106TPDA04014

衛生福利部食品藥物管理署委辦計畫

「推動新興生醫產品GMP評鑑符合性計畫」

新興生醫產品 GMP 訓練活動(3)、(4)

日期：民國 106 年 6 月 13 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

張華盛 GMP 專家/社團法人中華無菌製劑協會

時 間 表

時 間	內 容	講 師
8:30-9:00	報 到	
9:00-9:10	長 官 致 詞	TFDA 風管組代表
9:10-10:30	➢ ICH Q8：Pharmaceutical Development 說明 ➢ ICH Q9：Quality Risk Management 說明	TPDA 張華盛 GMP 專家
10:30-10:50	休 息	
10:50-12:10	➢ ICH Q9：Quality Risk Management 說明(續) ➢ ICH Q10：Pharmaceutical Quality Systems 說明	TPDA 張華盛 GMP 專家
12:10-13:10	午 餐	
13:10-14:30	➢ 電腦化系統確效	TPDA 張華盛 GMP 專家
14:30-14:50	休 息	
14:50-15:50	➢ 數據完整性	TPDA 張華盛 GMP 專家
15:50-16:10	交 流 討 論	TFDA 風管組代表 及講師
16:10-16:30	課 後 測 驗	

目　　錄

頁次

ICH Q8/Q9/Q10, CSV & Data Integrity

ATMPs / HCT/Ps training course

2017 Jun 13th

Jack Chang

Content 內容

- ICH Q8:Pharmaceutical Development
  藥品開發
- ICH Q9:Quality Risk Management
  品質風險管理
- ICH Q10:Pharmaceutical Quality Systems
  製藥品質系統
- Computerized System Validation
  電腦化系統確效
- Data Integrity
  數據完整性

Evidence:
Data & Records

Safety

Efficacy

Do not place patients at **risk** due to inadequate:
Safety, Quality and Efficacy.

GMP principle

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「品質-安全-風險」

安全是指系統在一定的條件之下，以一可接受的風險等級運作的品質表現

Safety is … the **quality** of a system that allows the system to function under predetermined conditions with an acceptable level of **risk**.

- 美國FAA的飛航標準安全資訊分析中心（FSAIC）

Safety

Efficacy

Quality

ICH Guideline

•…
•Q8
•Q9
•Q10
•…

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E-platform_Data flow - Data Integrity for GxP

Throughout product Lifecycle 貫穿產品生命週期 (ICH Q12 LCM)

(ICH Q11)

Pharmaceutical Development 藥品開發 → Technology Transfer 技術轉移 → Commercial Manufacturing 商業化生產 → Product Discontinuation 產品終止

ICH Q8 QbD

Investigational products 研究用產品

GMP

Goals 安全 S 有效 E 品質 Q

ICH Q10 PQS

Scientific based
Risk based
Knowledge based
System based

Approach

PQS要素

Action (CA/PA) System
CA/ PA) 制度
Change Management System / Management Review
變更管理制度 / 管理審查

ISO 9000

Enablers 驅動因素

Knowledge Management 知識管理

Quality Risk Management 品質風險管理 ICH Q9 QRM

Continual Improvement 持續改進

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Link Back to Patient Risk
QRM throughout the product lifecycle

Pharmaceutical Development 藥品開發 → Technology Transfer 技術轉移 → Commercial Manufacturing 商業化生產 → Product Discontinuation 產品終止

Design 設計

Process 製程

Materials 物料

Facilities 廠房

Manufacturing 生產

Distribution 銷售

Patient 病患

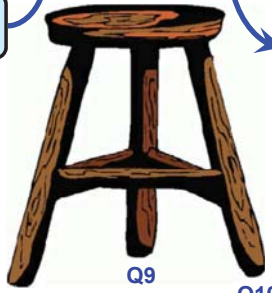
Opportunities to impact risk using quality risk management
使用品質風險管理影響風險的機會

QRM

Reduce Risk

QbD

PQS



Q8(R2) Q9 Q10 Q11/Q12

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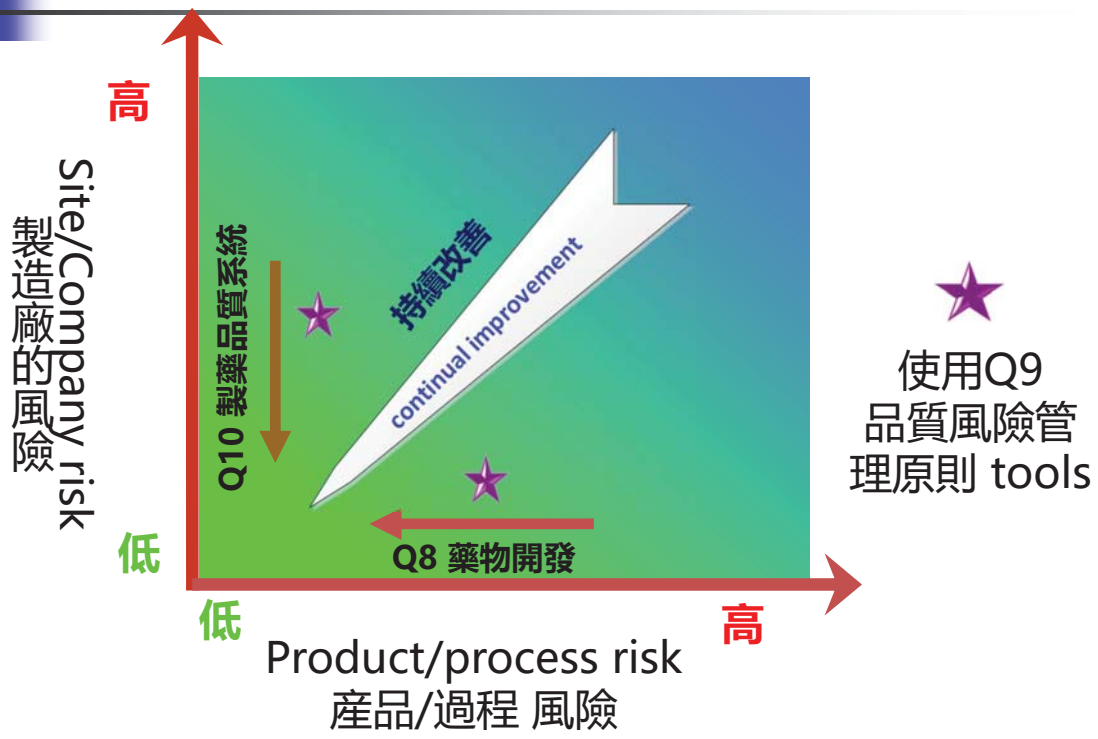
ICH Q8/Q9/Q10 relevant
相互參照



使用Q9
品質風險管
理原則 tools

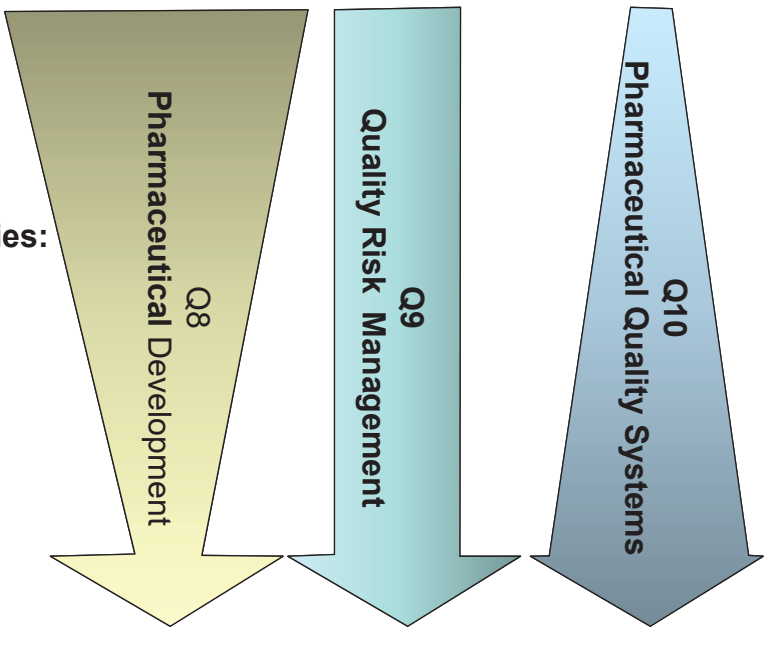
Base: J. Ramsbotham, Solvay Pharm. NL / EFPIA

How ICH Q8, Q9 and Q10
Working together

Formulation Activities:
- QTPP Definition
- Pre-Formulation Studies
- Formulation Screening
- Optimization & Selection

Process Development Activities:
- Process Screening
- Lab Scale Development
- Scale-Up Studies

Manufacturing Activities:
- Commercial Scale Manufacturing
- Batch Release
- Continual Verification & Improvement



ICH Q8
"Pharmaceutical Development"
QbD

"藥品開發"

ICH Q8 intent

- Scientific/Risk/Knowledge based approach
- QbD – Design space, Control strategy…etc
- PAT – real time control CPPs …
- Real time release testing = RTRT (Product = Process)
- New validation model → connect with OQ?

GMP製造 就這麼簡單

Input

機 料

人流
物流
數據流

MACHINES MATERIALS

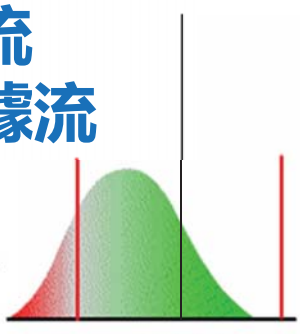
環境

過程

ENVIRONMENT

MANPOWER METHODS

人 法



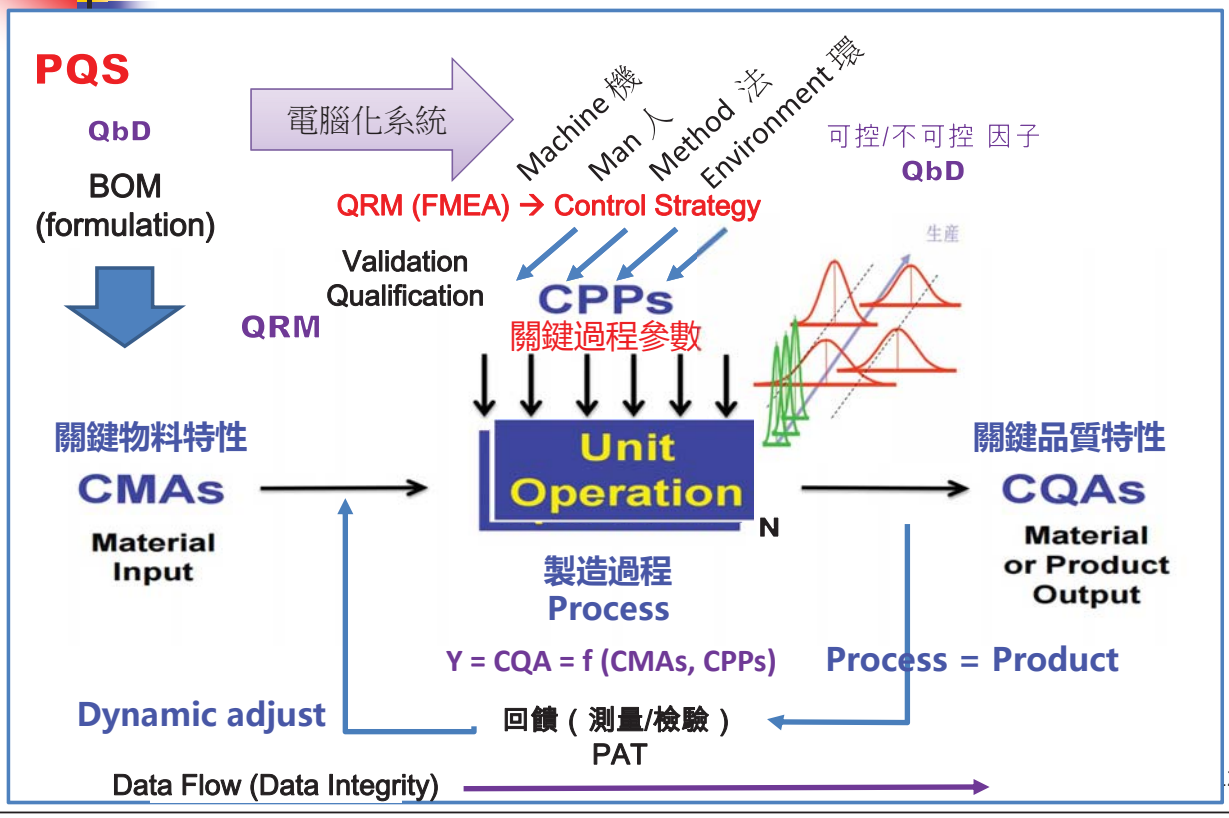
製程能力 Cpk

COQs,→Q/C/D/S

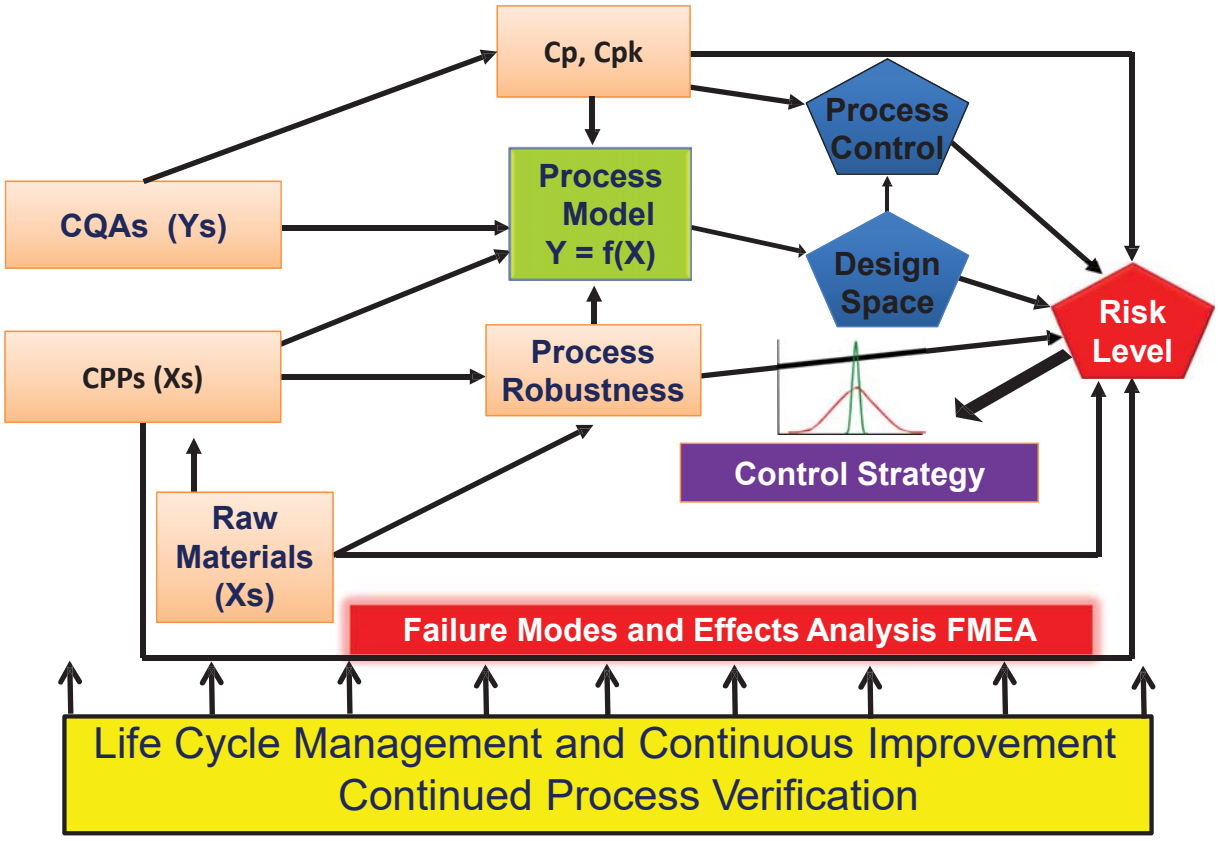
CPPs, CCP

Output

How GMP operations



How QRM work during LCM?



