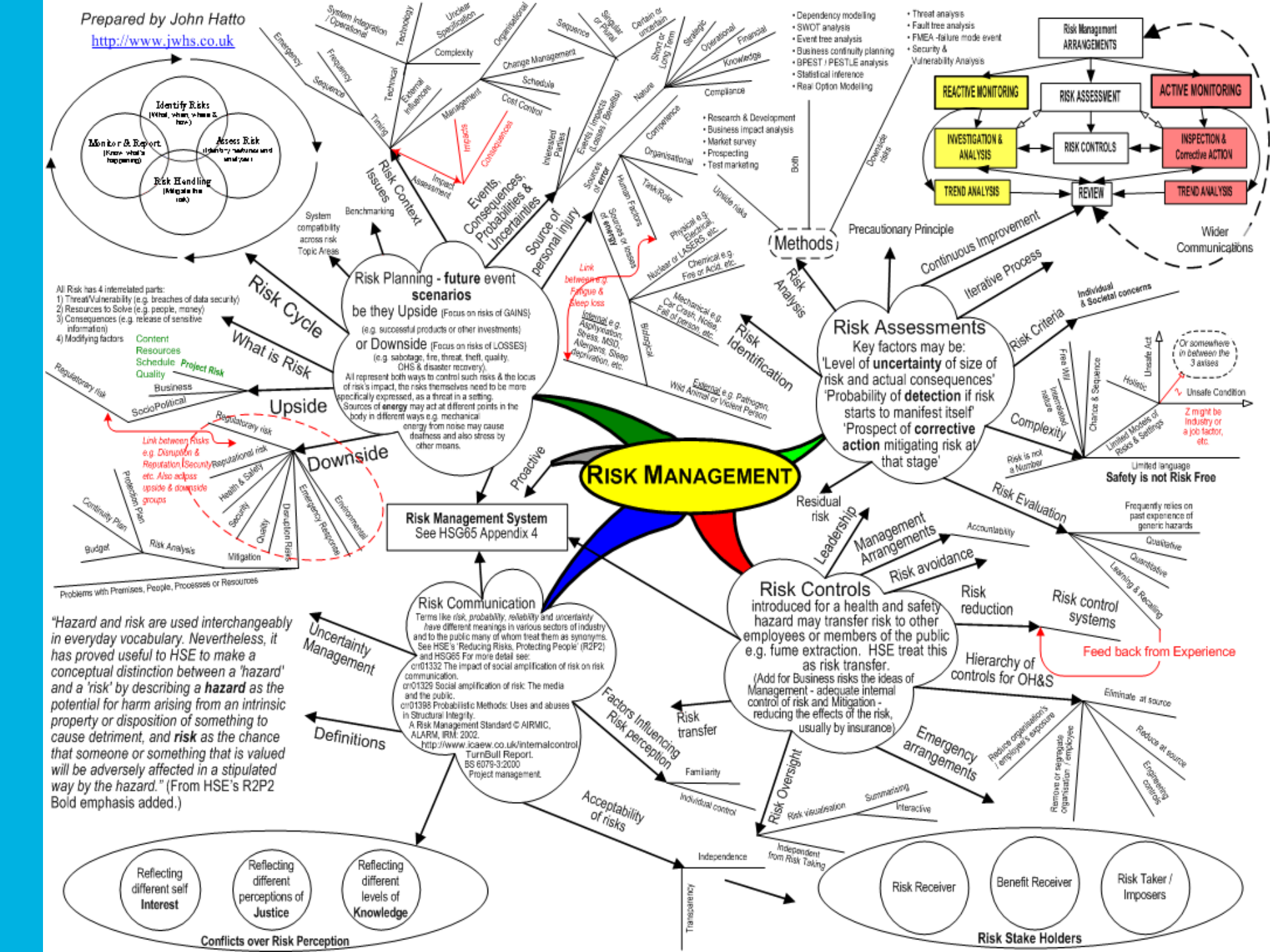
Table of contents

1. Introduction
2. Why we need risk assessment
3. ICH Q9 – Quality Risk Management
4. Risk assessment in GDP
5. Risk assessment tools
6. Case studies
7. Summary

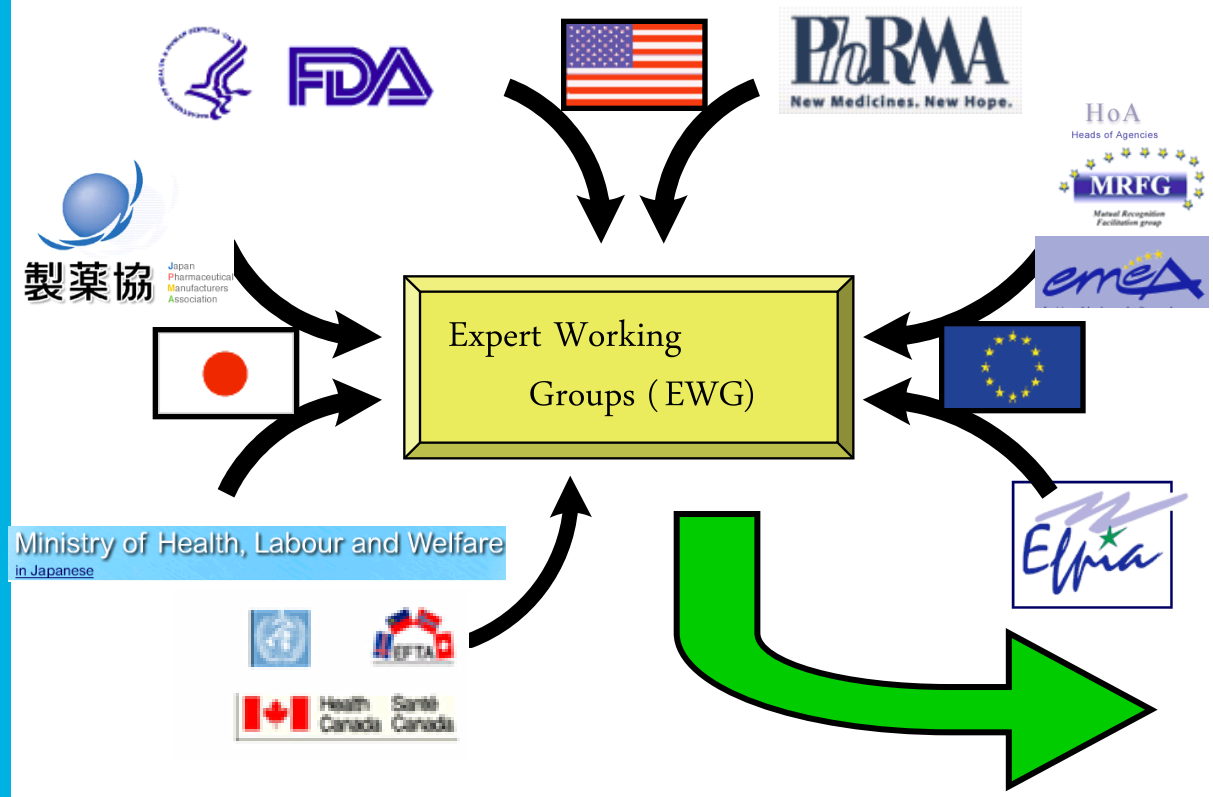
1. Introduction – Risk Assessment 風險評估

What is Risk Assessment?