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QPTT – 目標產品品質要求

- QPTT是產品開發設計的基礎，通常包括：
  - Clinical setting (臨床方式），給藥途徑，劑型，輸送系統
  - 劑量（dosage strength）
  - 包裝系統（container closure system）
  - 影響藥品代謝動力學的特性（release，delivery，dissolution aerodynamic performance）
  - 產品品質指標（無菌，純度，安定性，釋放型式 ...等）

QbD 開發的流程 - ICH Q8

- 首先建立所要開發的產品的 QTPP (Quality Target Product profile) – Quality, Safety, Efficacy
- 確定潛在的 CQAs (Critical quality attributers)-C&E matrix 因果矩陣 + Flow_map
- 通過風險分析找出可能影響 CQAs的物料屬性 (CMA) 和關鍵製程參數 (CPPs) - FMEA
- 通過DOE實驗建立 Design Space 數學模式
- 建立和實施管控策略 CCP and PAR (Proven Acceptable Range) – Control plan (PAT detection?)
- 在產品的生命週期內進行不斷地改進 CIP

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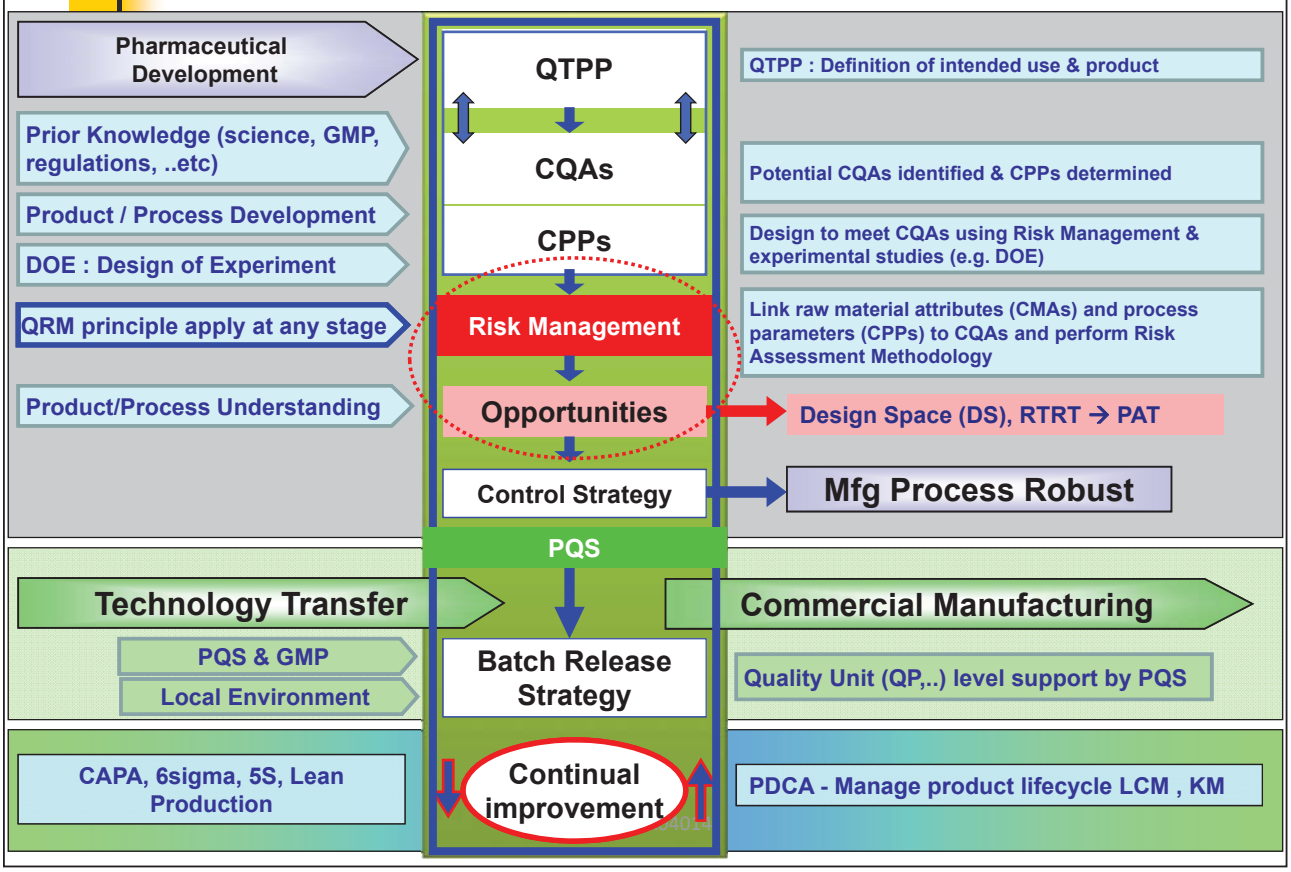
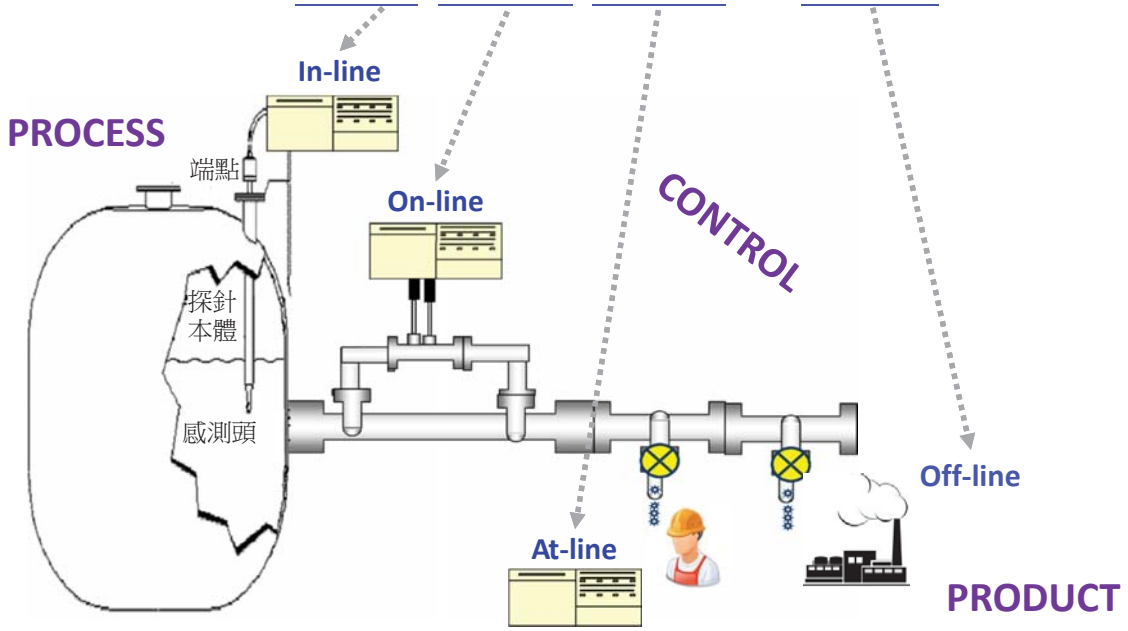
Key Steps for a product under QbD



PAT – Real Time analysis
Process control = Product control

What are In time, on time, at time and off time test?



Real time release testing=RTRT → PAT → In-process tests in lieu of end product testing (FDA)

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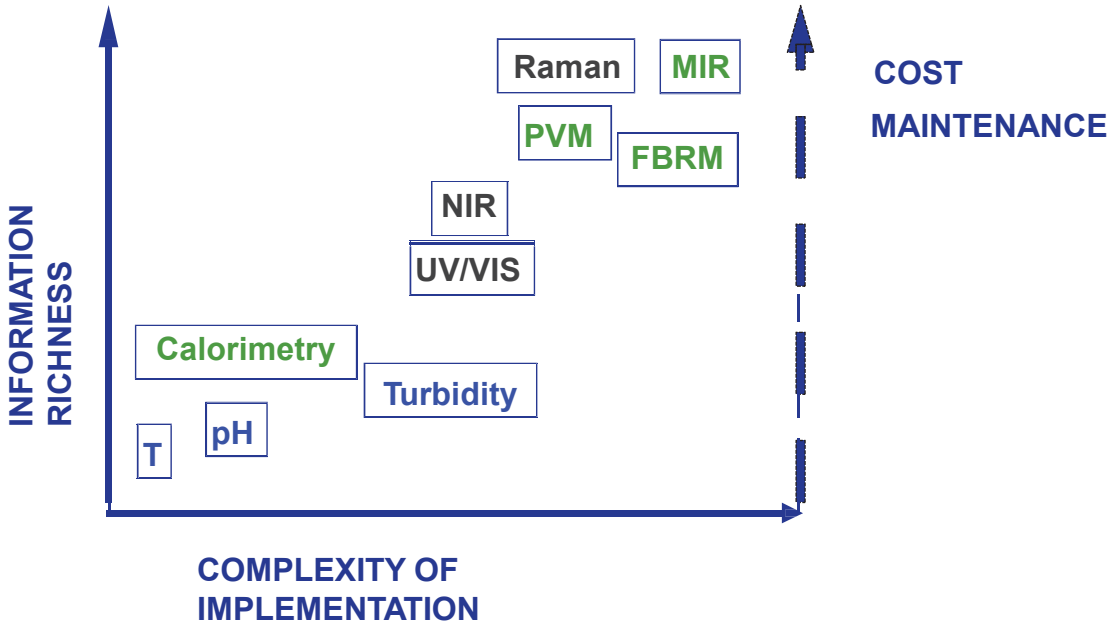
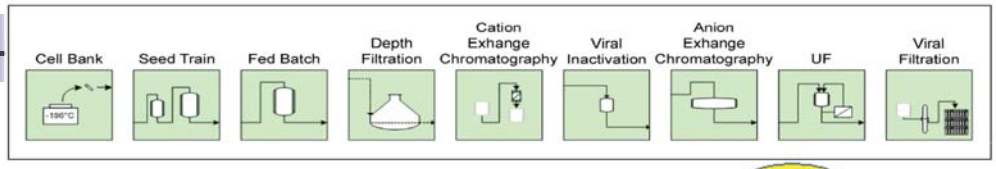
PAT approach
Some sensors example



Fermentation Process example
RM - CQA/CPP…



- Concentration

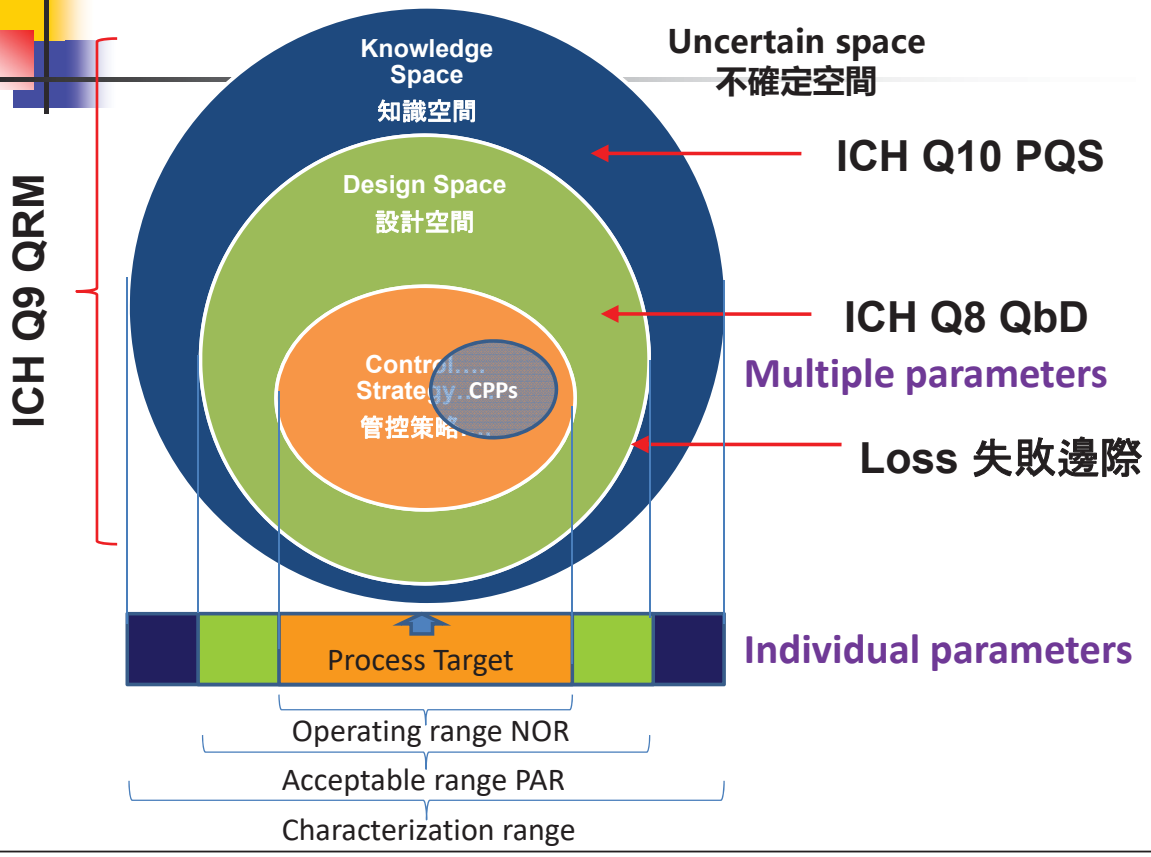
9	9	9	9	3	3	9	1	1	1	3	9	9	9	9	9
Mycoplasma	Vial Contamination	Identity	Acidic Variant Levels	Yield	Concentration (UV Assay)	Purity Assay (HPLC)	Visual Appearance	Osmolality	pH	Purity	Residual Host Cell Protein	Residual Host Cell DNA	Bioburden	Endotoxin	Viral Clearance

- Cleaning
- Bi-product
- Speed
- Contamination
- Etc…

電腦化系統各類參數測量 CPPs by PAT
Application on bio-pharmaceutical

參數 P	感測器 Sensors	參數 P	感測器 Sensors
溫度 T	熱電偶、熱敏電阻、鉑電阻溫度計	D_{CO2}	CO_2電極、膜管傳感器
罐內壓力	隔膜式壓力錶	醇類物質濃度	生物感測器、膜管傳感器
氣體流量	轉子流量計、熱品質流量計、孔板流量計	各種培養基組分、代 謝產物濃度	生物感測器
攪拌轉速 S	轉速感測器	NH_4^+	氨離子電極、生物傳感器、氨電極
攪拌功率 W	應變計		
料液量 q	測力感測器	金屬離子濃度	離子選擇性電極
氣泡 b	接觸電極	排氣中的P_{O2}	熱磁氧分析儀、氧化鋯氧分析儀
流加物料流量 m	轉速感測器		
pH	複合玻璃電極		
氧化還原電位	複合鉑電極	排氣中的P_{CO2}	紅外氣體分析儀
D_O	複膜氧O_2電極、膜管傳感器	培養液濁度或菌體濃 度	光導纖維法、等效電容法

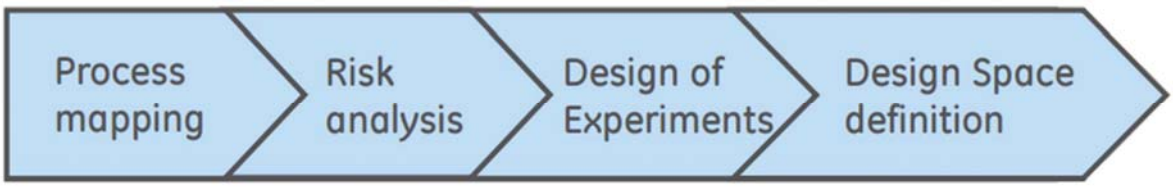
Process Understanding



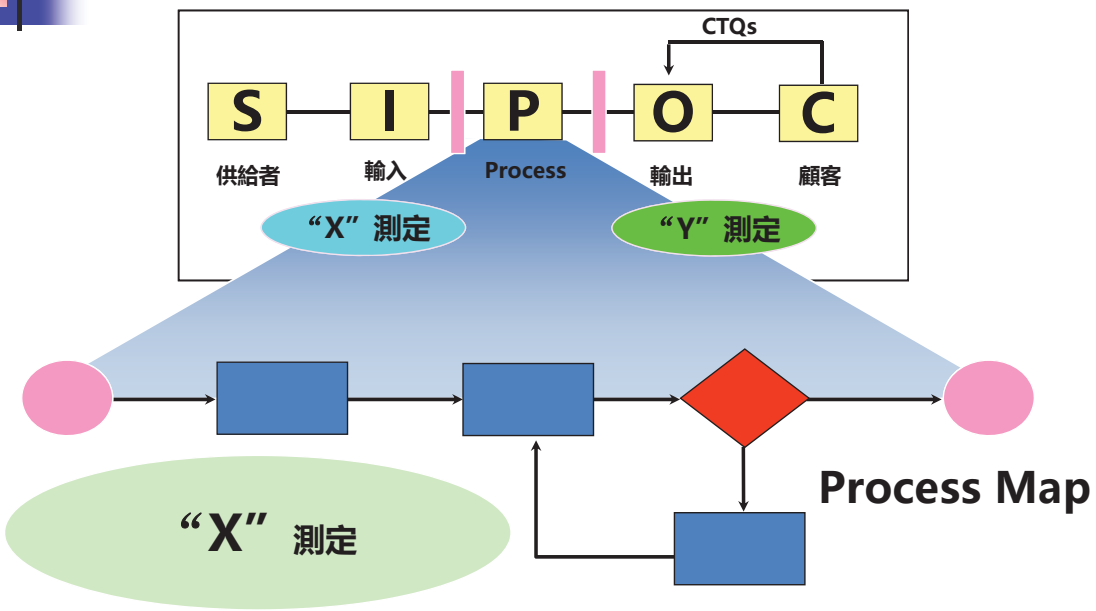
QbD workflow
Defining the process design space

Four key steps

1. Process mapping
2. Risk analysis (e.g. FMEA)
3. Design of experiments (DoE)
4. Execution and analysis, definition of design space