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*
- *Q*uality

  Chemical and pharmaceutical QA
- *S*afety

  In vitro and in-vivo pre-clinical studies
- *E*fficacy

  Clinical studies in human subject
- *M*ultidisciplinary

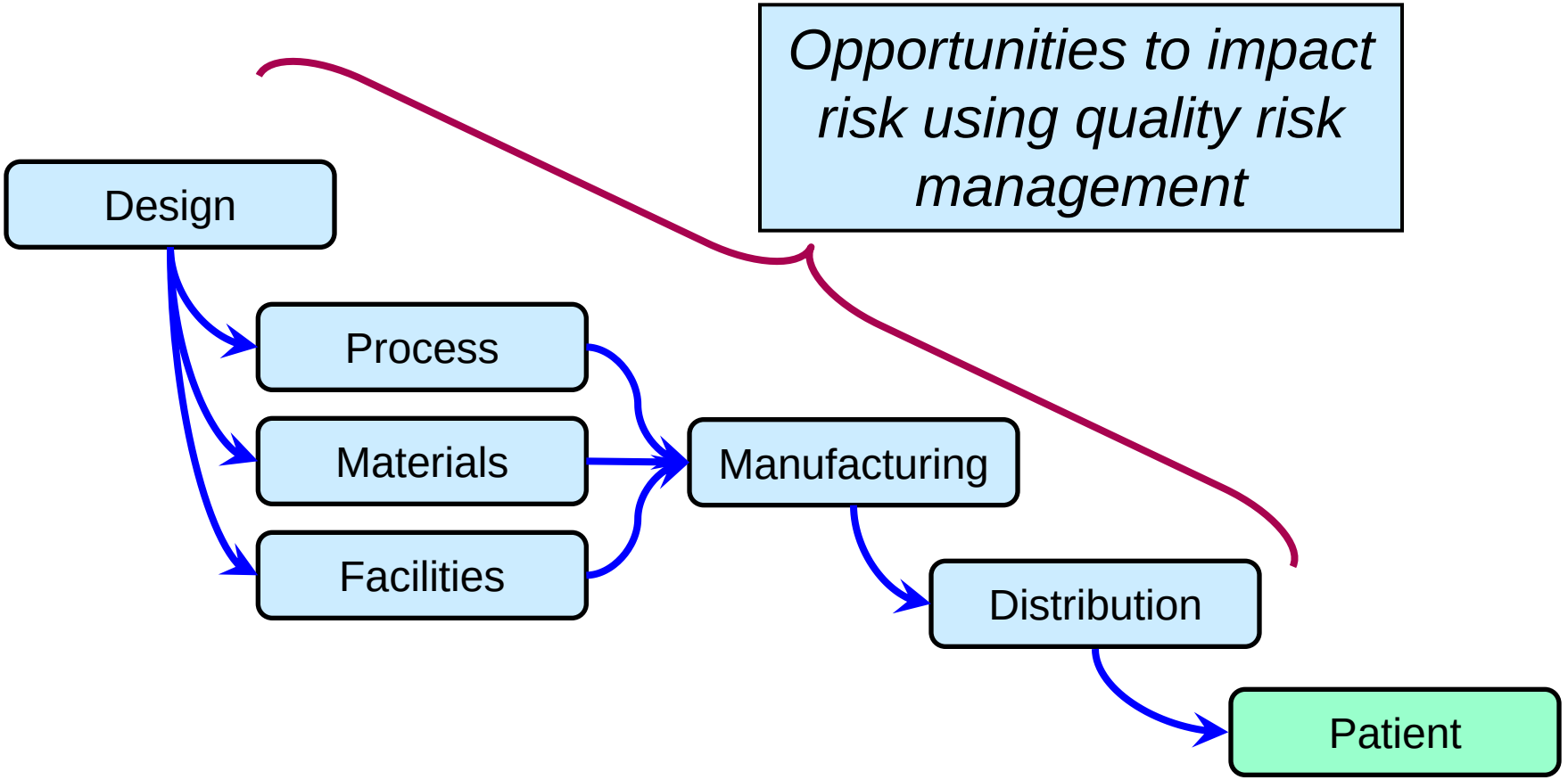
  General topics

Impax

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



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.

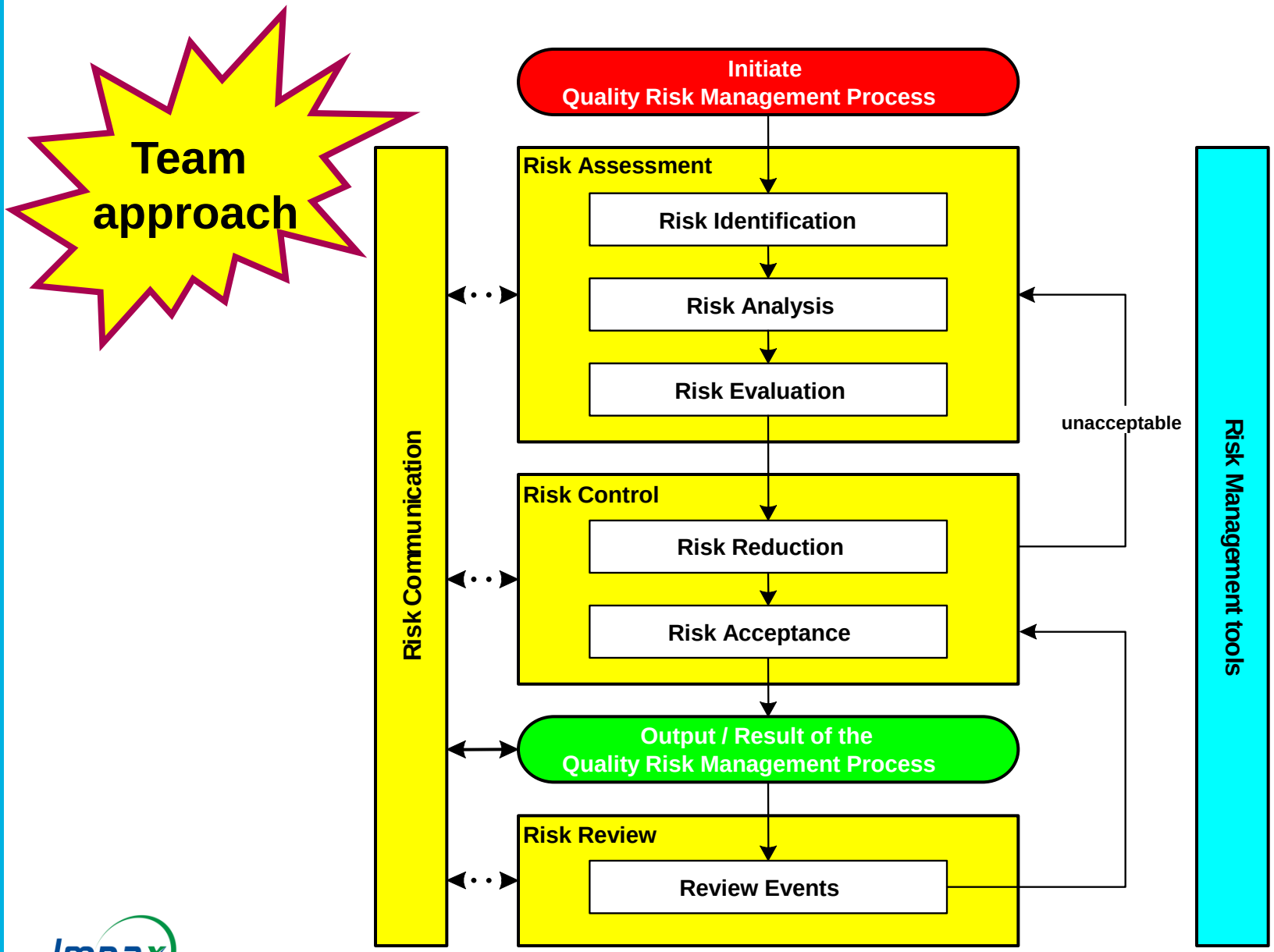
3. ICH Q9 – Principles 原則

Two primary principles:

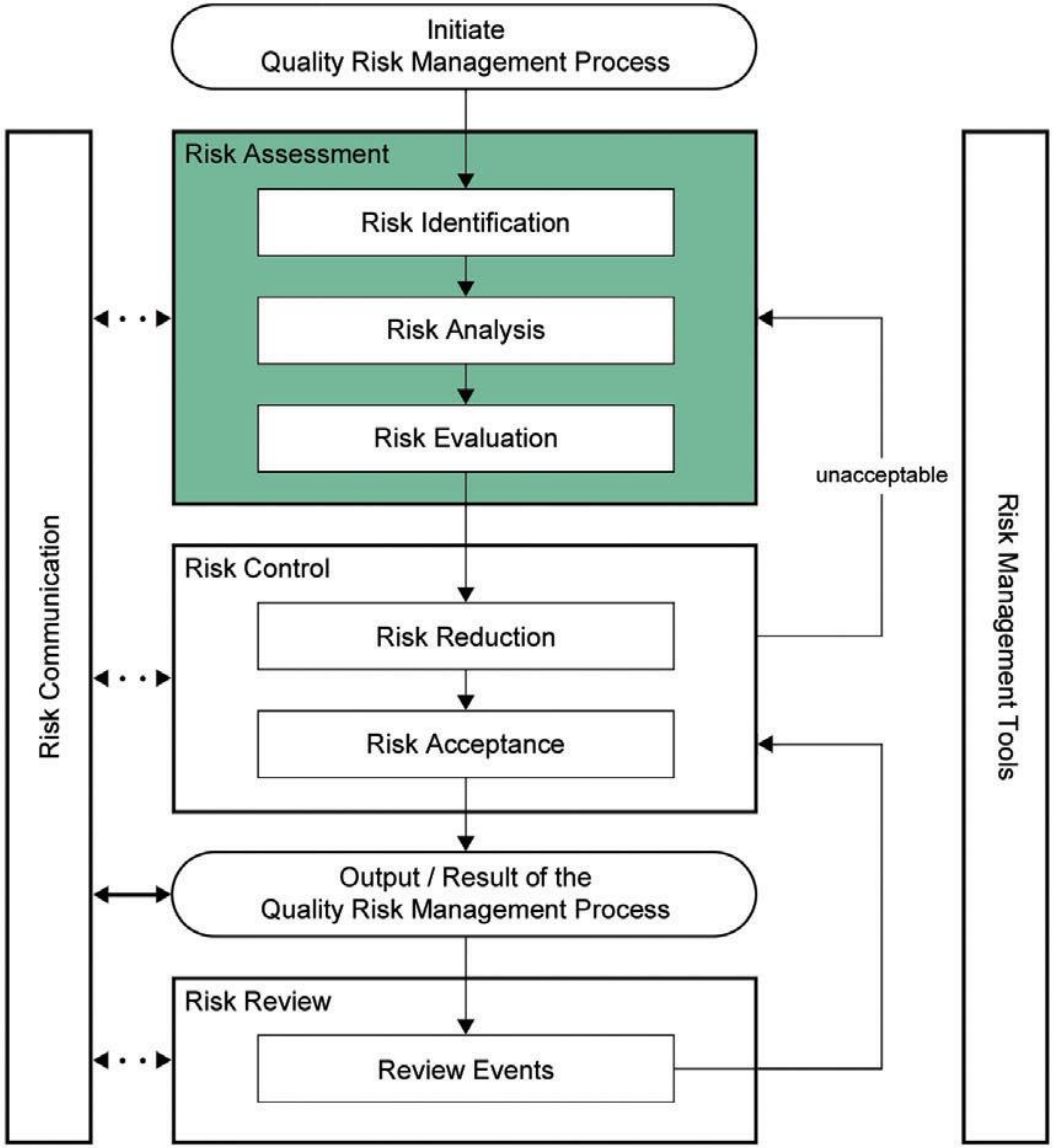
The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

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 – Risk Assessment 風險評估

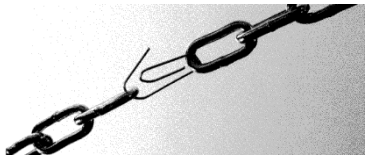


3. ICH Q9 – Risk Assessment 風險評估

- *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!

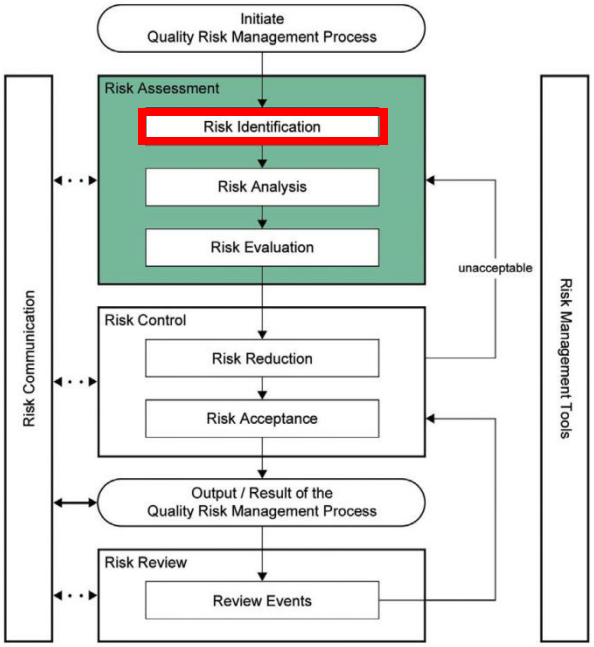
3. ICH Q9 – Risk Assessment



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**

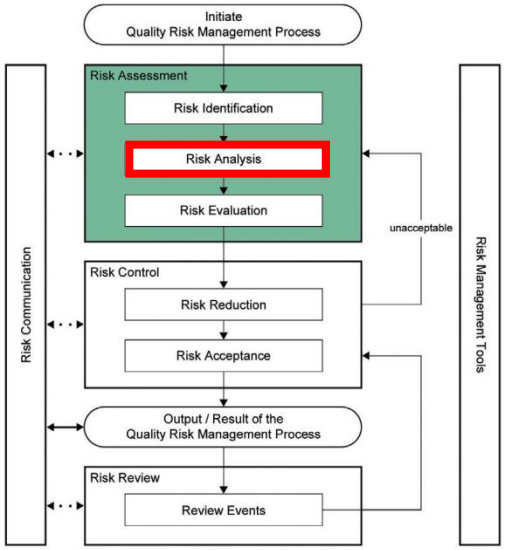


3. ICH Q9 – Risk Assessment

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)

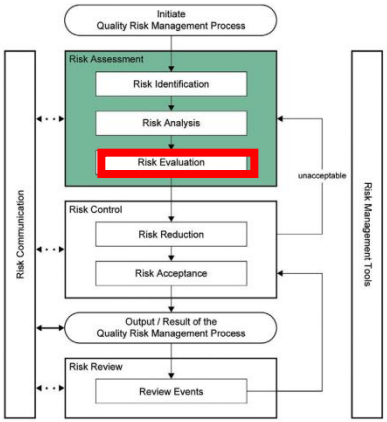


3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation 風險評價

"What is the risk?"

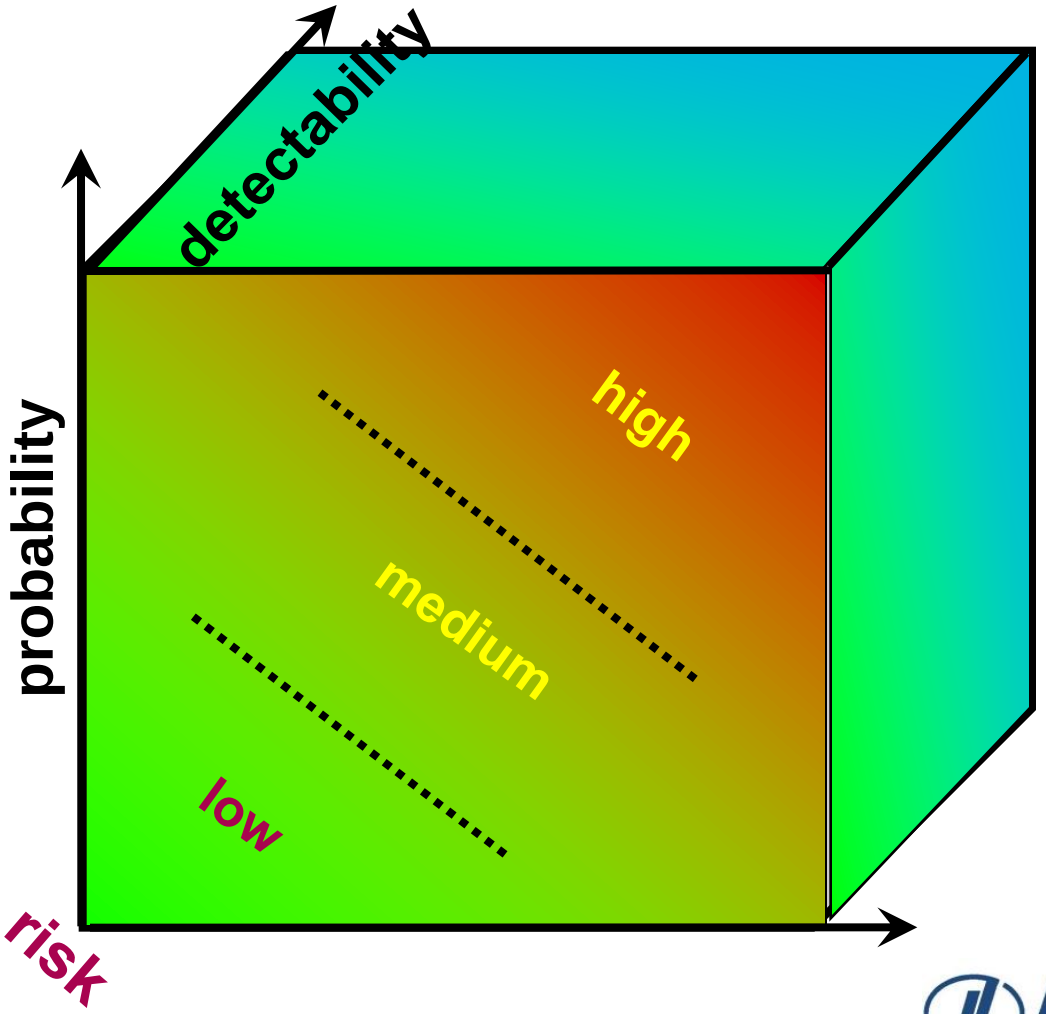
- Compare the identified and analysed risk against given risk criteria
- Consider the strength of evidence for all three of the fundamental questions
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?