Process Map

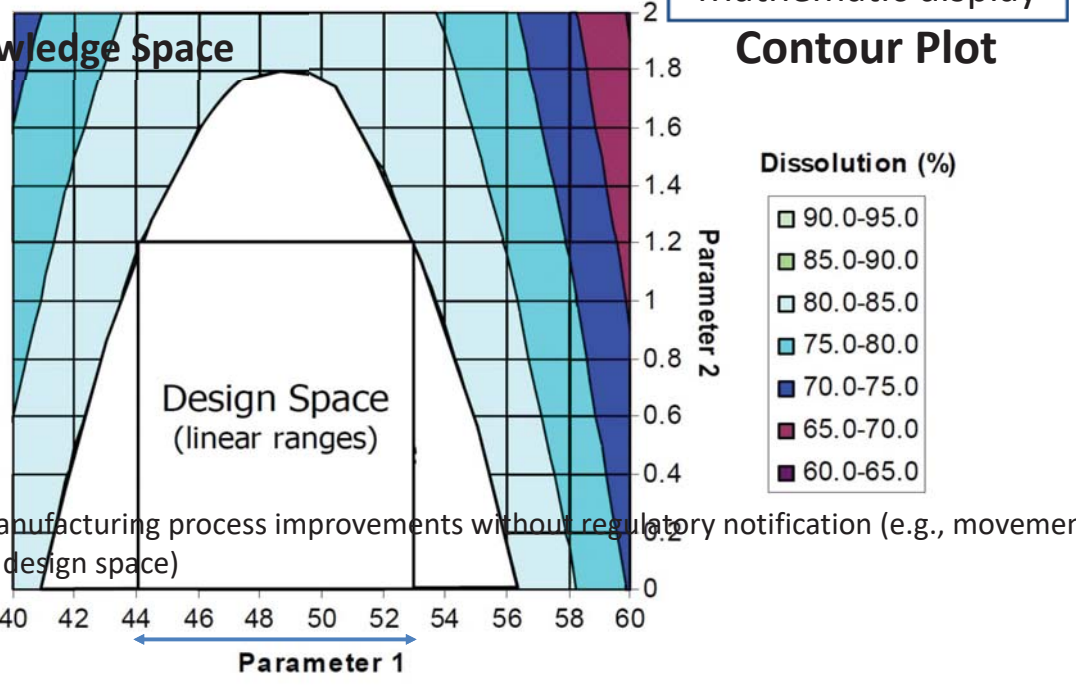


$Y = f(X_1, X_2, \ldots, X_n)$

QbD vs. Design Space DOE approach

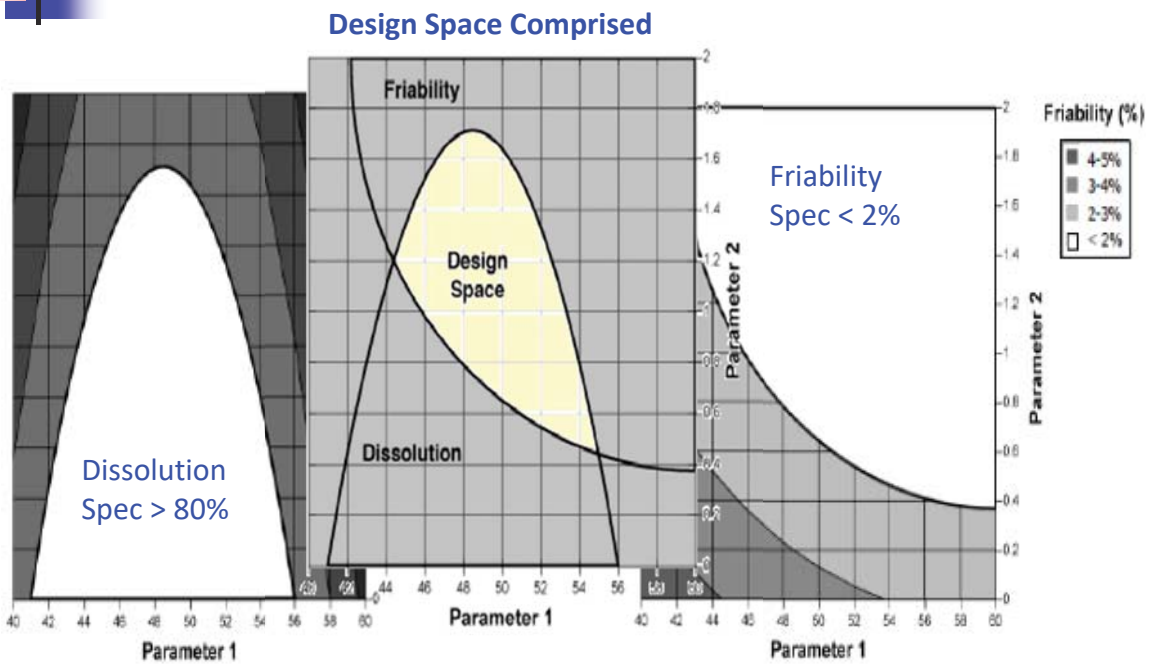
Mathematic display

Knowledge Space



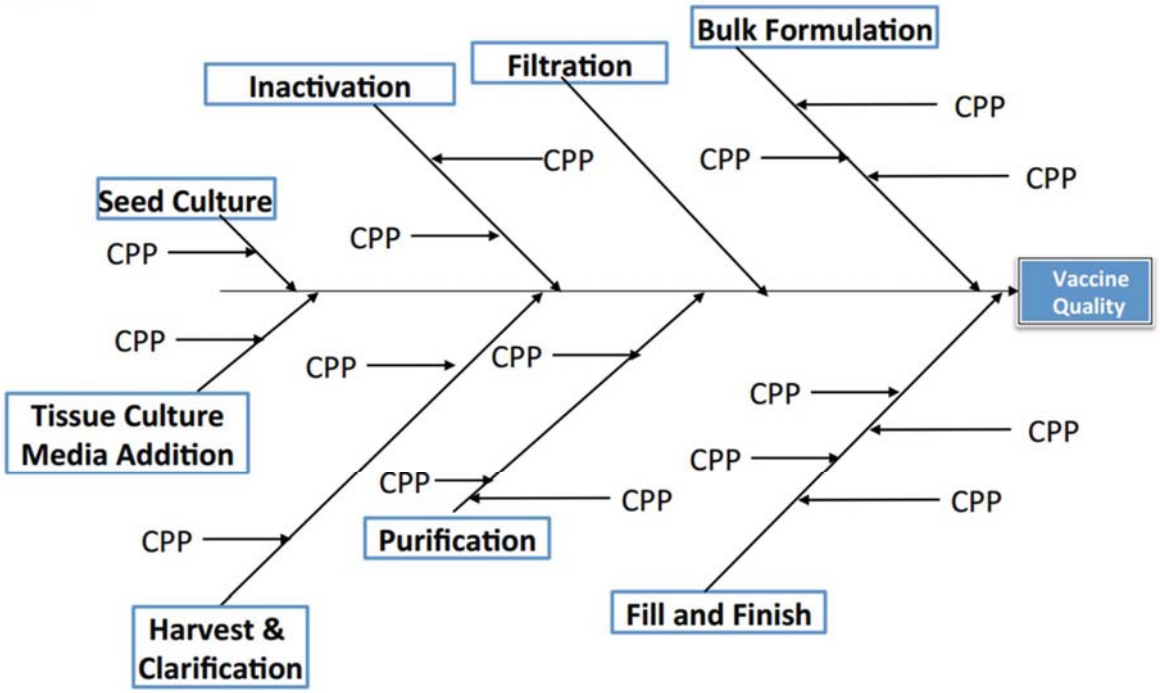
FDA - Manufacturing process improvements without regulatory notification (e.g., movement within a design space)

Dissolution and Friability = f (P1, P2)



Contour Plots

Defining Unit Operation and CPPs Biological



QTPP → CQAs by QRM

	Safety	Efficacy	Quality
Potential CQA 1			
Potential CQA 2			
Potential CQA 3			
Potential CQA 4			
Potential CQA 5			

Low impact Medium impact High impact

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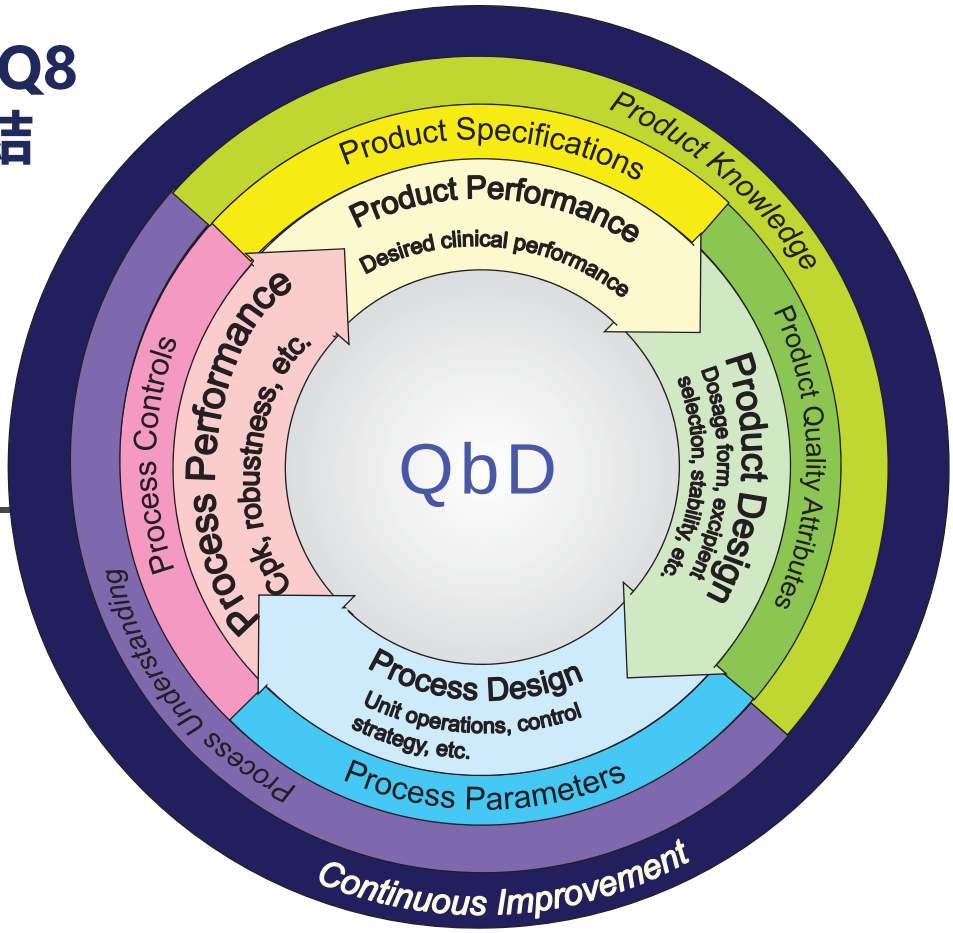
ICH Q8 總結



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ICH Q9
"Quality Risk Management"

"品質風險管理"

If anything can go wrong, it will.

我們經常擔心的事，就必定會發生！

-- Murphy's Law

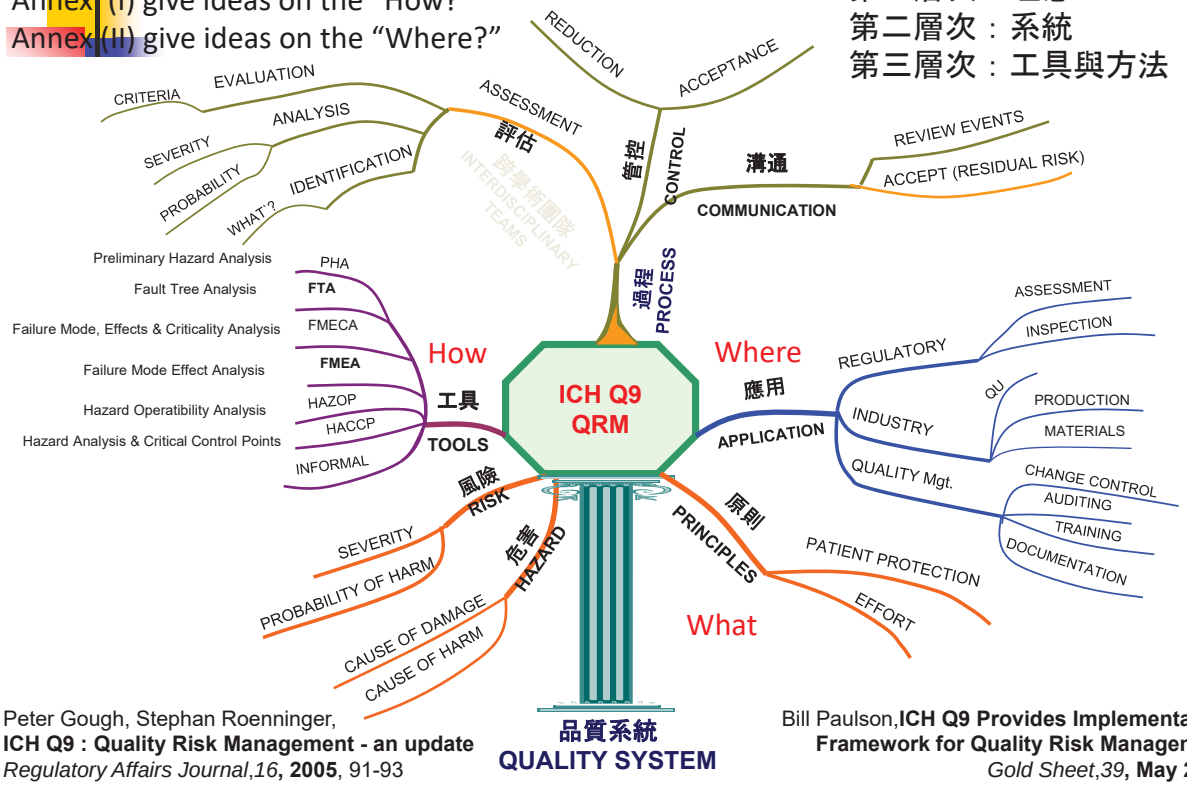
風險 ISO9001:2015 (ISO31001)
R = f (expected result, uncertainty)

不確定性 對 **目標** 的 **影響**

- 註 1： 影響是指**偏離預期**，可以是正面的或負面的
- 註 2： 通常，“風險”被描述為**潛在事件**
- 註 3： 通常，“風險”被表述為某個事件（包括環境變化）的**後果**及其**發生可能性**的組合
- 註 4： “風險”一詞有時僅在有負面結果的可能性時使用
- **不確定性** 是指，對事件(event)、其 後果或可能性 的 認識或了解 方面的資訊的 缺乏或不完整 的狀態

The ICH Q9 document:
Main body explains the “What?”
Annex (I) give ideas on the “How?”
Annex (II) give ideas on the “Where?”

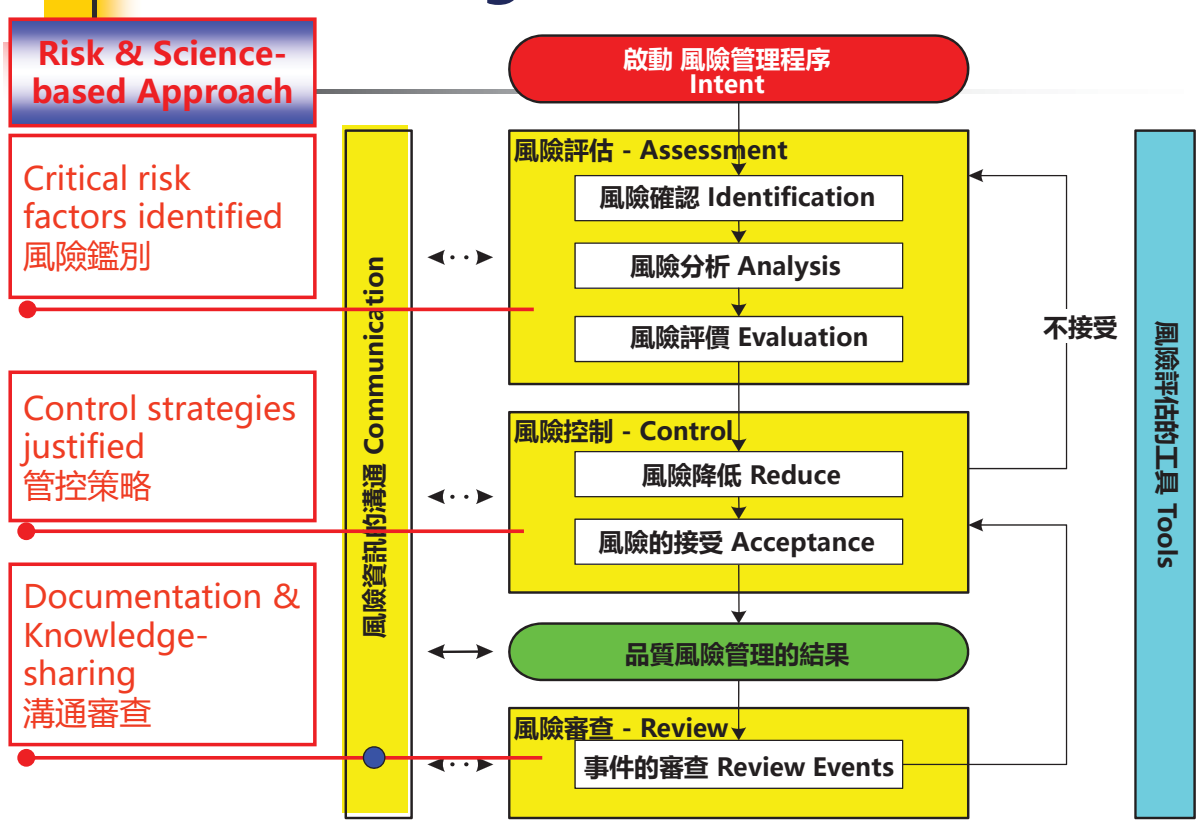
風險品質管理應用架構
第一層次：理念
第二層次：系統
第三層次：工具與方法



Peter Gough, Stephan Roenninger,
ICH Q9 : Quality Risk Management - an update
Regulatory Affairs Journal,*16*, **2005**, 91-93

Bill Paulson,**ICH Q9 Provides Implementation Framework for Quality Risk Management**
Gold Sheet,*39*, **May 2005**

ICH Q9 general Process



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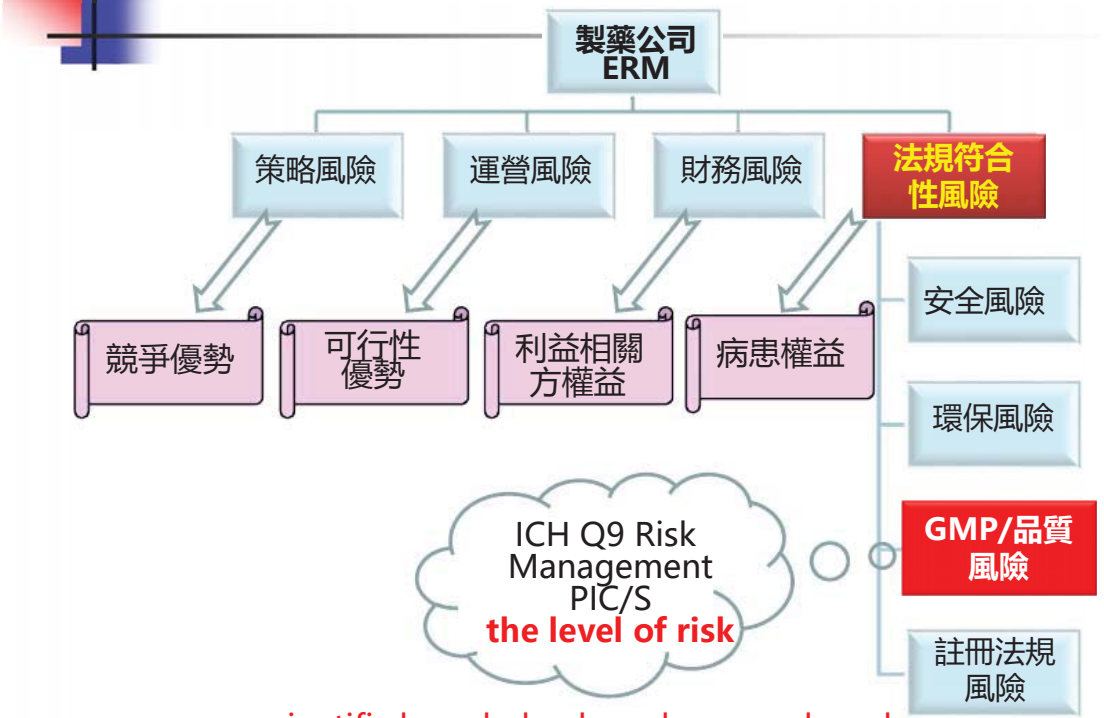
ICH Q9 品質風險管理範圍



scientific knowledge based approach and link to the protection of the patient

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How To Use QRM As An Enabler
如何將品質風險管理作為助力

e.g.操作風險、環境、設備、IT、設計要素等

CIA

品質體系、控制、測量、法規符合性等

PQS/ISO/GMP

e.g.品質屬性

CQAs

e.g.製程操作與品質參數

CPPs/Control plan

Risk Management
風險管理

Risk That Occur = Problems

當風險發生 = 問題產生

Uncertainty 不確定 → **RISK 風險** → **Problem 問題**

Hazards 危害/危險源/風險源

A: Severity 嚴重性

B: Occurrence 發生機率

C: Detection 難測度

Failure 失效

R = A X B X C

Or

R = X + Y+ Z +…

(合計)

Harm 傷害

Disaster 災害

Loss…損失

風險量化

Risk (一般情況) =
嚴重度 X 頻度 — General

Risk (複雜系統) =
嚴重度 X 頻度 X 不確定度 — Process

Risk (未知狀況) =
嚴重度 X 頻度 X 知識程度 — Design

Risk = f (expected result, uncertainty)

什麼是風險？
ICH Q9

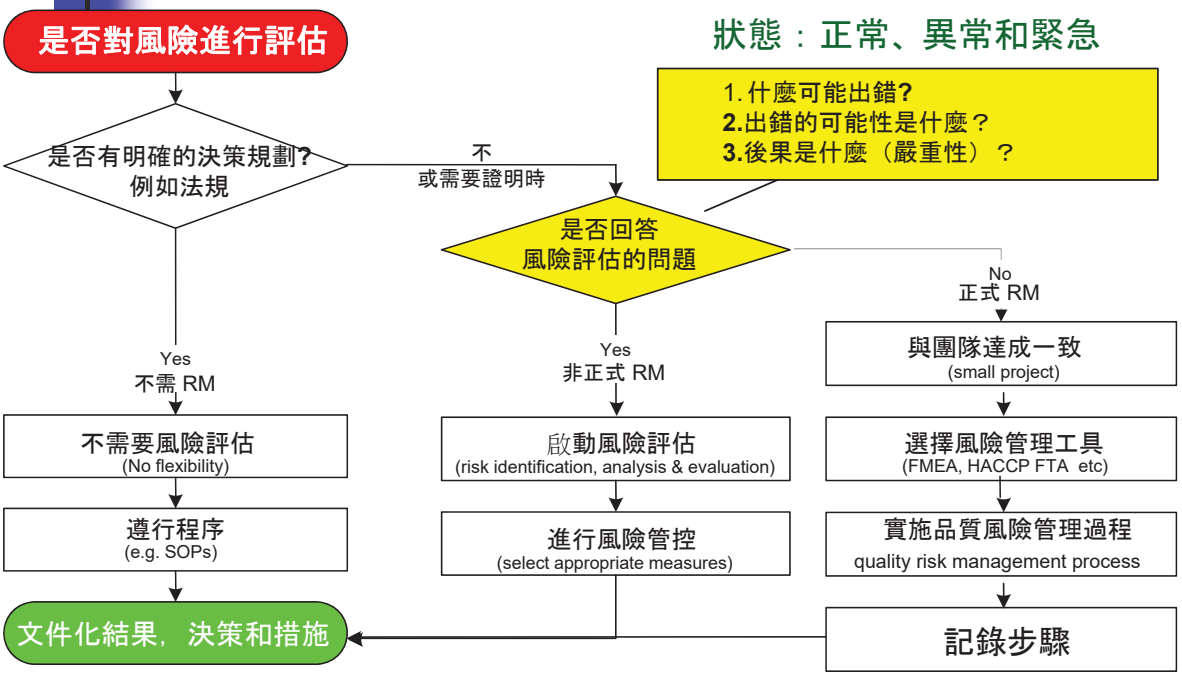
“風險”是危害(危險源 hazard)發生的
可能性和嚴重性的組合
缺一不可

*The combination of the **probability** of **occurrence** of harm and the severity of that harm (ICH Q9)

風險開始於”意圖 Intent ”

Hazard: The potential source of harm. (ICH Q9)

When to apply QRM?
什麼時機應用?