3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

Parameters for evaluating risks



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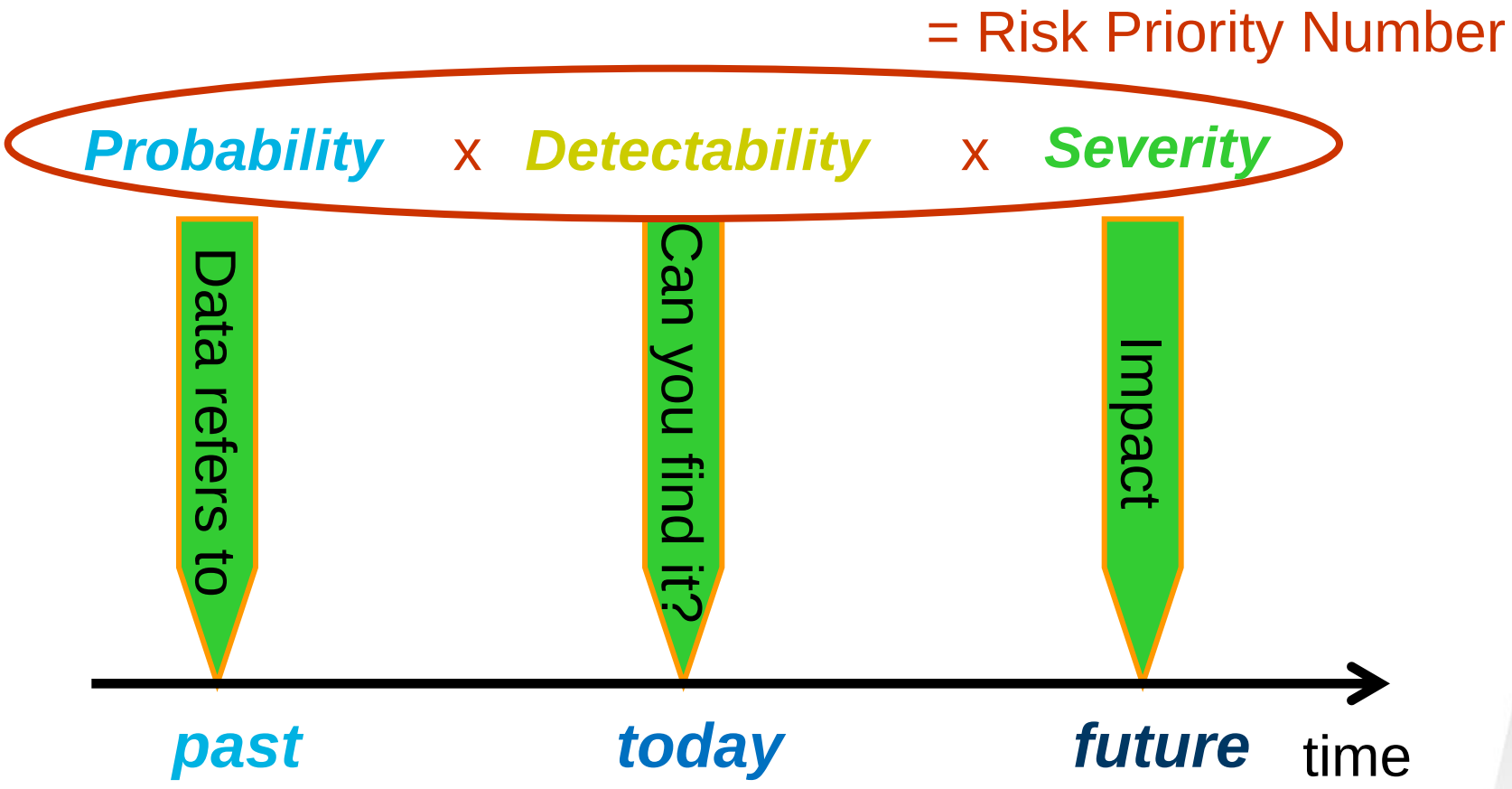
3. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

A picture of the life cycle

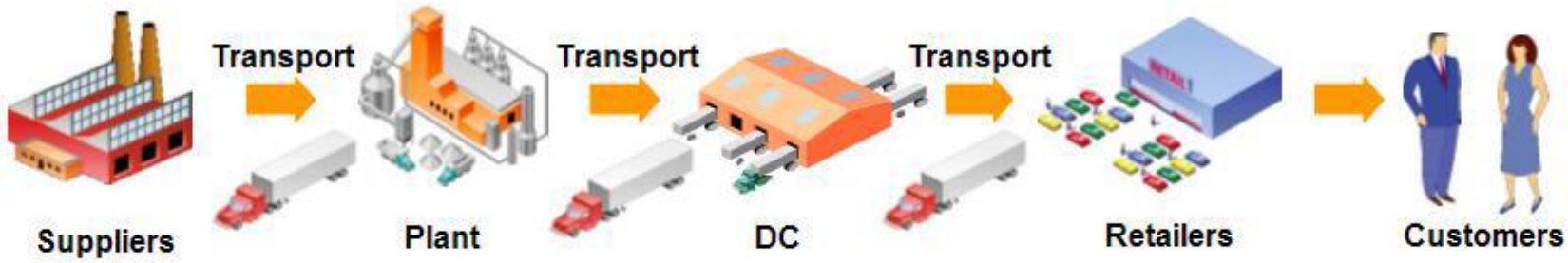


4. Risk Assessment in GDP 優良運銷規範的風險評估

- Risk to assess, control, and review
  - **What are the risk sources?**

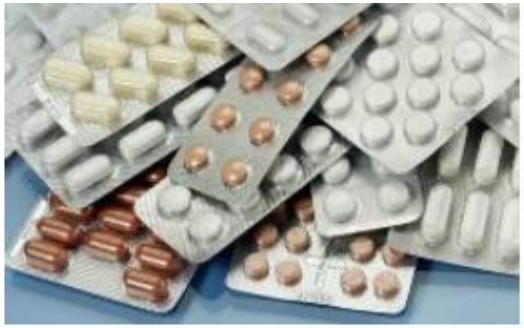
Preface

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.



4. Risk Assessment in GDP

- Risk Sources – Equipment 設備



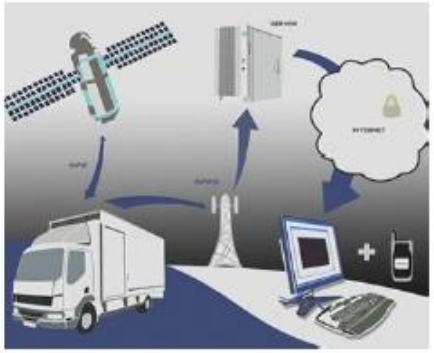
1. Product packaging

2.Storage

3. Shipping container

4. Transport vehicle

5. Monitoring system



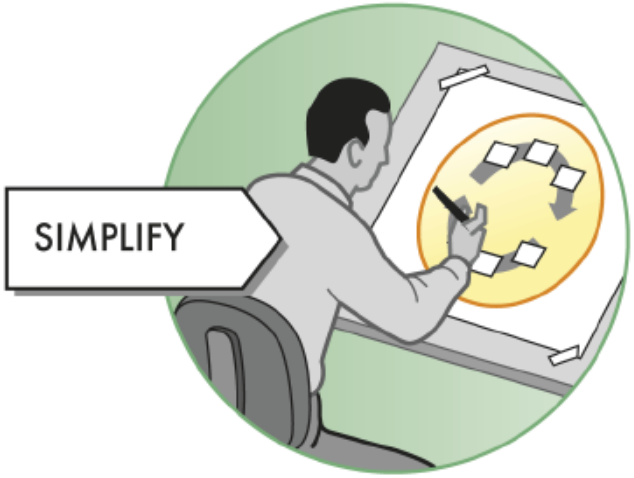
6. Data- and communication system

Equipment and its components must be qualified/validated to eliminate and to reduce the risk of failures.

4. Risk Assessment in GDP

- Risk Sources – Processes 流程

1. Pre-shipment
    - Planning
    - Procedures / SOPs / Process flows
    - Risk assessments
    - Contingency plans
    - Equipment qualification/validation
    - Packout assembly
    - Export documentation
2. In-transit
    - Loading/unloading transport vehicle
    - Transit nodes
    - Cargo handling processes
    - Communication processes
    - Custom inspection/clearance
3. Post-shipment
    - Roles and responsibilities towards temperature excursions
    - Storage of the goods
    - Inventory management



Application of Lean Six Sigma drives continuous improvement of processes and reduces failures

4. Risk Assessment in GDP

- Risk Sources – People 人員

1. Skilled people
   - Knowledge, experience and understanding of equipment, processes and external factors.

2. Unskilled people
   - No or limited knowledge, experience and/or understanding of equipment, processes and/or external factors.

3. Bad actors
   - Skilled or unskilled people who on purpose mislead others and/or mistreat products including theft, counterfeiting and exposure to extreme temperatures.

4. Risk Assessment in GDP

- Risk Sources – People

Types of Human Error

1. Misunderstanding – Teach your written policies and procedures repetitively
2. Forgetfulness – Create a checklist or a Poka Yoke
3. Wrong identification – Mark, label, color, etc., for easy recognition
4. Lack of experience/skill – Improve your hiring or training systems
5. Willful ignoring of rules or procedures – Hold people accountable
6. Slowness – Remove bottlenecks; create standards of performance; measure results
7. Inadvertent or sloppiness – Apply an improvement methodology
8. Lack of standardization – Reduce and simplify; create procedures, templates, etc.
9. Intentional/sabotage/not caring – Warn or terminate the person immediately
10. Surprise – Unexpected, infrequent and random causes are more difficult to eliminate

4. Risk Assessment in GDP

- Risk Sources – External factors 外在環境因素

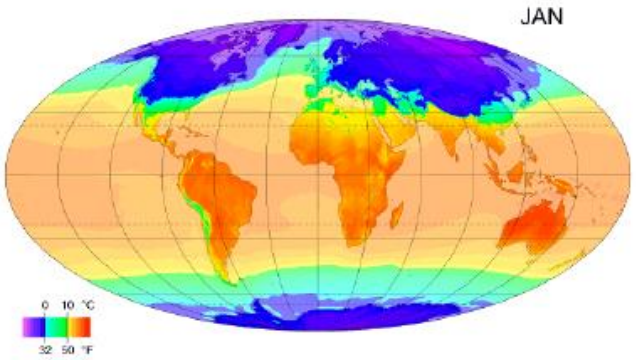
1. Environmental factors
   - Natural disasters
     - Storms
     - Flooding
     - Bush fire
     - Earthquake
     - Volcanic eruption
   - Extreme cold / hot weather
   - Diseases / pandemic
2. Geopolitical factors
3. Economic factors
4. Technological factors
   - Power supply
     - Power failure
     - Power surges (temporary increase in voltage in power lines)
     - Brownouts (power falls below the given amount from the utility)
     - Load shedding (rotating the availability of electricity between all customers)

Contingency plans are critical to handle external risk factors.

4. Risk Assessment in GDP

- Risk Sources – External factors

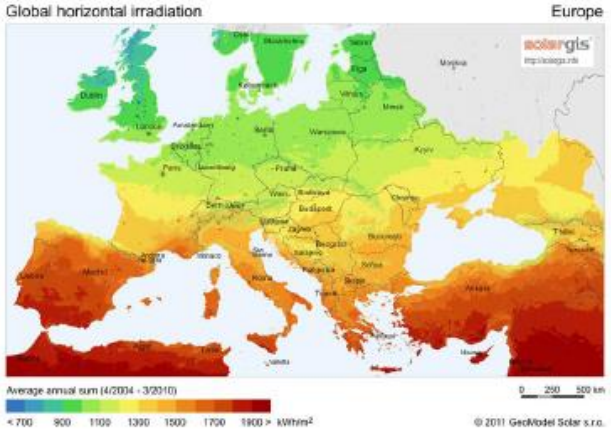
Seasonal variation



Altitude (-6.5 °C per 1000 m)