Based on K. Connelly, AstraZeneca, 2005

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ICH Q9 EWG
品質風險管理工具適用範圍

Application \ Approach	PHA	HACCP	HAZOP	FTA	FMEA	FMECA	ZHA
Early in Development (w/ little information)	X			X	X		
Analyzing Existing Systems	X				X		
Prioritizing Hazards / Risk	X				X		
Product	X			X	X		X
Process	X		X	X	X	X	X
Facility	X				X		
Physical / Chemical / Biological / Hazards		X	X		X		X
Support Identification of All Critical Parameters		X			X		
Investigating Complaints to Fully Understand Root Cause				X		X	
Monitor Effectiveness of Risk Mitigation					X		
Application					X		
Service					X		
CAPA					X	X	
System					X		X

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Rigor and Formality of QRM Approaches

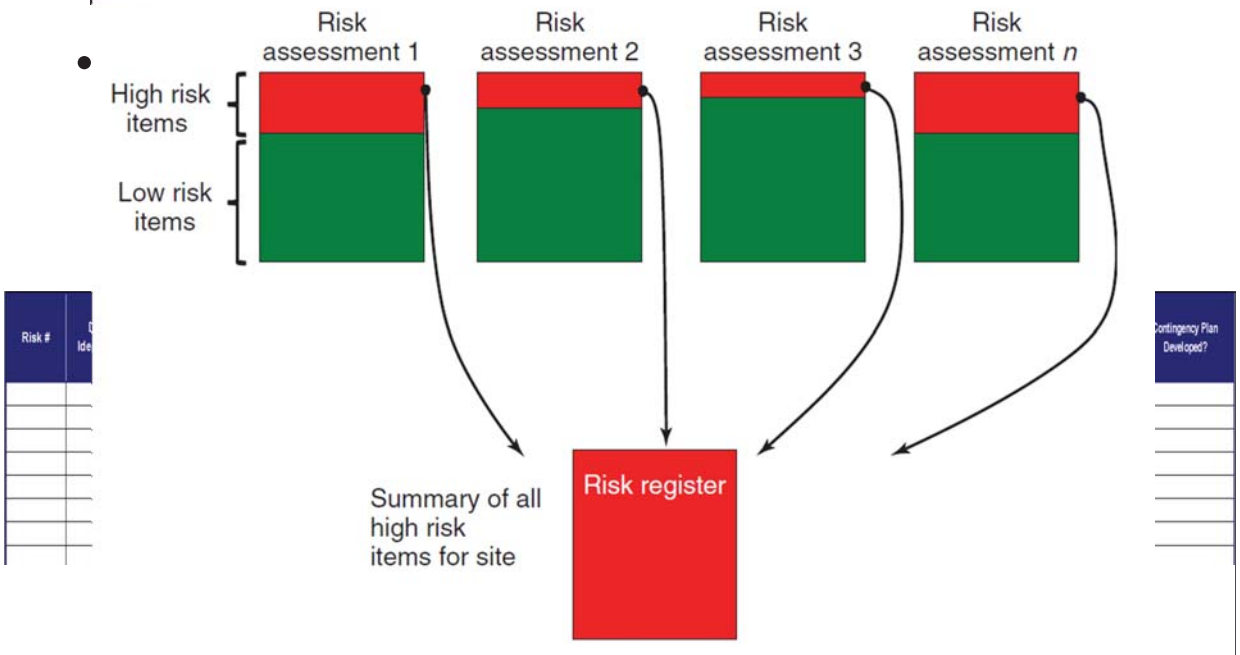
Critical 關鍵性
決定RM方法難易

Technical /Scientific Rationale
製程/科學原理

Simple Risk Assessment (e.g. risk ranking, checklist, decision tree)
簡單的風險評估

Detailed Risk Assessment (e.g. PHA, FMEA, FTA)
詳細的風險評估

Risk register 風險登錄表



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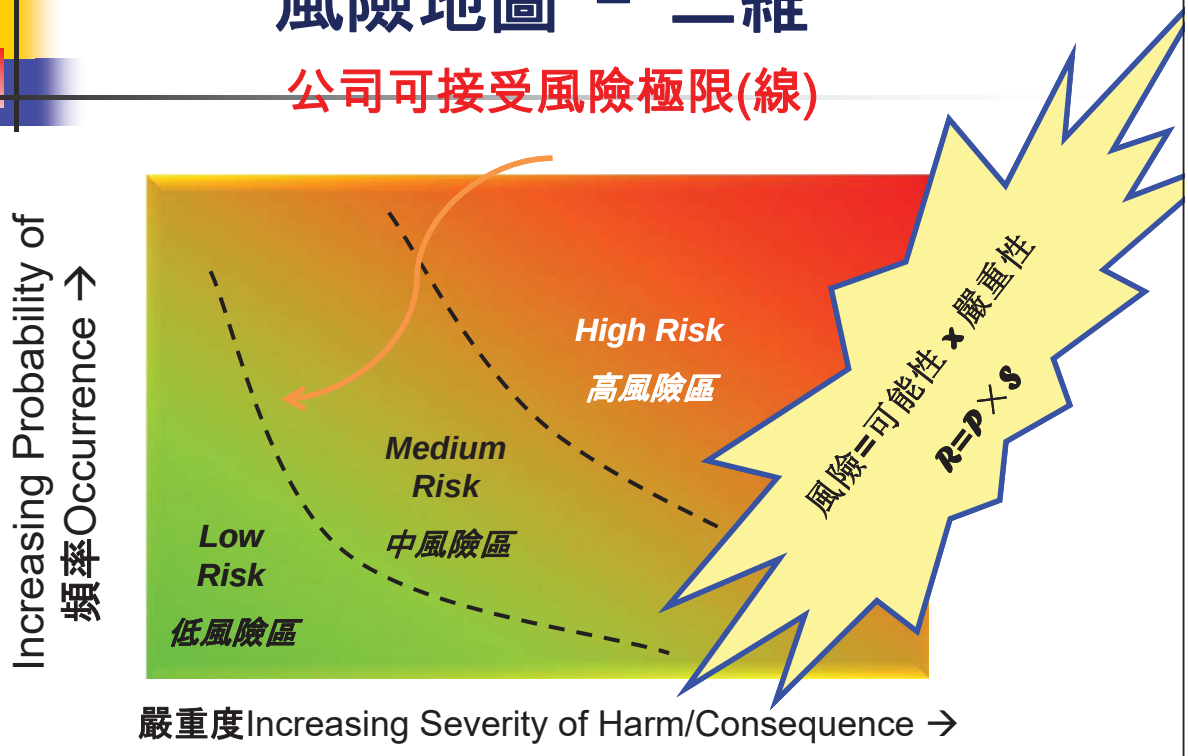
風險地圖 – 二維

公司可接受風險極限(線)



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品質風險管理基本工具

Risk Level 風險水準		Likelihood 可能性		
		Low 低	Medium 中	High 高
Consequence 結果	High 高	M	H	H
	Medium 中	L	M	H
	Low 低	L	L	M

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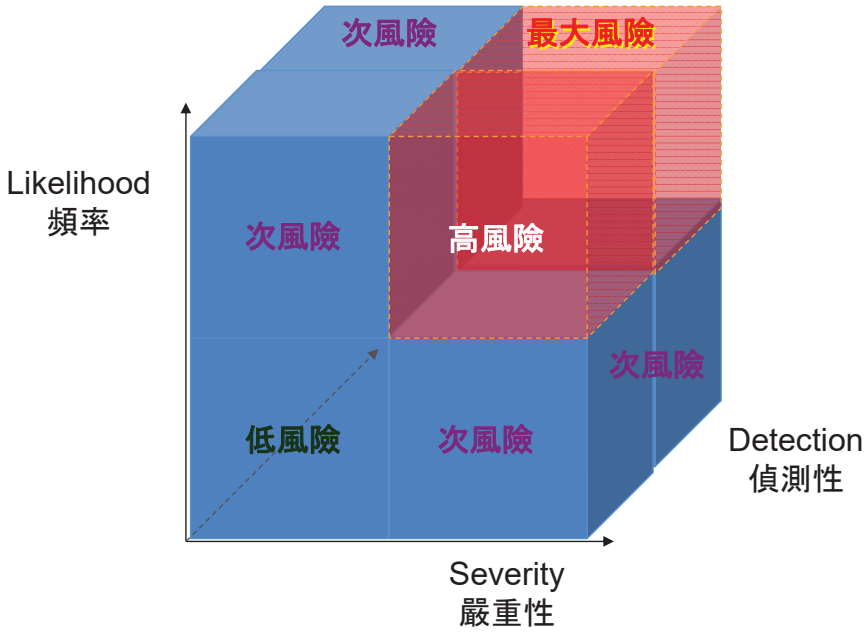
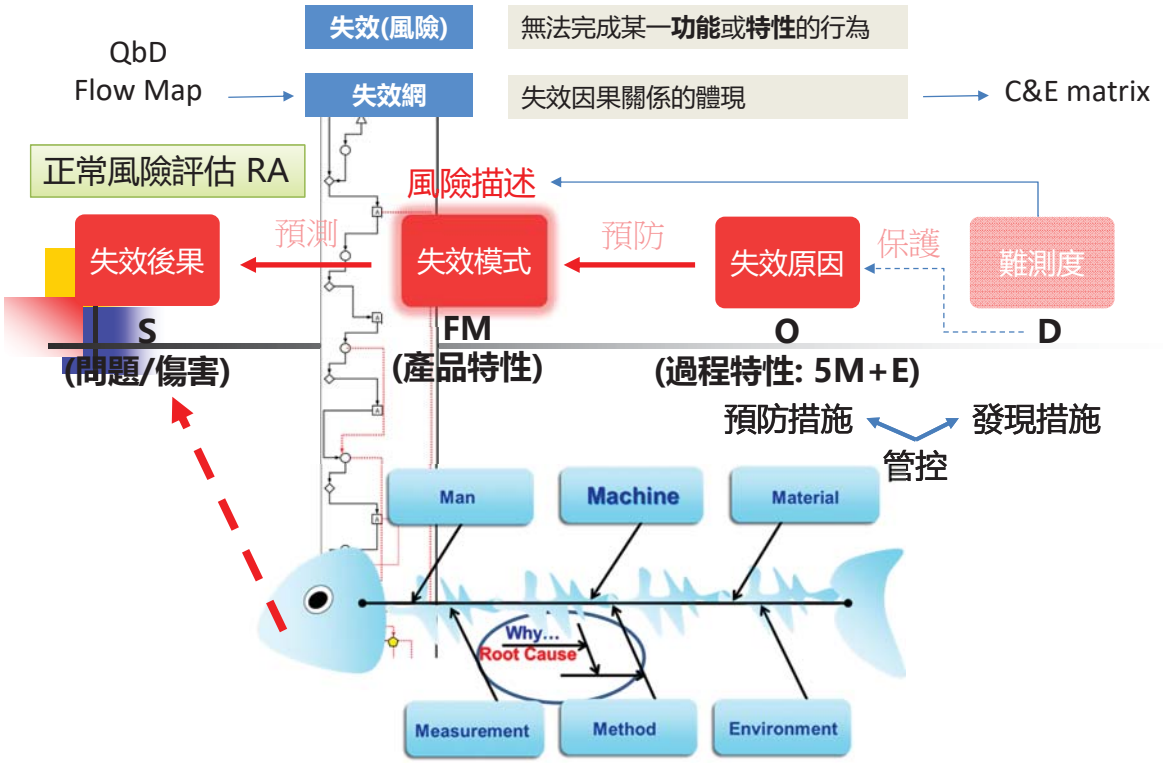
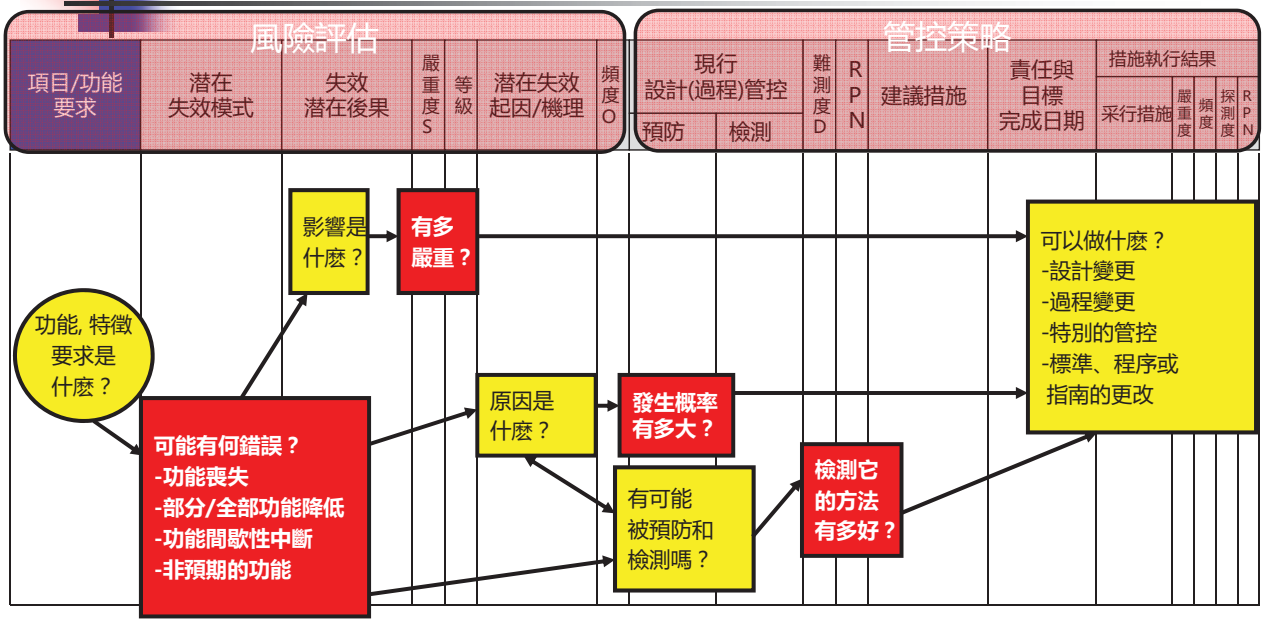
風險地圖 - 三維
系統 複雜 or 關鍵 時使用



風險管理 – FMEA → Lesson learned
在功能分析的基礎上，對每一個功能建立失效，並根據失效產生的原因及其導致的後果建立失效網



潛在失效模式與影響分析順序
QRM vs. FMEA



R1: QRM 四大基本問題是：什麼可能出錯(識別)？出錯的可能性(O概率)？出錯的結果是什麼(S嚴重性)？對於危害的事前可檢出性(D可檢測性/難測度)？

R2: 等級 → *關鍵製程　**標準：1.安全，法規　2.關鍵　3.一般

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風險評級（SOD）general guide

測量範圍 1-10	RPN
嚴重性 x 發生機率 x 可偵測性	<70
	71-99
	>100

S 嚴重度	
嚴重	後果嚴重 Ø非常重大的 GMP違規 Ø可能對患者造成危害
中等	後果嚴重程度中等 Ø嚴重GMP違規 Ø可能對患者造成不良影響
較小	非嚴重後果 Ø輕微GMP違規 Ø對患者無不良影響

O 發生機率	
高	危害很可能發生
中	危害可能發生
低	危害不太可能發生
極小	危害發生的可能性極小

D 可偵測性	
高	通過管控很可能檢測出危害或其影響
中	通過管控可能檢測出危害或其影響
低	通過管控不太可能檢測出危害或其影響
無	無適當的檢測管控手段

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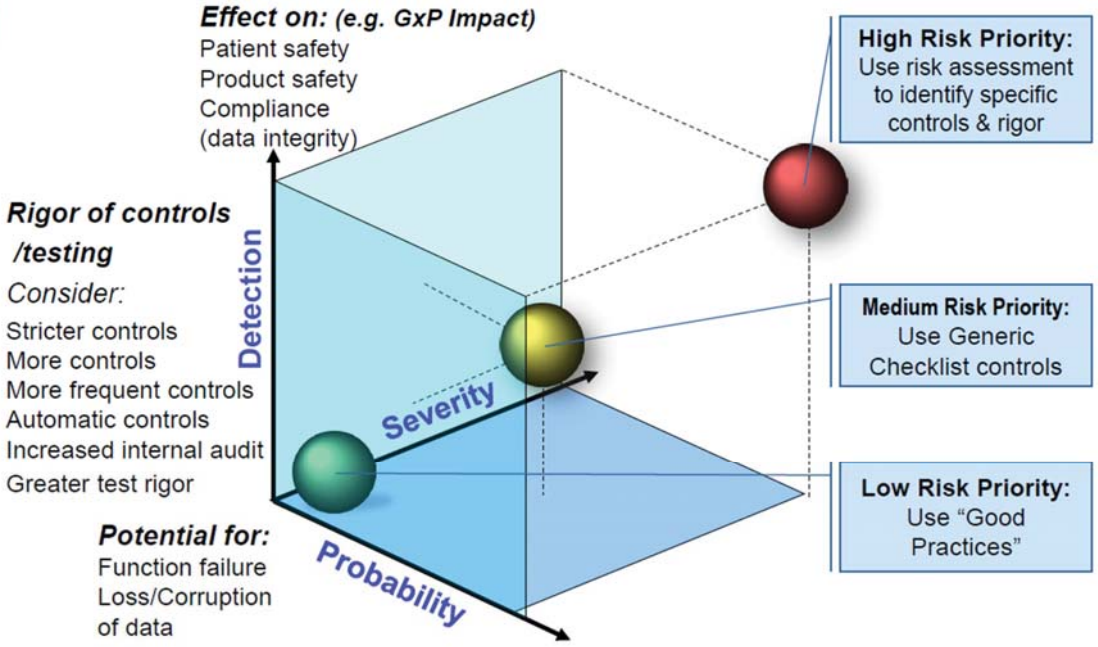
Risk Based Approach – GxP Impact FMEA