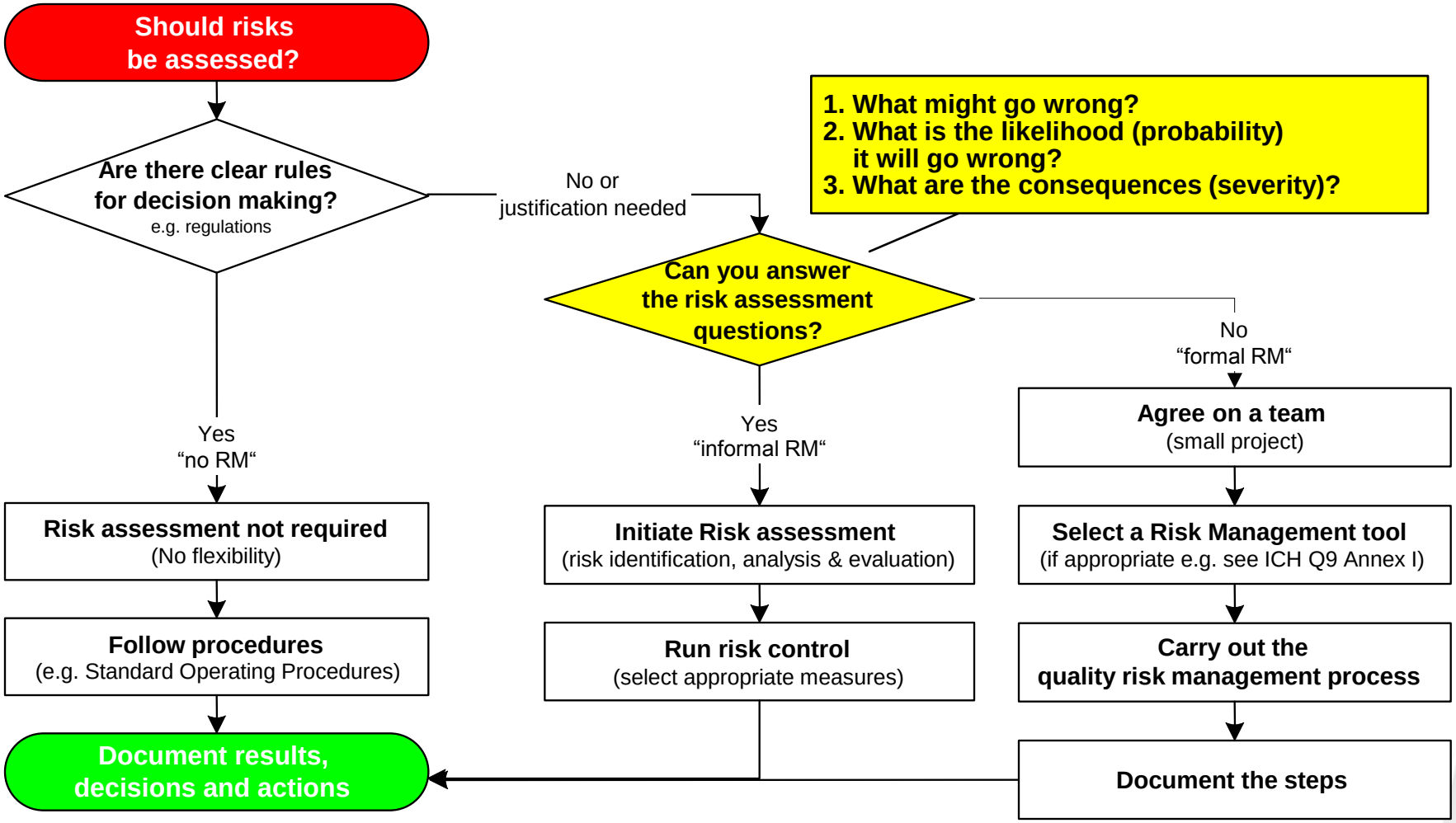
Daily temperature variation

Sun insolation versus latitude



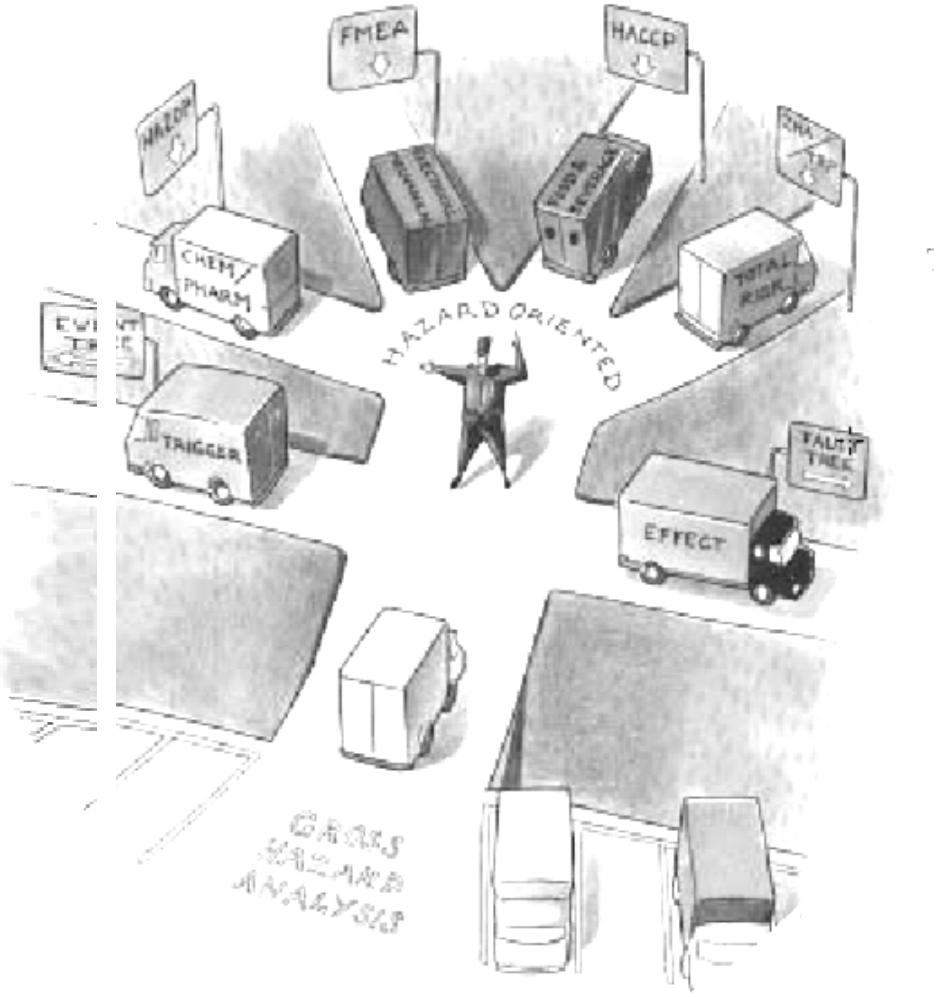
4. Risk Assessment in GDP

- When to apply Risk Assessment



Based on K. Connelly, AstraZeneca, 2005

5. Risk Assessment Tools 風險評估工具

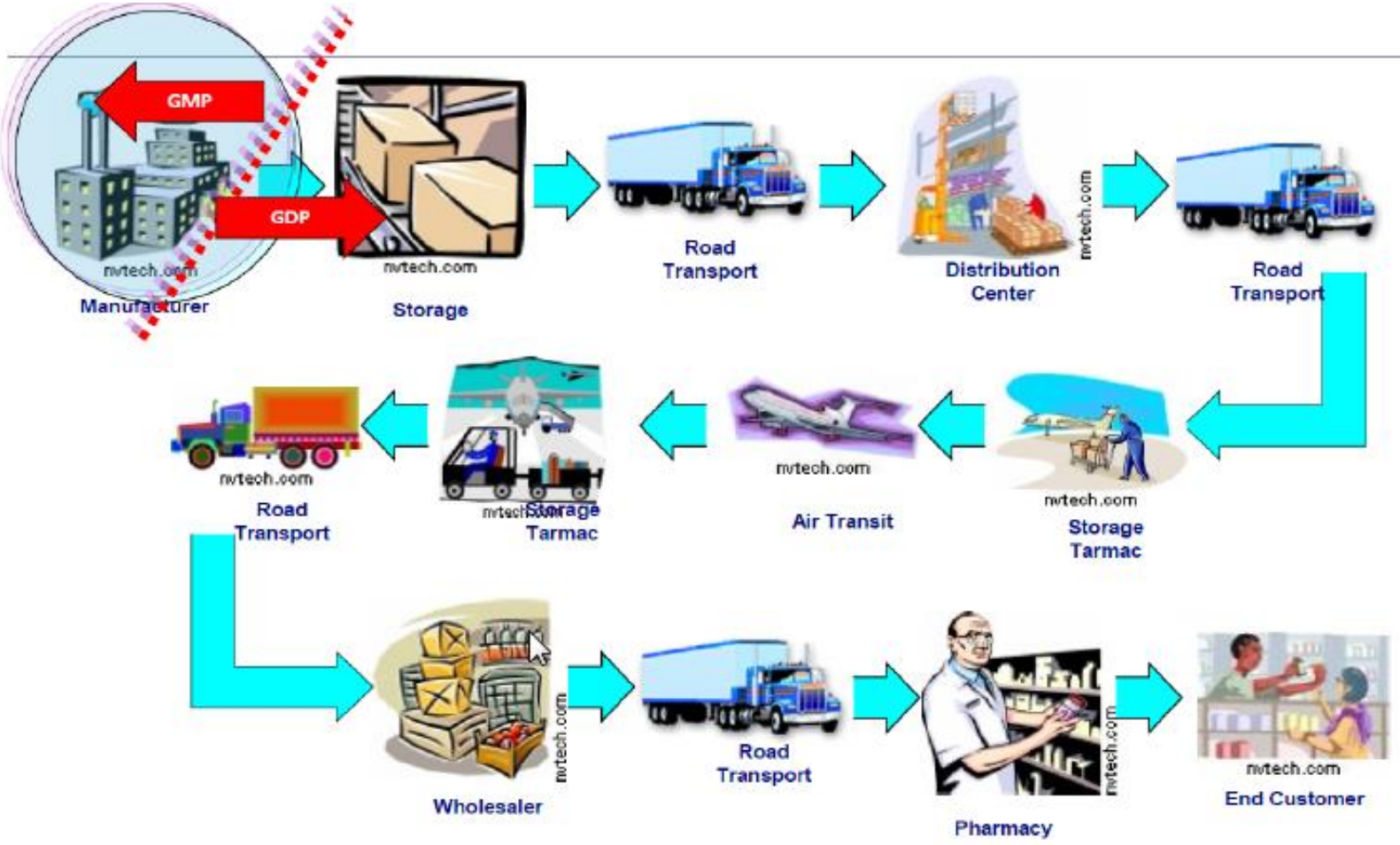


One method “all inclusive”?