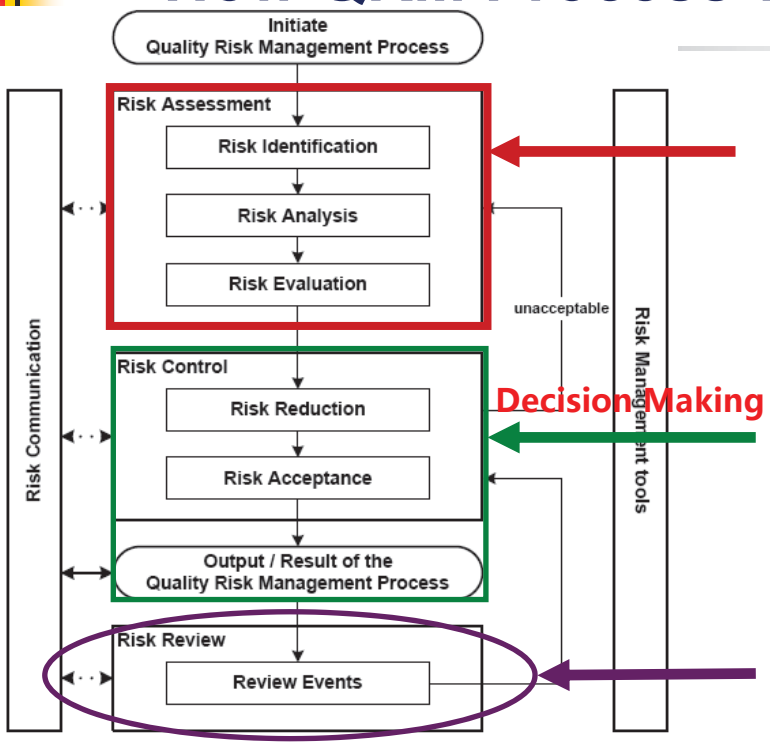
The x (probability-complexity), y (severity-GMP criticality) axes, the z axis (degree of rigor-detection)

FMEA for fill line change over Aseptic filler application

風險評估 | 管控策略

System ID Usage	Failure Mode	Potential Effects	S	Potential Causes	O	Current Controls	D	Detection	RPN
Gaskets and silicone tubing changed between products to prevent cross-contam1nat'1on	Gaskets and tubing not changed out between products	Residual product could remain in tubing or gaskets, contam1nat'1n g next product	5	Operator error, inadequate instructions	5	None	4	Use documented second operator check to ensure change over is performed	100
Filler is cleaned in place to ensure removal of residual product	Filler not cleaned properly	Residual product could contaminate next product	5	CIP not performed	1	Filler interlocked to prevent use without CIP/SIP	1	Current controls are adequate	5
			5	Excessive temperature on initial rinse causes protein denaturation	1	Over temperature alarm and cycle abort	1	Periodic testing and calibration of alarms	5
			5	Automatic chemical addition fails	3	Conductivity alarm to detect failure to add chemicals	2	Periodic testing and calibration of alarms	30

ICH Q9 vs. Q8
How QRM Process work!



Process Development
失效模式分析
原因探究

Decision Making

Control Strategy Development
現行製程管控方法
預防?檢測?

Continual Improvement of the product
變更管理/KM

FMEA for fill line change over Aseptic filler application

System ID Usage	Failure Mode	Potential Effects	S	Potential Causes	O	Current Controls	D	Detection	RPN
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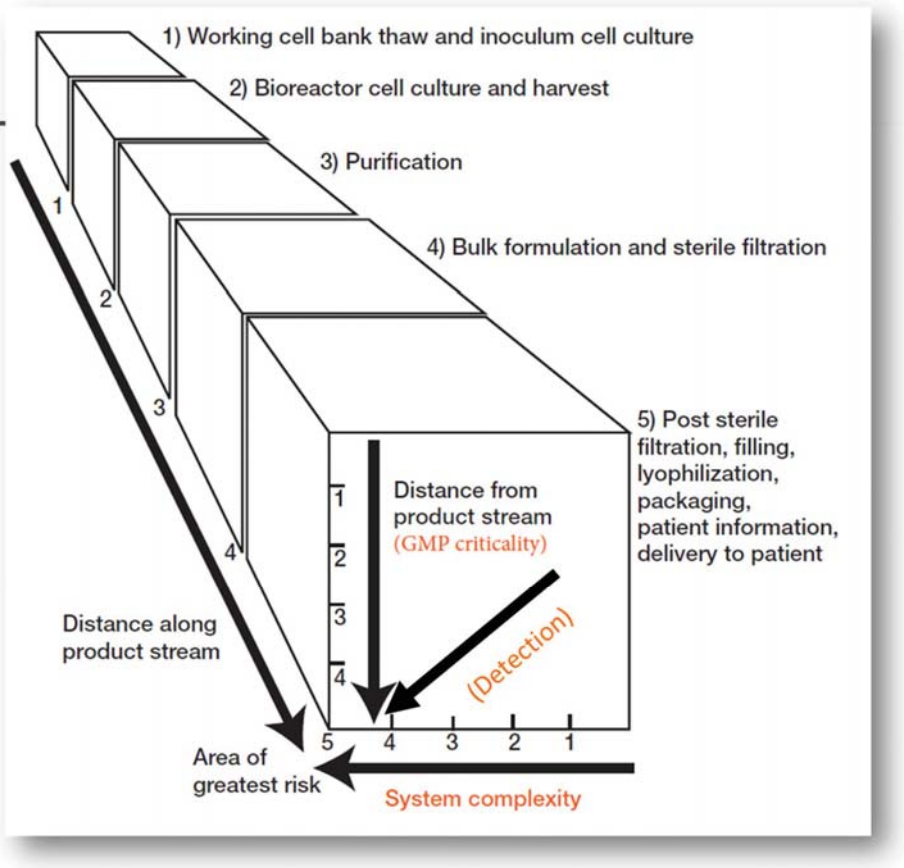
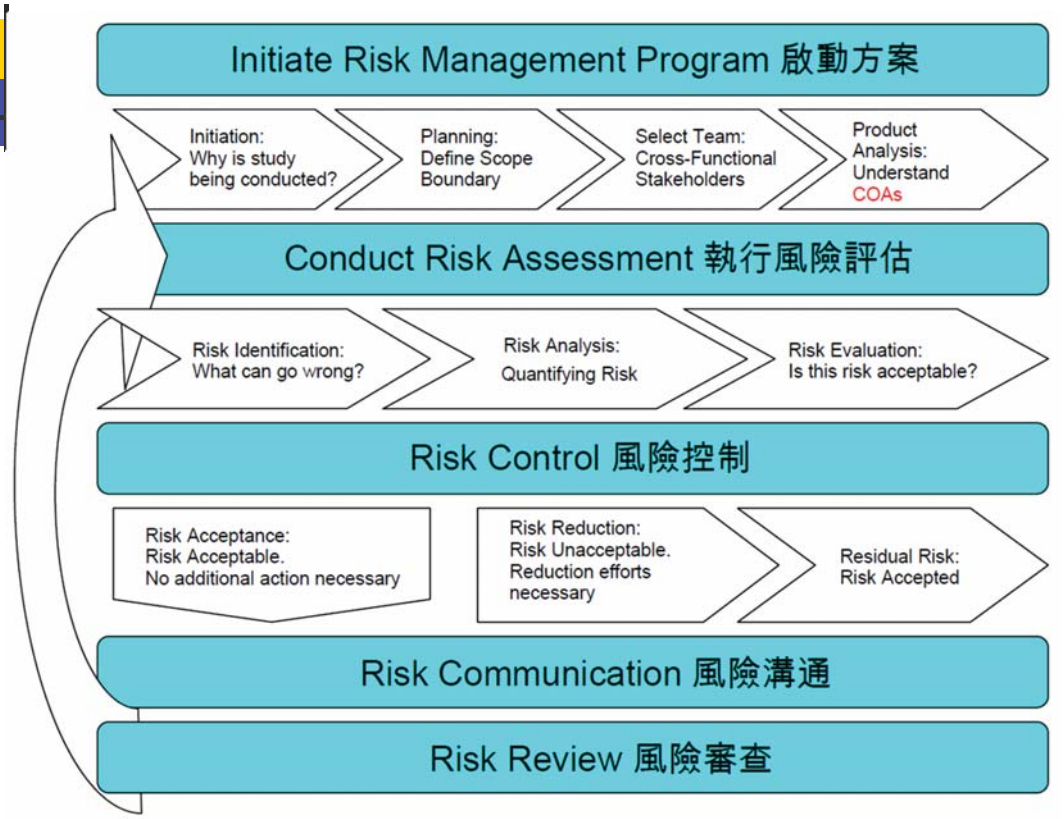


QRM 總結

品質風險管理的貫徹和落實 PDCA

- 確定公司的品質風險管理政策 Policy
- 成立品質風險管理小組， 成員資格， 許可權，責任的確定 Team
- 確定具體的產品的風險容忍度準則 Criteria
- 制定品質風險管理計畫 Plan
- 按照產品的生命週期進行品質風險管理 Do
- 管理層定期的管理審查， 審查風險管理過程完整性， 和風險管理文件 Check and Act



ICH Q10
"Pharmaceutical Risk Management"
PQS

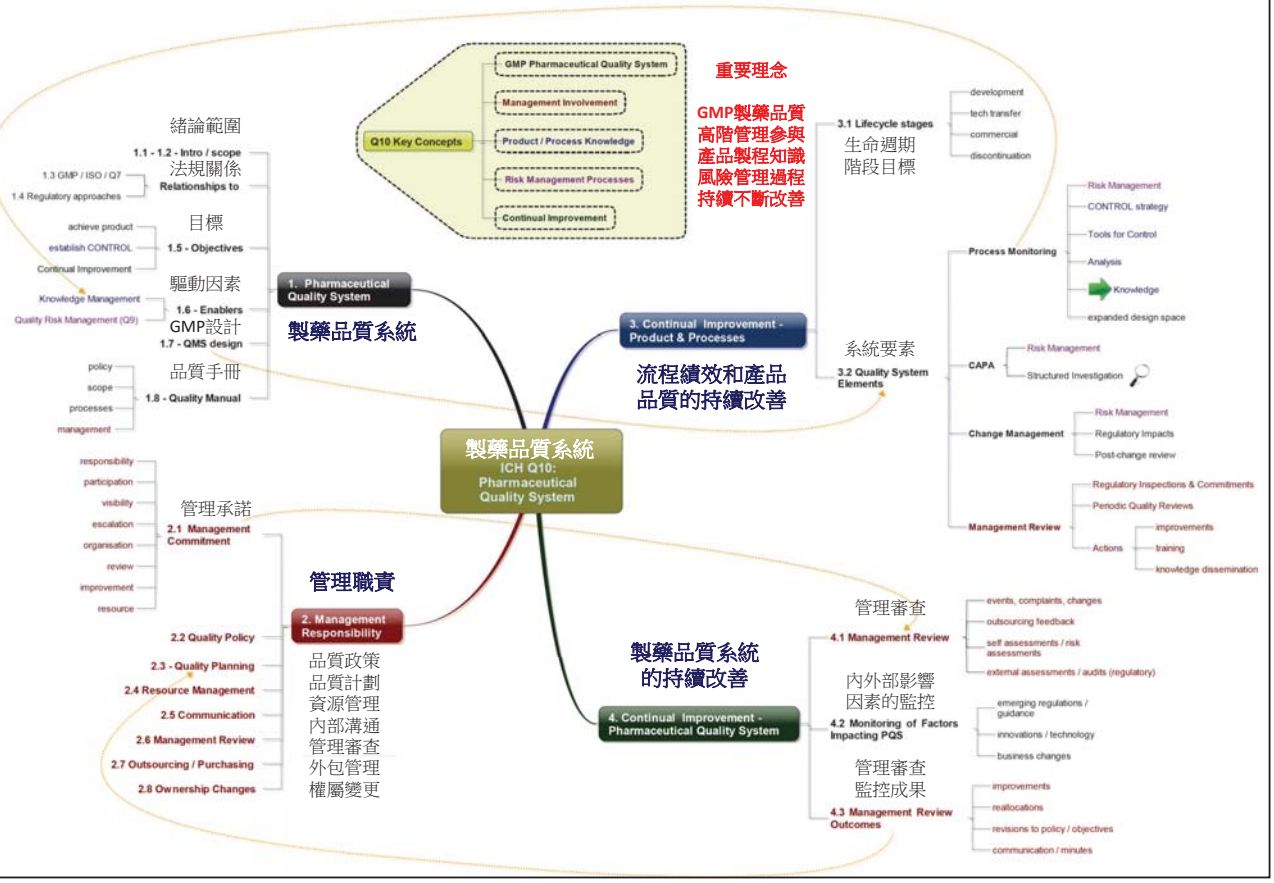
"製藥品質系統"

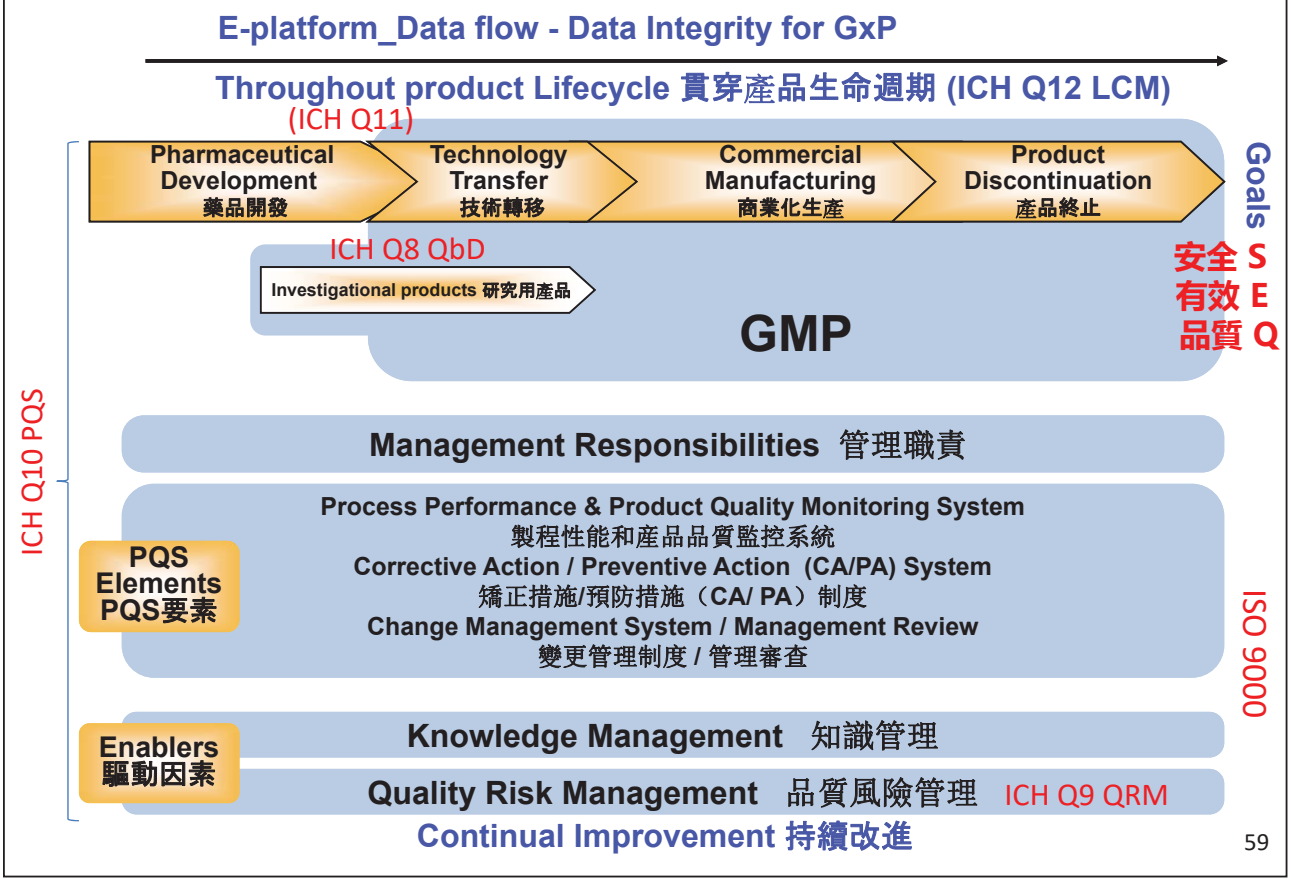
ICH Q10 Pharmaceutical Quality System

- PQS 製藥品質系統
- No intent to create new regulatory expectations
- 彌補**PICS GMP**在品質管理系統上的不足

ICH Q10 is intended to encourage the use of science and risk based approaches at each lifecycle stage.

ICH Q10 PQS Index





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What is ICH Q10?