5. Risk Assessment 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

5. Risk Assessment Tools – Process map 流程圖



5. 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

5. 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

5. 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

5. 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

5. Risk Assessment Tools – FMEA

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

Decrease Detectability

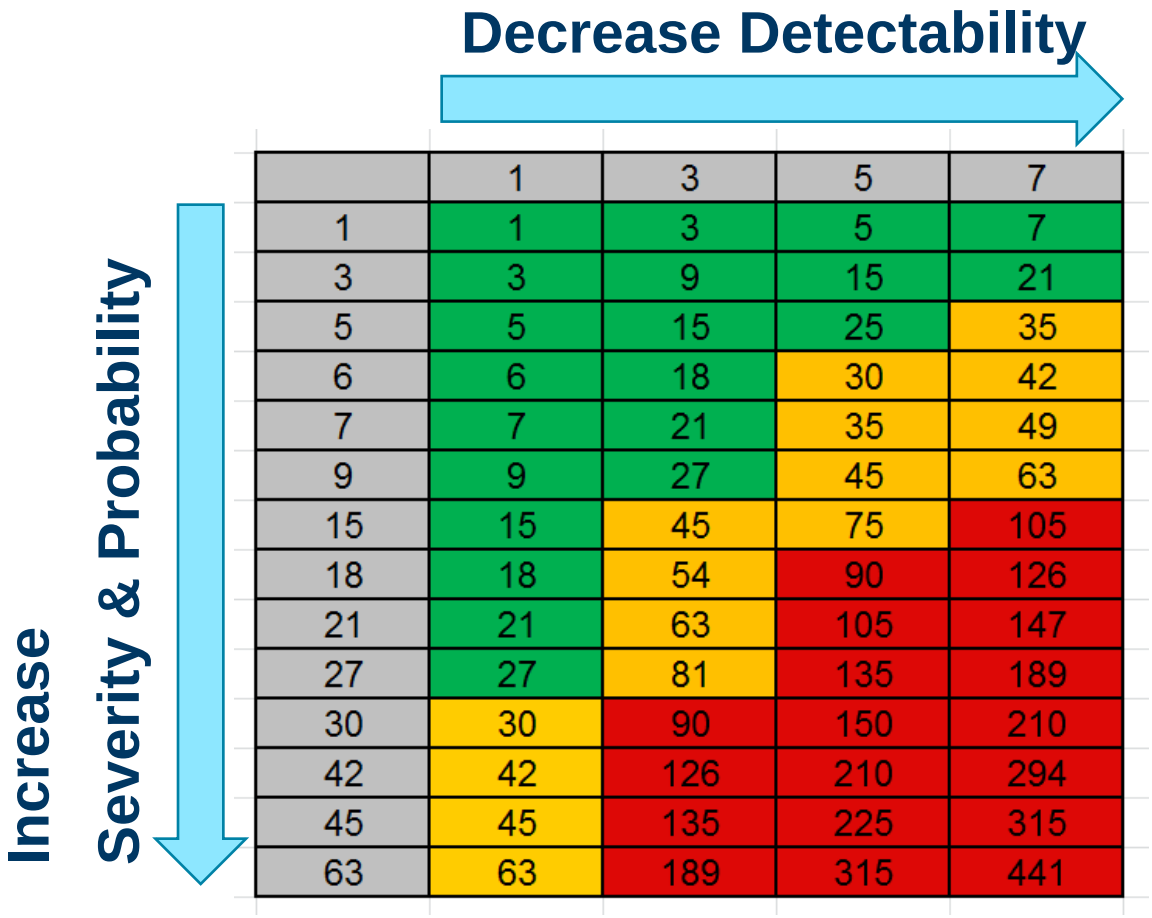
Increase Severity & Probability

	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

5. 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

5. Risk Assessment Tools – FMEA

How to design a FMEA table

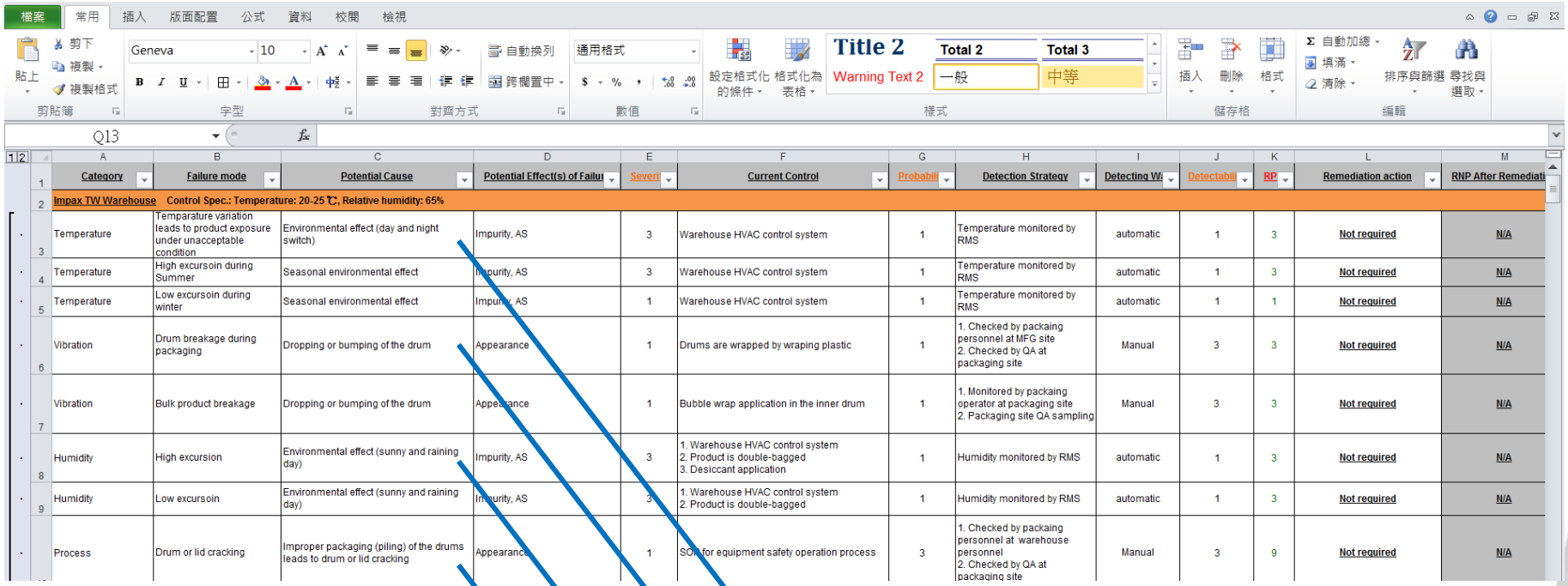
Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk sources (phenomena and root cause)

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

5. Risk Assessment Tools – FMEA

How to create a FMEA table



	Category	Failure mode	Potential Cause	Potential Effect(s) of Failu	Severi	Current Control	Probabili	Detection Strategy	Detecting W	Detectabili	RP	Remediation action	RNP After Remediati
2	Impax TW Warehouse	Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%											
3	Temperature	Temparature variation leads to product exposure under unacceptable condition	Environmental effect (day and night switch)	Impurity, AS	3	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	3	Not required	N/A
4	Temperature	High excursoin during Summer	Seasonal environmental effect	Impurity, AS	3	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	3	Not required	N/A
5	Temperature	Low excursoin during winter	Seasonal environmental effect	Impurity, AS	1	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	1	Not required	N/A
6	Vibration	Drum breakage during packaging	Dropping or bumping of the drum	Appearance	1	Drums are wrapped by wraping plastic	1	1. Checked by packaing personnel at MFG site 2. Checked by QA at packaging site	Manual	3	3	Not required	N/A
7	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
8	Humidity	High excursion	Environmental effect (sunny and raining day)	Impurity, AS	3	1. Warehouse HVAC control system 2. Product is double-bagged 3. Desiccant application	1	Humidity monitored by RMS	automatic	1	3	Not required	N/A
9	Humidity	Low excursoin	Environmental effect (sunny and raining day)	Impurity, AS	3	1. Warehouse HVAC control system 2. Product is double-bagged	1	Humidity monitored by RMS	automatic	1	3	Not required	N/A
	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

Temperature

Vibration

Humidity

Process

5. 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

5. Risk Assessment Tools – FMEA

Example 1, Drum appearance: Severity = 1

Example 2, API Degradation: Severity = 3

Example 3, Low toxic impurity: Severity = 6

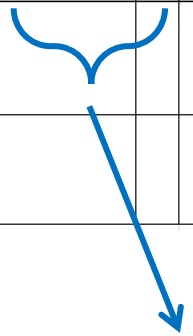
Example 4, High toxic impurity: Severity = 9

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

5. 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

5. 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

5. 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

5. Risk Assessment Tools – FMEA

Example 1, Temp logger: Detectability = 1

Example 2, QA and Operator checking: Detectability = 3

Example 3, Operator checking: Detectability = 5

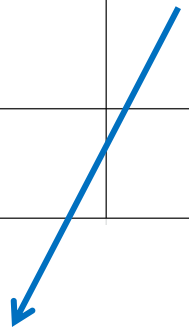
Example 4, N/A: Detectability = 7

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

5. 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**)