- **ICH Q10 is a guideline on the essential elements of a PQS throughout the product life cycle** Q10是關於PQS在整個產品生命週期中基本要素的指南
- **ICH Q10 complements Q8 and Q9** Q10/Q9/Q8互補
  - **ICH Q8 - strengthens the link between development and manufacturing** Q8加强了開發與製造之間的關聯
  - **ICH Q9 - as an enabler of the PQS** Q9作爲PQS的促成者
- **Implementation of PQS should provide enhanced assurance of product quality** PQS的實施應該爲產品質量提供更大的保證
- **GMP is applicable to the Manufacturing part of the life cycle** GMP適用於生命週期的製造部分
  - **Manufacturing of Investigational (medicinal) Product** 製造研究用產品
  - **Manufacturing of commercial products** 製造上市產品

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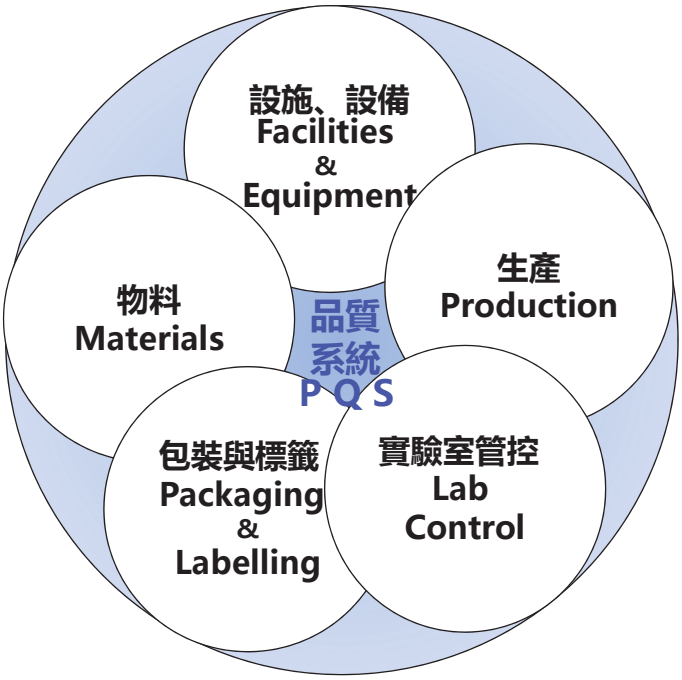
What is ICH Q10?

- **A ICH Q10 type PQS reinforces/introduces some elements e.g.** Q10類型的PQS强化/引入了一些元素 例:
  - **Link manufacturing and development (incl. feedback)** 連接製造和開發 (包括回饋)
  - **Continual improvement** 持續改善
    - **Products** 產品
    - **Processes** 過程
    - **PQS itself** PQS本身
  - **Role and Responsibilities of Senior Management** 高管角色及責任
  - **Quality Risk Management and Knowledge Management**品質風險管理和知識管理
  - **Product Lifecycle** 產品生命週期
    - **Development through to Discontinuation** 從研發到終止
  - **Management of outsourcing and purchasing material** 管理外包和採購物料

CI of Process Performance and Product Quality
製程性能和產品品質的持續改進

- **Lifecycle Stage Goals**
  生命週期階段目標
  - Pharma. Development
    藥品開發
  - Tech Transfer
    技術轉移
  - Manufacturing
    製造
  - Product Discontinuation
    產品停產
- **PQS**
  藥品品質系統
  - Monitoring
    監測
  - Corrective/Preventive Actions
    糾正/預防措施
  - Change Management
    變更管理
  - Management Review
    管理審查

US FDA GMP 6 system based Risk Based approach



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Continual Improvement

Product Quality and Process Performance

- Utilize the knowledge gained in commercial production to continually improve the product and process.
- Utilize a knowledge management system
- Identify sources of process variation
- Use quality risk management to identify and prioritize indicators for monitoring and utilize feed forward feed backward mechanisms.
- Verify a state of control
- Provide key inputs to enrich the design space, and to enable innovative approaches to the process validation lifecycle

藥品開發	技術轉移	商業化生產	產品終止
製程和產品知識以及整個開發過程對製程和產品的監測能被用於建立生產的管制策略	對製程放大活動的監測能爲製程性能以及爲成功整合到生產中去提供初步的指示在轉移和製程放大活動中獲取的知識有助於進一步發展管制策略	應運用良好的製程性能和產品品質監測系統來確保性能管控幷確定改進領域	一旦生產終止，如安定性研究等監測應繼續直到該研究完成應根據區域法規要求繼續對已銷售產品的實施適宜的措施

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Continual Improvement

CAPA System

- **Investigation of non-conformances**
  - **Reactive → deviations, rejections, complaints, recalls, observations from audits and inspections**
  - **Proactive → feedback from trends**
- **Structured investigations to seek root cause**
- **Use QRM to ensure degree and formality is commensurate with level of risk**
- **Should result in enhanced knowledge and improvement**
- **Not just reacting to non-conformances**
- **Focus on preventative actions**
- **Need effective tracking / follow up processes**

藥品開發	技術轉移	商業化生產	產品終止
尋找產品或製程的變異性當將矯正措施和預防措施整合到反復設計和開發的流程中，CAPA方法是有用的	CAPA可以作爲一種有效的系統用於回饋，前饋和持續性改進	使用CAPA，同時應評估這些措施的有效性	產品終止後，仍應進行CAPA應考量市場上的存在產品的影響，同時還有其他產品可能受到的影響

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Continual Improvement

Change Management System

- **Evaluate changes under the principles of quality risk management**
- **Refer to the design space and existing product/process knowledge**
- **Expertise needed should include development, manufacturing, quality, regulatory and medical to evaluate the impact on product quality**
- **Set acceptance criteria for change and evaluate after implementation**
- **Knowledge gained should be included in the knowledge management system**
- **Assess the need for a regulatory system realizing the benefits from using Q8 and Q9 principles**

藥品開發	技術轉移	商業化生產	產品終止
變更是研發進程中既有的部分，應被記錄；變更管理流程的正式程度應與產品開發的階段相符	變更管理系統應當提供記錄技術轉移活動過程中對製程所做的管理和調整的文件	在大規模生產時，應有一個正規的變更管理系統品質部門的監測應為適宜的基於科學和風險的評估提供保證	產品終止後的任何變更也應執行相應的變更管理系統

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Continual Improvement

Management Review

Process Performance and Product Quality

- Results from inspections and assessments
- Periodic quality reviews
  - Customer satisfaction – complaints, recalls
  - Conclusions of process performance and product quality monitoring
  - Effectiveness of process and product changes
- Appropriate actions
  - Improvements to manufacturing processes
  - Training and/or realignment of resources
  - Capture and share knowledge

藥品開發	技術轉移	商業化生產	產品終止
展開管理審查以確保產品和製程設計的充分性	展開管理審查以確保開發的產品和製程適用於大規模生產	如上描述，管理審查應有結構化的系統，以支援持續性的創新	管理審查應包括產品安定性和品質申訴等專案

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Knowledge Management

- Systematic and lifecycle approach to acquiring, analyzing, storing and disseminating knowledge on products, processes, components
- Provides the basis for science and risk-based approaches in the Quality System
  - Product and process development
  - Manufacturing
  - Change management
  - Continual improvement

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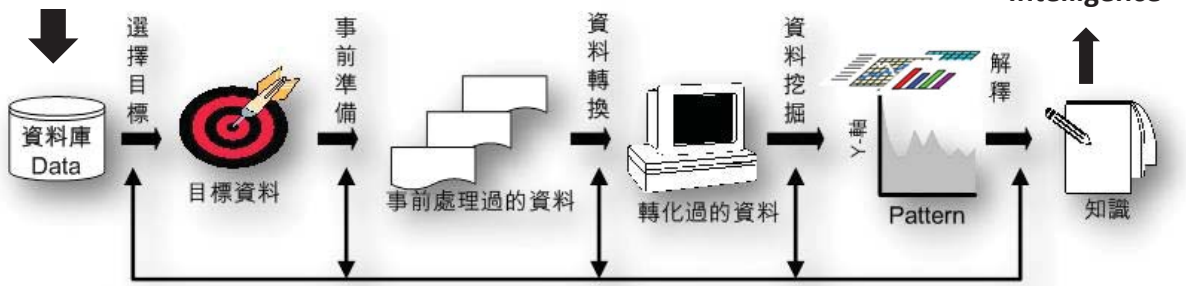
From know nothing to know how Knowledge Management

Input e.g.:
CAPA, FMEA, APR, Deviation, OOS, Audit, Lesson learned, Best practice, Operations…

Decision making

Know How



Raw Data — Data Analysis — Information — Knowledge

Know Nothing — *Know What* — *Know Why*

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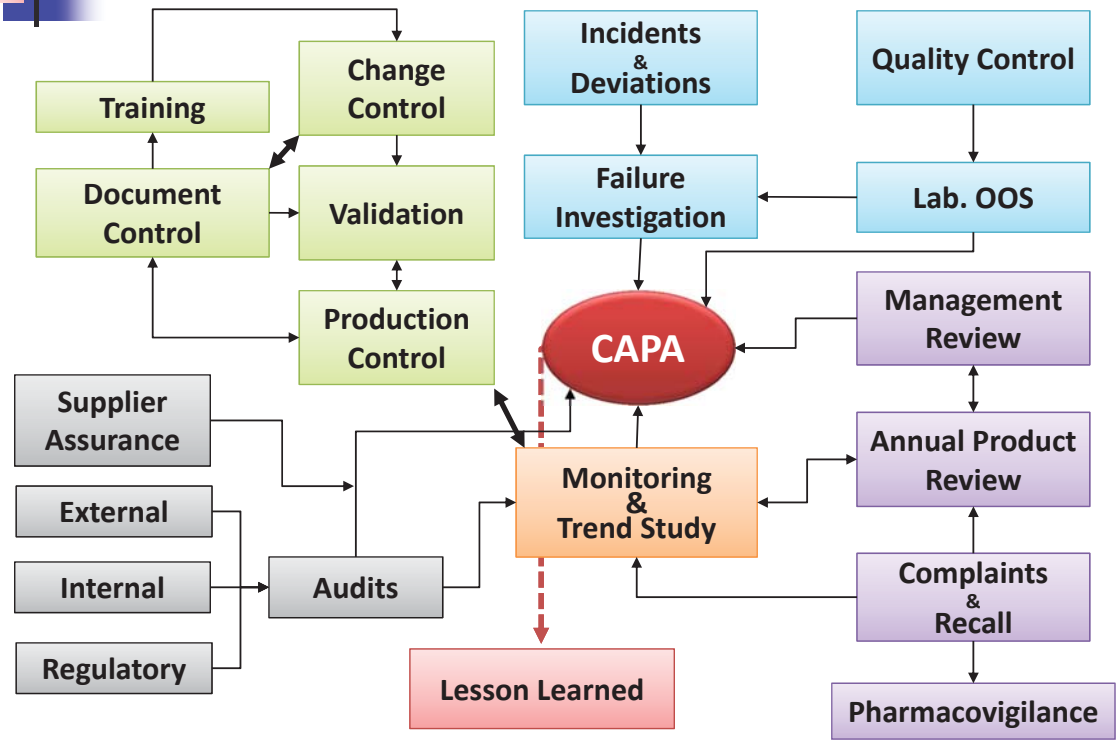
CIP thru CAPA Knowledge Management



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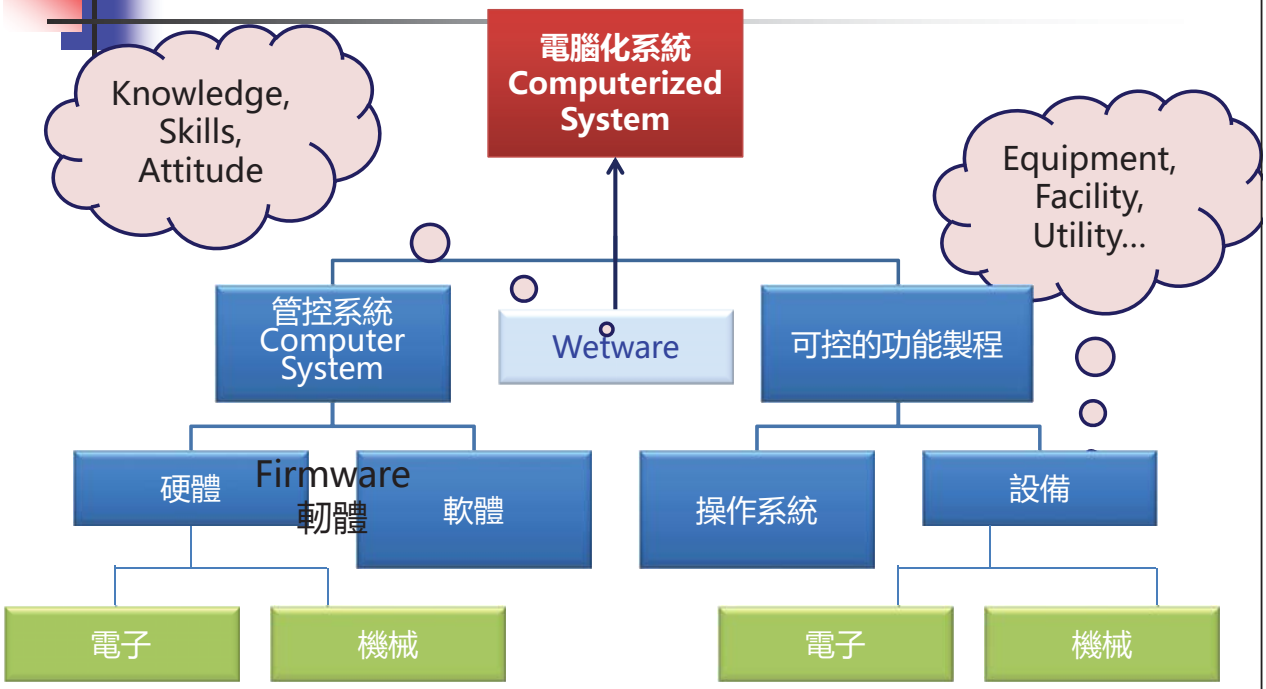
How to Implement ICH Q10 – Summary
實施 PQS- 流程總結

Step 1 Define & Establish Quality System 品質系統的建立和完善
Step 2 Develop a Quality Plan with well defined Quality Objectives 制定品質計畫和品質目標
Step 3 Complete a Gap Assessment 完成差距分析
Step 4 Determine & complete a Remediation Plan containing all required CAPAs for implementation of the new quality system 確定和完成實施新品質系統的補救計畫/CAPAs
Step 5 Define and complete training 制定并完成相關訓練
Step 6 Execute & complete the action items (CAPAs) of Quality Plan 執行和完成品質計畫活動/項目(CAPAs)
Step 7 Implement the new quality system 新的品質系統建立
Step 8 Verify the implementation of the new system, including training 確認新系統的實施情況, 包括訓練
Step 9 Monitor and continuously improve the new system 新系統的監控和持續的改進

Computerized System Validation
CSV

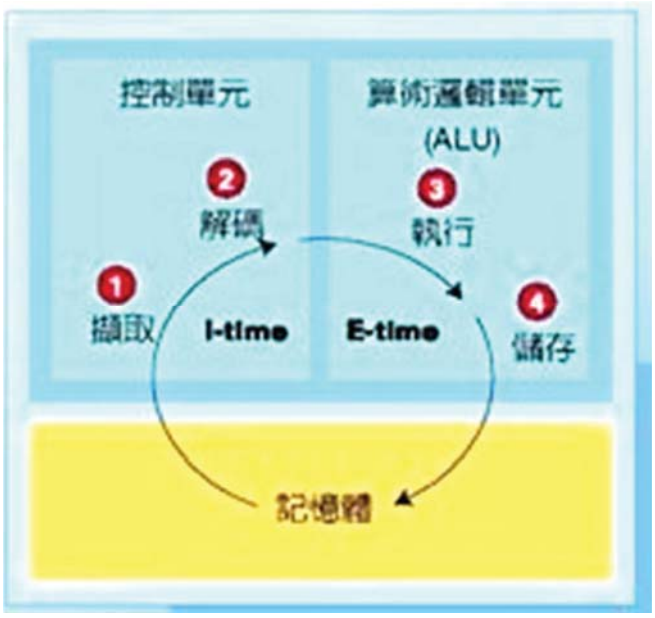
“電腦化系統確效”

CSV 定義及範圍

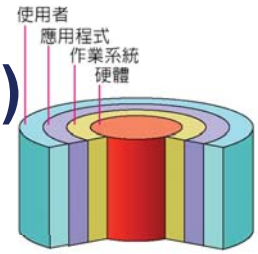


電腦的四種主要元件 Hardware

CPU:執行儲存在記憶體中的程式指令



機器週期 (I-time + E-time)

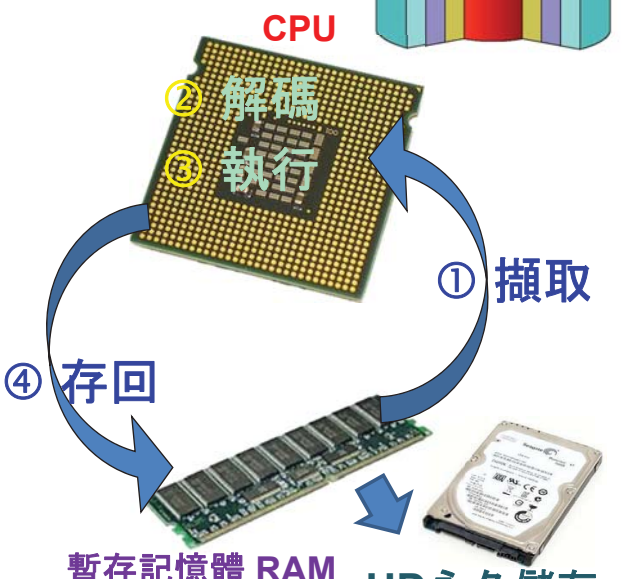


機器週期是指CPU執行一個指令所需的時間，包含了四個步驟：

1、擷取
2、解碼
3、執行
4、存回

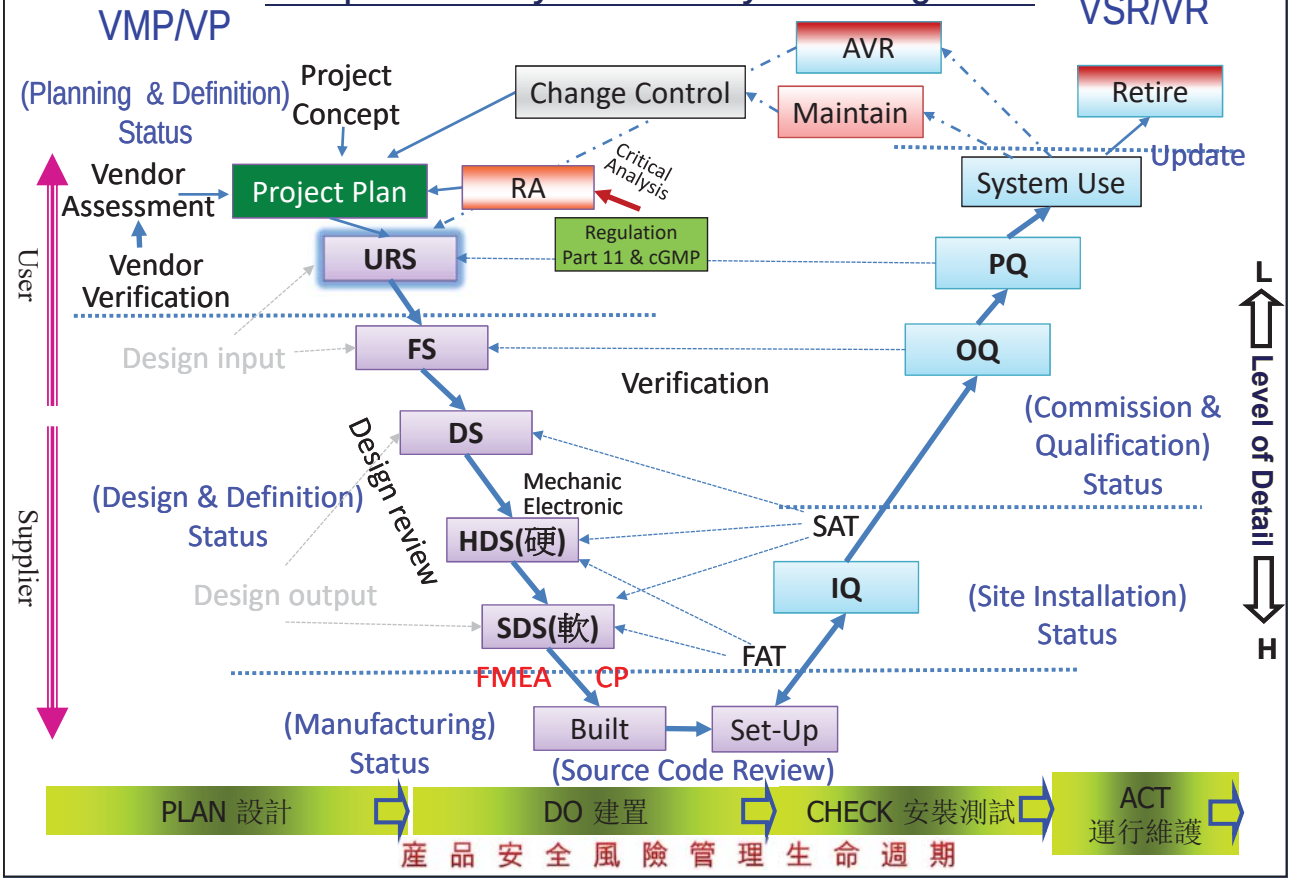
擷取與解碼階段合稱為指令時間(Instruction time，I-time)

執行與回存與指令執行有關，合稱為執行時間(Execution Time，E-time)

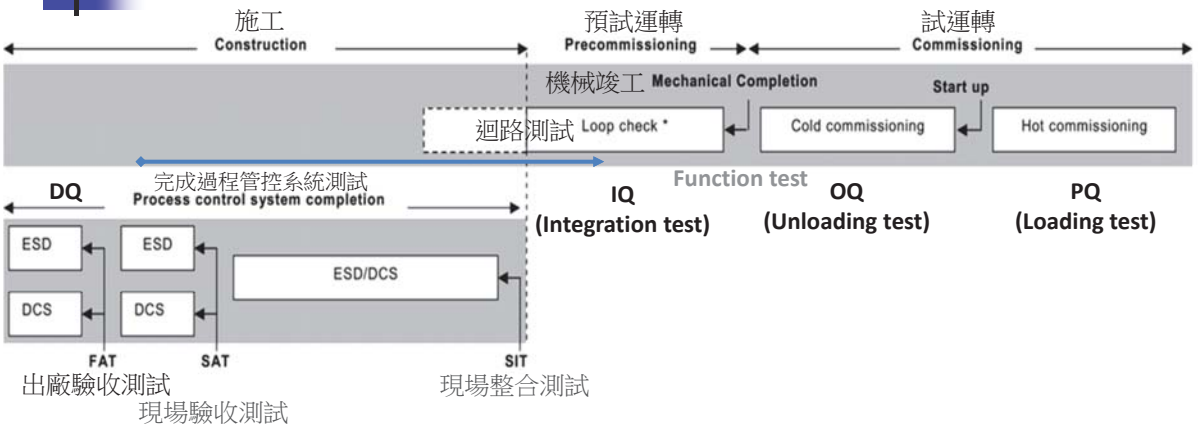


Paper or electronic?

V-Model CSV (data integrity)
Computerized System Life Cycle Management



IEC-62381-2006
Automation FAT and SAT/SIT



FAT 先決條件
Prerequisite for FAT
- SW complete
- System hooked up
- Vendor in-house test completed

SAT 先決條件
Prerequisite for SAT
- Shipment of system to site
- Proper installation
- System start-up

SIT 先決條件
Prerequisite for SIT
- Systems properly connected
- SAT complete

NOTE The loop check can actually be started during the construction phase once the required infrastructure has been installed.

Function checks include 1nterlock checks, complex function checks, and sequence or batch logic checks. These tests are part of the SAT but cannot be conducted until after loop checks

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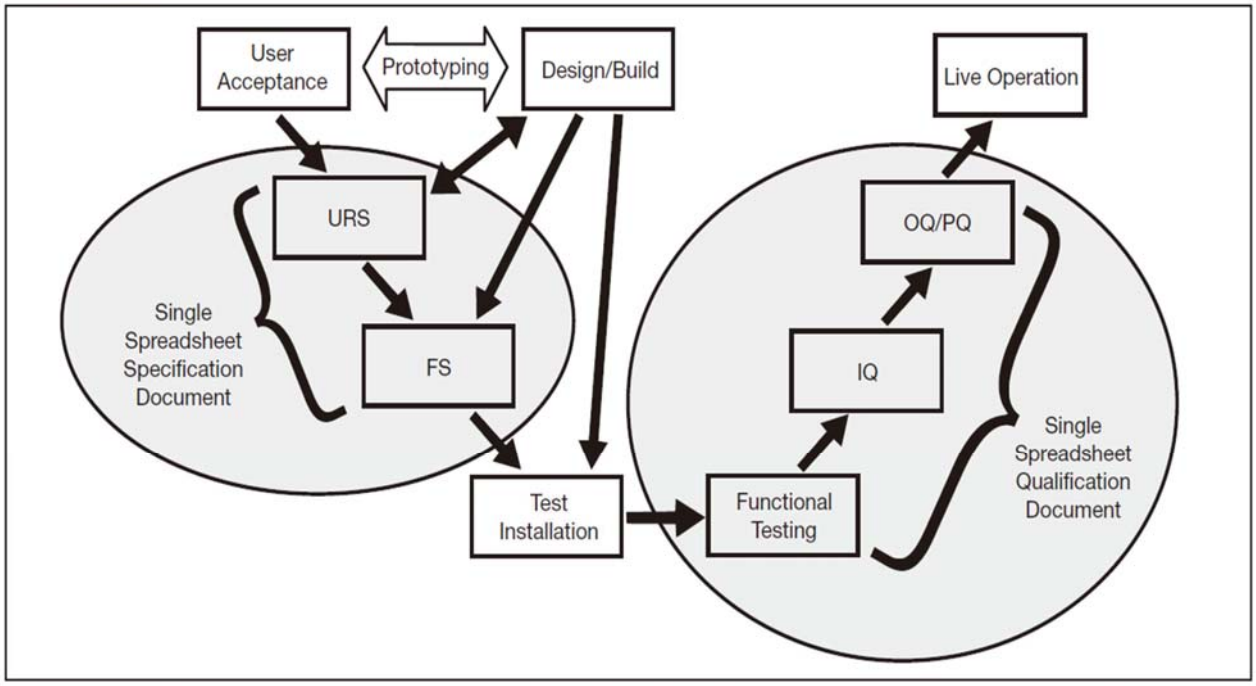
Spreadsheet validation - V model Office Excel example



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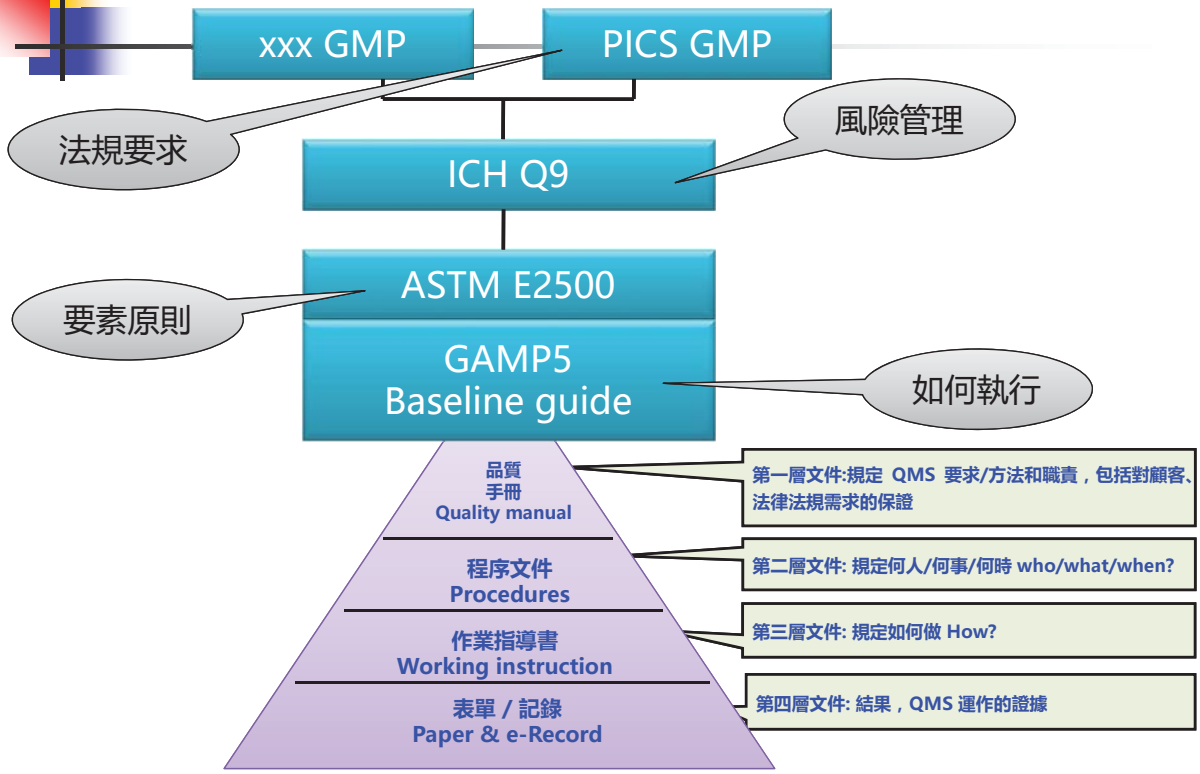
PQS infrastructure for CSV



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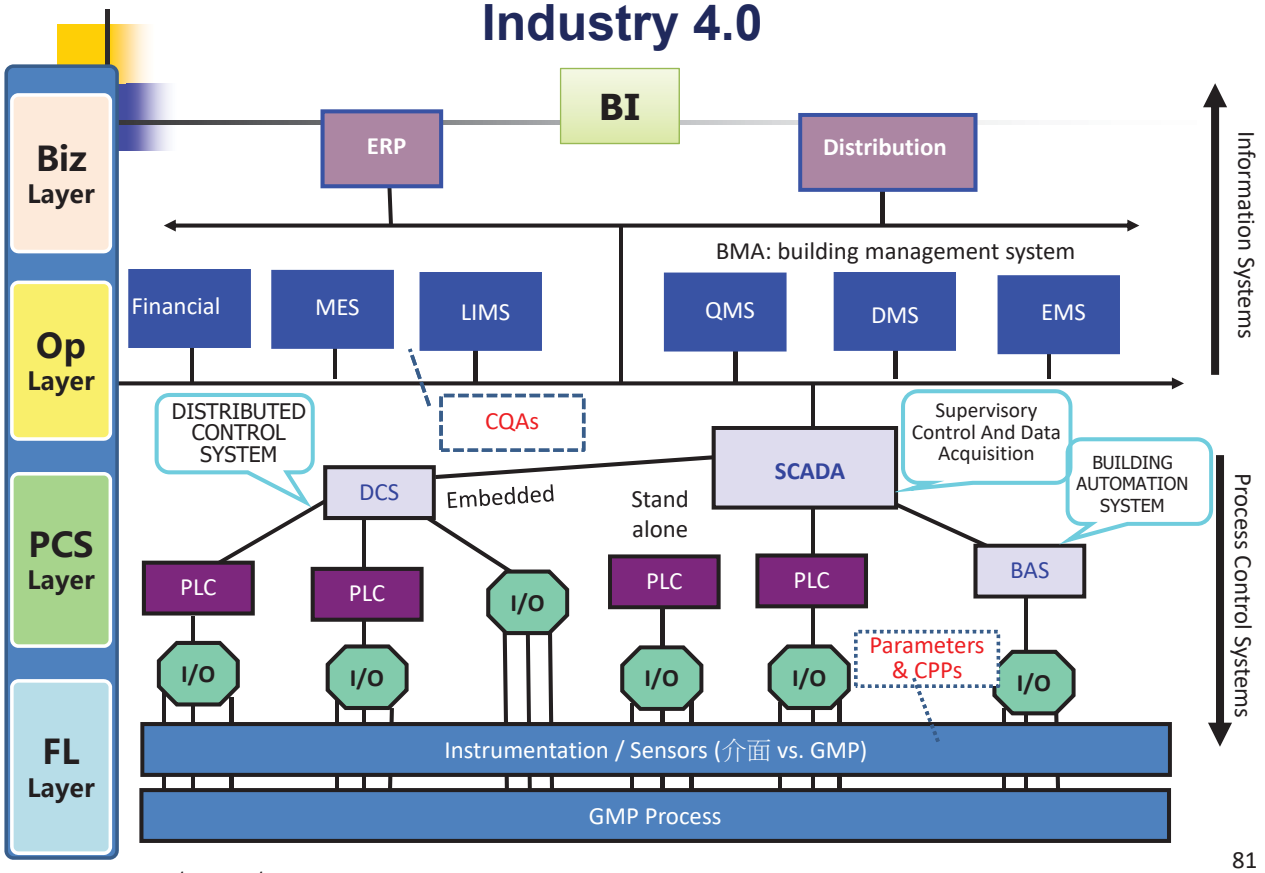
Operational Systems Architecture Industry 4.0



I/O: input/output

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GAMP5 Hardware Categories
硬體類別

Category 類別	Typical Approach 典型方法
一. Standard Hardware Components 標準硬體部件	1. Document manufacturer or supplier detail, serial number and version number 通過文件記錄下生產廠家或供應商的詳情、序號和版本號 2. Correct installation to be verified 確認正確的安裝 3. Configuration Management and Change control apply 適用組態管理和變更管制
二. Custom Built Hardware Components 定制製造的硬體部件	As per above plus:上述內容再加上： 1. Design specification 設計說明 2. Acceptance testing 接受度測試 3. Configuration and Change control apply 適用配置和變更過管控

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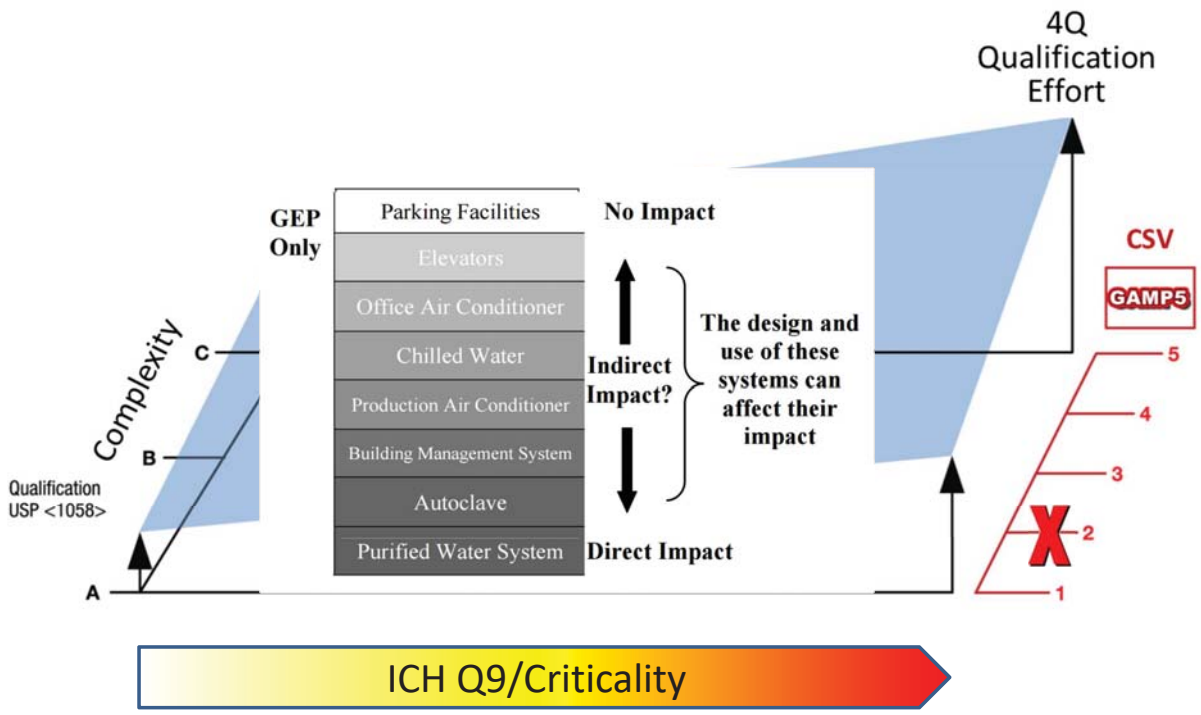
GAMP5 Categorization & Validation
品質風險管理應用於電腦確效

Review...

風險 複雜度 Complexity 越大

Category	Software Type	Validation Approach
1	OS, DB, MW…	Record version. The operating system will be challenged indirectly by the functional testing of the application.
2	Firmware 移除…因其不再僅限於功能…	Only for GAMP4 NA
3	Non-Configurable Software	Record version and verify operation against user requirements. Consider auditing the supplier for critical and complex applications.
4	Configurable Software	Record version and configuration, and verify operation against user requirements. Consider auditing the supplier for critical and complex applications. Manage any bespoke/custom programming as Category 5 software.
5	Customizable Software	Audit supplier and validate complete system (SDLC).