5. Risk Assessment Tools – FMEA

How to create a FMEA table

Do not ship via this route

Change to a better packaging material

Request VUN in the airport

Revise SOP for personnel training

5. 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
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 Control: reduce risk level to acceptable level (**Risk acceptance**)

6. 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. 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

6. 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

6. 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

6. 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

6. 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%											

6. 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		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

6. 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

6. 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

6. 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

Impax

6. Case Study VI – Your term

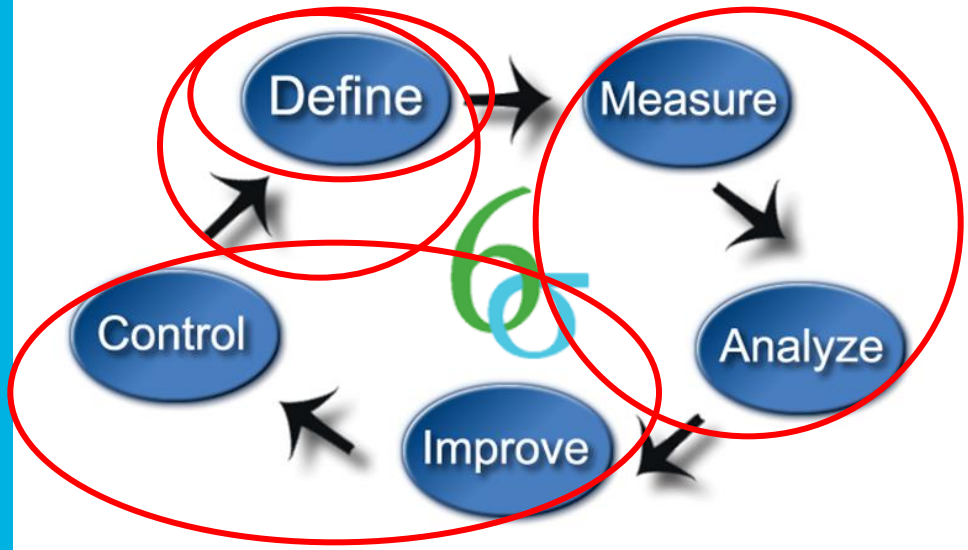
Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

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

7. Summary



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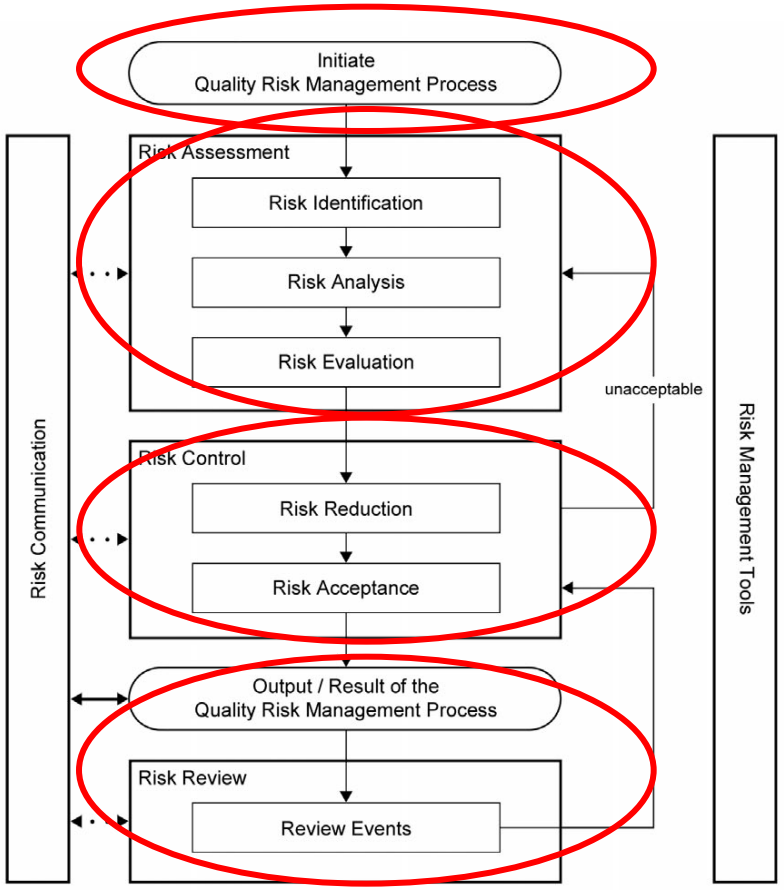
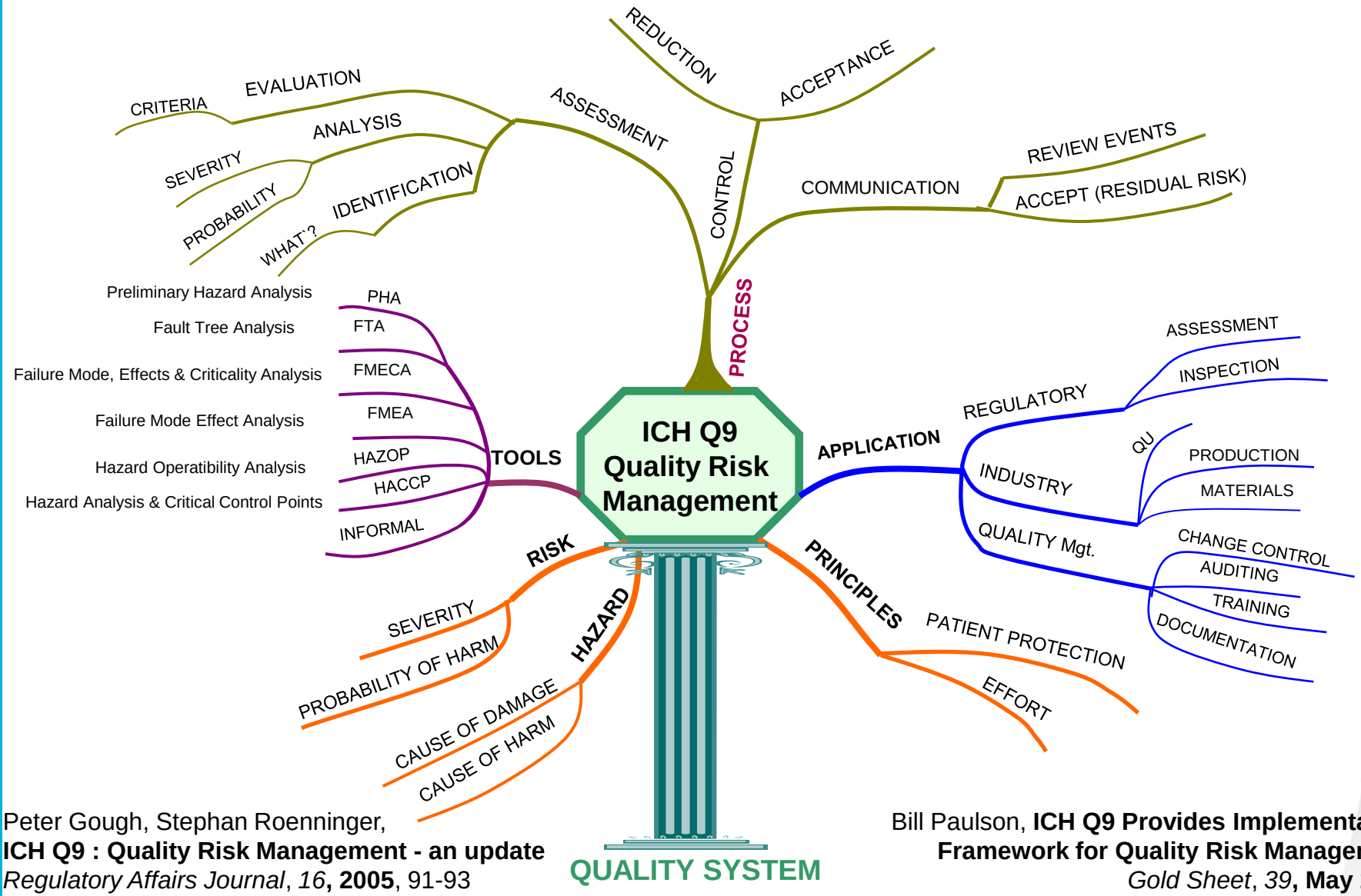


ICH Q9

7. Summary



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Thank you for your attention

Questions?