Different Approaches of USP, GAMP5 & Application of ICH Q9 QRM



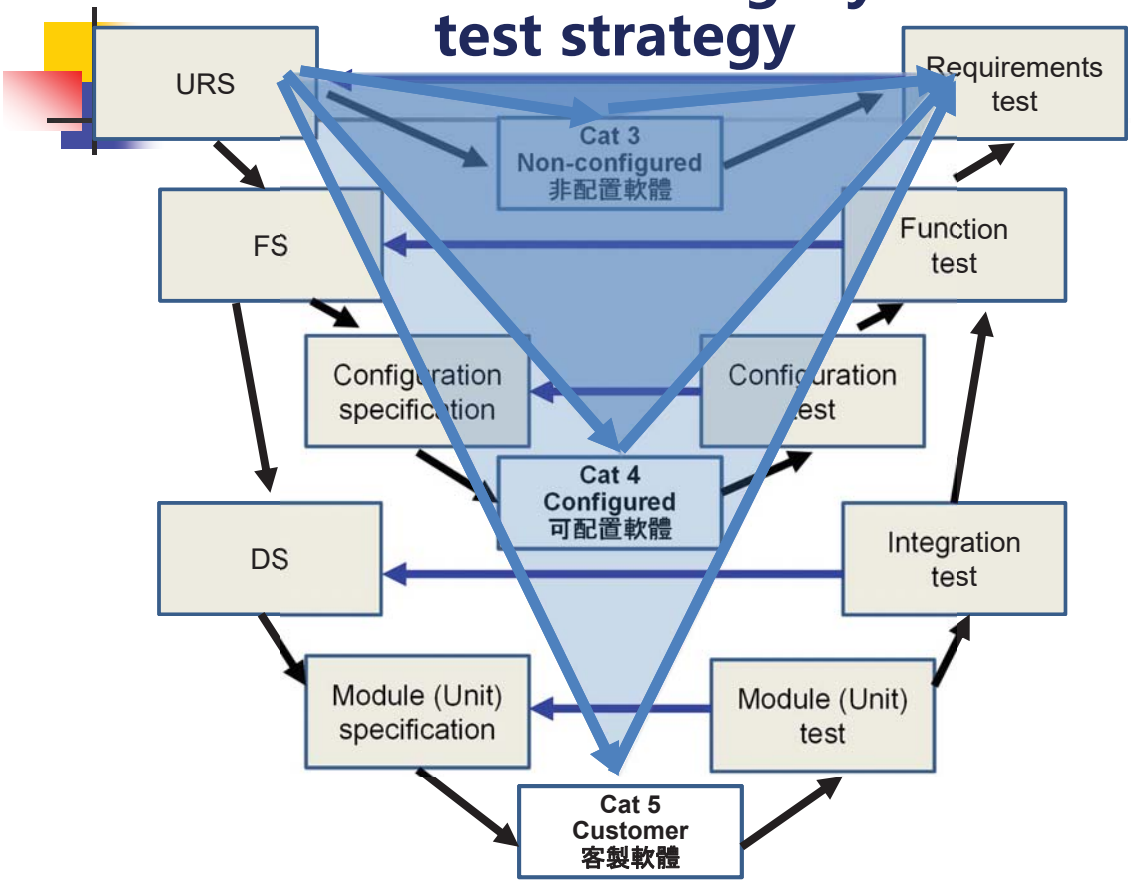
電腦化系統發展及確效生命週期

	SDLC階段	交付	風險評估 GAMP 分類			
			1	3	4	5
計劃	可行性研究	可行性研究報告	√	√	√	√
	工程計畫	工程計畫	√	√	√	√
		供戶評估			√	√
		確效計畫	√	√	√	√
		費用申請	√	√	√	√
設計	需求定義系統設計	用戶需求說明（URS）	√	√	√	√
		系統設定			√	√
		原始程式碼和配置			√	√
	系統測試	單體測試（白盒測試）				√
		集成測試（黑盒測試）			√	√

電腦化系統發展及確效生命週期

	SDLC階段	交付	風險評估 GAMP 分類			
			1	3	4	5
接收	系統驗收及確認	可行性研究報告安裝確效（IQ）方案和報告	√	√	√	√
		操作確效(OQ)方案和報告			√	√
		製程/性能確效(PQ)方案和報告		√	√	√
		人員訓練	√	√	√	√
		釋放通知	√	√	√	√
使用和維護	使用和維護	問題報告	√	√	√	√
		變更管制	√	√	√	√
		系統管理	√	√	√	√
		安全程序	√	√	√	√
		備份/存檔/災難恢復	√	√	√	√
		維護日誌	√	√	√	√
		週期性審查	√	√	√	√
		人員持續訓練	√	√	√	√
除役	系統除役	工程計畫（除役系統）	√	√	√	√
		系統除役報告	√	√	√	√

Software category test strategy



Approach To System Register Contents

Type of System	System Register Guidance	Examples
Laboratory System	One entry per system. A separate entry is required for each physical system of the same type.	pH Meter, Ultrasonic Bath, Mass Balance, HPLC, FTIR, Chromatography Data System, Robotic Systems
Process Control	One entry per system. A separate entry is required for each physical system of the same type.	Intelligent/Smart Instruments PLCs SCADA System Distributed Control Systems Expert Control Systems
Desktop Applications	One entry per GxP spreadsheet/database applications.	Spreadsheet applications. Database applications including Access.
IT System	One entry per production system instance. Care must be taken to ensure sites understand which multi-site systems they use.	SAP R/3 BPCS/JDE LIMS LAN/MAN/WAN

Examples of System Categorization

Laboratory Systems	Categories
pH Meter	3
Ultrasonic Bath	3
Mass Balance	3
High Performance Liquid Chromatography (HPLC)	1, 3, 4
SCADA system (no user defined macros)	1, 3, 4
SCADA system (with user defined macros)	1, 3, 4, 5
FTIR Spectrophotometry	1, 3, 4
Chromatography Data Systems (CDS)	1, 3, 4, 5
Laboratory Robotic Systems	1, 3, 4, 5
Standard interfaces to other connected systems	3 or 4
Bespoke/customized interfaces to other connected systems	5

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Examples of System Categorization

Process control systems type	Categories
Loop Controllers	3
Smart Instruments (analogue transmission of process variable)	3
Smart Instruments (digital transmission of process variable)	3
Intelligent Instruments (without control/logic functions)	1,3
Intelligent Instruments (with control/logic functions utilised)	1, 4
PLCs (customised system)	1, 5
PLCs (embedded system with no customisation	1, 4
SCADA system (no user defined macros)	1, 3, 4
SCADA system (with user defined macros)	1, 3, 4, 5
DCSs (standard configuration)	1, 3, 4
DCSs (customised e.g. Visual Basic routines)	1, 3, 4, 5
Data acquisition systems (configured, but no user macros/programming)	1, 4
Expert Control systems	1, 4, 5
Standard interfaces to other connected systems (e.g. MRPII,ERP, LIMS, MES)	3 ,4
Bespoke/customised interfaces to other connected systems	5

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Examples of System Categorization

Desktop Application	Categories
Spreadsheet Applications (no user configuration)	3
Spreadsheet Applications (user configuration of standard functions)	4
Spreadsheet Applications (user defined macros/programming, e.g. VBA macros or calculations, report queries developed with SQL, any other bespoke/custom programming)	5
Database Applications (user configuration of standard functions)	4
Database Applications (user defined macros/programming, e.g. VBA macros or calculations, report queries developed with SQL, any other bespoke/custom programming)	5
Statistical Analysis Package (user configuration of standard functions)	4

Examples of System Categorization

IT System	Categories
Enterprise Resource Planning (ERP)	1, 3, 4, 5
Manufacturing Resource Planning (MRPII)	1, 3, 4, 5
Laboratory Information Management (LIMS)	1, 3, 4, 5
Electronic Document Management system (EDMS) e.g. EBR	1, 3, 4, 5
Engineering Maintenance Management system (EMS)	1, 3, 4, 5
Distribution System e.g. EDI	1, 3, 4, 5

Examples of System Categorization

Element	Detail
General Management	Training, Service level agreements, contracts, etc.
Servers and Mainframes	Installation, changes, decommissioning, hardware/software maintenance, management of outsourced services, service start up and shut down, job scheduling, system monitoring, problem logging/tracking/reporting, etc.
Network Management	Installation, changes and decommissioning, management of third party networks, hardware/software maintenance, service monitoring, problem logging/tracking/reporting, etc.
Desktop Management	Establishment of standard desktop, hardware/software installation, changes, decommissioning, maintenance of virus protection, distribution of software upgrades, etc.
Security Management	Physical security, logical security, password ageing, user account management, access rights, installation of anti virus software, handling of virus alerts and infections, etc.
Data Management	Back-up and restoration of data, media management, long term data archiving, etc.
Quality Management	Internal audit process, document management, record management, corrective and preventative action, process improvement, GxP training, etc.

Inventory Register
公用設施和設備的風險登錄

Equipment Inventory, QC Laboratory Example -Example — 10-Aug-15

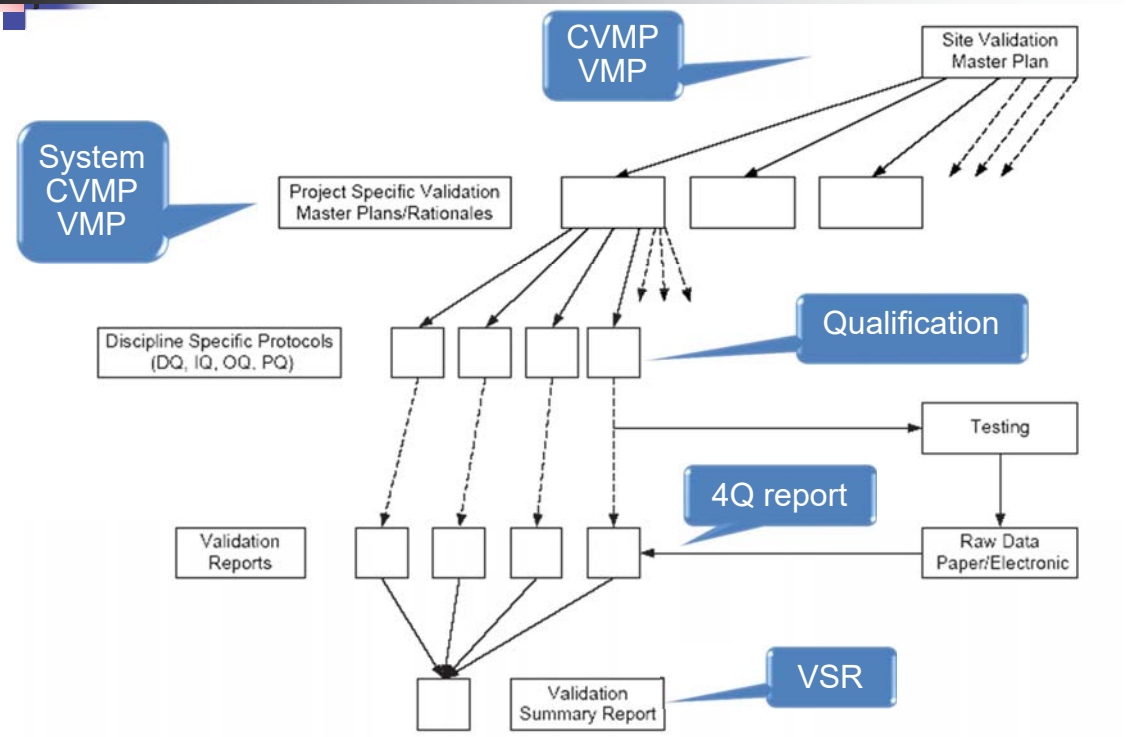
System ID	System Description	Components Details (Description/ Manufacturer/ Model / Serial) - Subsystem	Component Software / Firmware Name / Versions	Software GAMP Category
QAA/QC/AA/01	AA Spectrometer	AA Spectrometer, Perkin Elmer, 4100, serial 1063	Unknown	3
		Autosampler, Perkin Elmer, AS-90, serial 4170	Firmware version 2	3
		FIAS, Perkin Elmer, 400, serial 4716	Unknown	3
		Furnace, Perkin Elmer, HGA-700, serial 8119	Firmware version 2	3
		Furnace A/S, Perkin Elmer, AS-70, serial 3366	Firmware version 2	3
		Furnace cooler system, Perkin Elmer, N/A, serial 3062	Firmware version 2	N/A
		PC, Dell, Optiplex GX1, serial IN6DA	Microsoft Windows 2000, ver 1.01	1
			AA Winlab, ver 3.51	4
QAA/QC/GC/03	GC	Shimadzu GC, GC15A, serial 60270DN	Unknown	3
		Shimadzu Intergrator, CR4A, serial 85070LP	Firmware version 3.3	3
QAA/QC/LC/02	HPLC	HP pump, G1311A, serial DE72002618	Unknown	3
		HP autoinjector, G1329A, serial DE80301139	Firmware version 2	3
		HP degasser, G1314A, serial JP77304078	Firmware version 3.1	3
		HP column unit, G1316A, serial DE72003696	Firmware version 2	3
		HP column cooler, G1330A, serial DE3301381	Firmware version 1.1	3
		HP UV detector, G1322A, serial JP73007457	Firmware version 3.2	3
		HP navigation unit, G1323A, serial, DE53305011	Unknown	3
		PC:HP Vectra XA, serial FR72659138	PC firmware unknown	3
			Windows NT Ver 4.0	1
			HP Chemstation 3, Ver A.06.03	4
		Printer: HP laserjet 4000, serial NLEW0909855	Unknown	3
QAA/QC/UV/02	PE Lambda UV Spectrometer	PE Lambda 16, serial 60015	Unknown	3
		PC: Dell Optiplex GX1, R6J31	PC firmware unknown	3
		Printer: Epsom stylus colour 440, serial A577260772	MS Windows 2000, ver 4.00.950B	1
			UV Winlab, ver 2.80.03	4
QAA/QC/BL/01	Analytical Balance	Balance, Mettler, AE160, serial C65854	Firmware version 3	3

on Review Due	Non-GMP (Y/N)	Risk Level	Risk Priority
1	N	High	High
2	N	High	Low
1	N	High	Medium
1-Jan-01	N	Low	Low

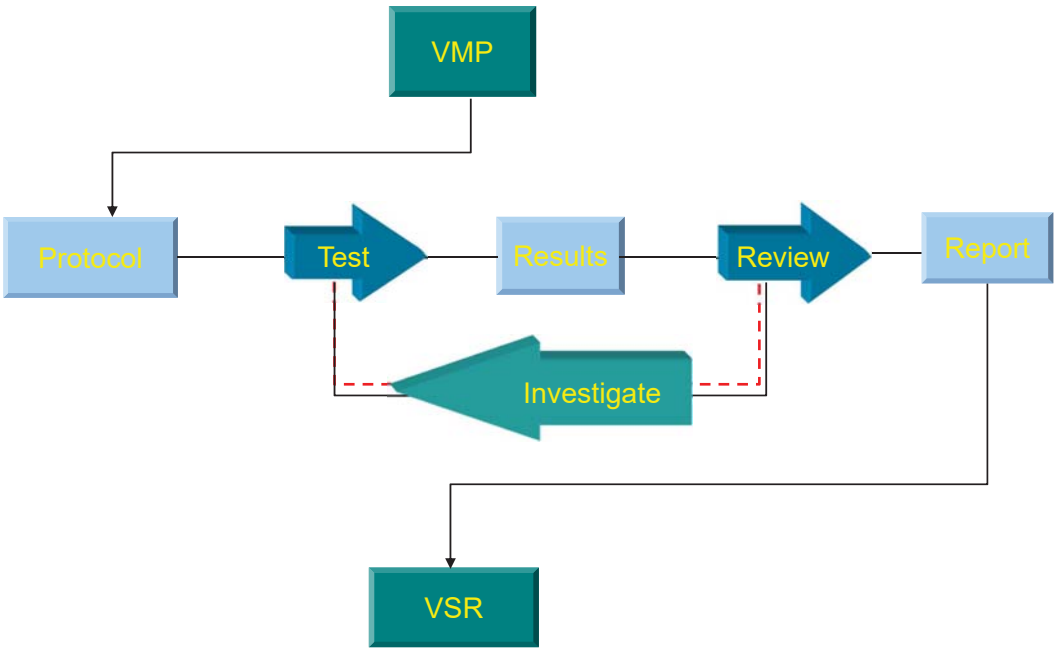
dated, plan to review against FSOP 0962.

原則上，生物製劑、無菌製劑風險風險度最大...

Validation Document Hierarchy CSV



Schematic Activity and Documentation Process flow



CSV 確效的要素

- **DQ：設計確效**

  確認系統、設備的設計滿足最初設計的意圖，並文件化的行為（設計審查）

- **IQ：安裝確效**

  確認所安裝的系統滿足事先批準的規格的要求，並文件化的行為 incl: FAT and SAT，又名 Integrity test

- **OQ：操作確效**

  確認系統在規定的整個運行範圍內，按照事先批準的規格的要求運行，並文件化的行為，又名 Function test，un-loading test

- **PQ：性能確效**

  確認系統在規定的運行環境中運行時，全部生產製程活動所發揮的執行、管控等性能，滿足事先批準的規格的要求，並文件化的行為，又名 Acceptance test，Loading test

Validation Summary Report VSR

VP ⟷ VSR

The Validation Summary report (VSR) cover:

➔ **Summarising the validation exercise, results and conclusions**

➔ **A best practice high level report**

➔ **Linking via cross referencing to lower level project records, detailed reports and protocols**

➔ **Qualification testing linked spec & criteria**

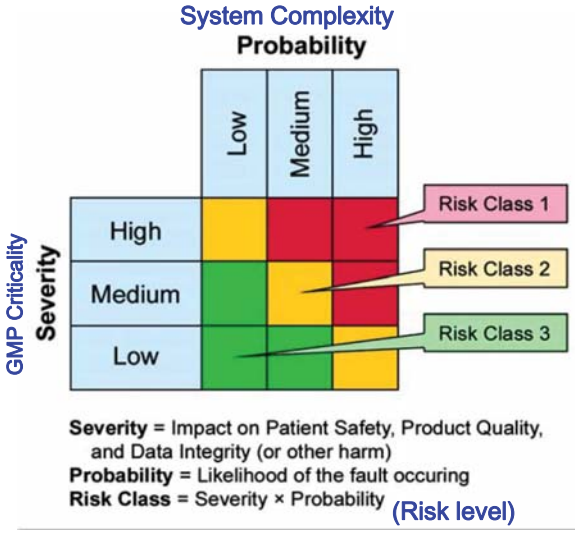
- ✓ **PQ vs. URS**
- ✓ **OQ vs. FS**
- ✓ **IQ vs. DS / DR**
- ✓ **Supplier audit reports**
- ✓ **Validation Master Plan (VMP) / Validation Plan (VP)**

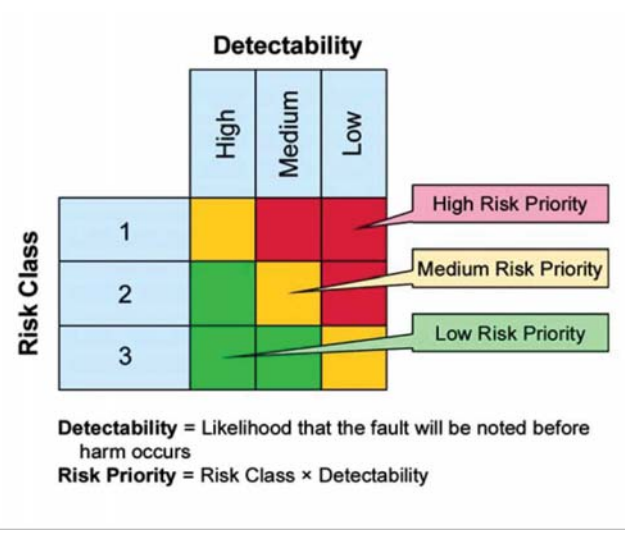
VSR總結整個流程是按照VP的計畫和策略實施的；其最重要的意義是總結確效過程中出現的異常和變更、矯正和預防措施；同時給出放行聲明以及運行維護方面的建議

QRM Application for CSV

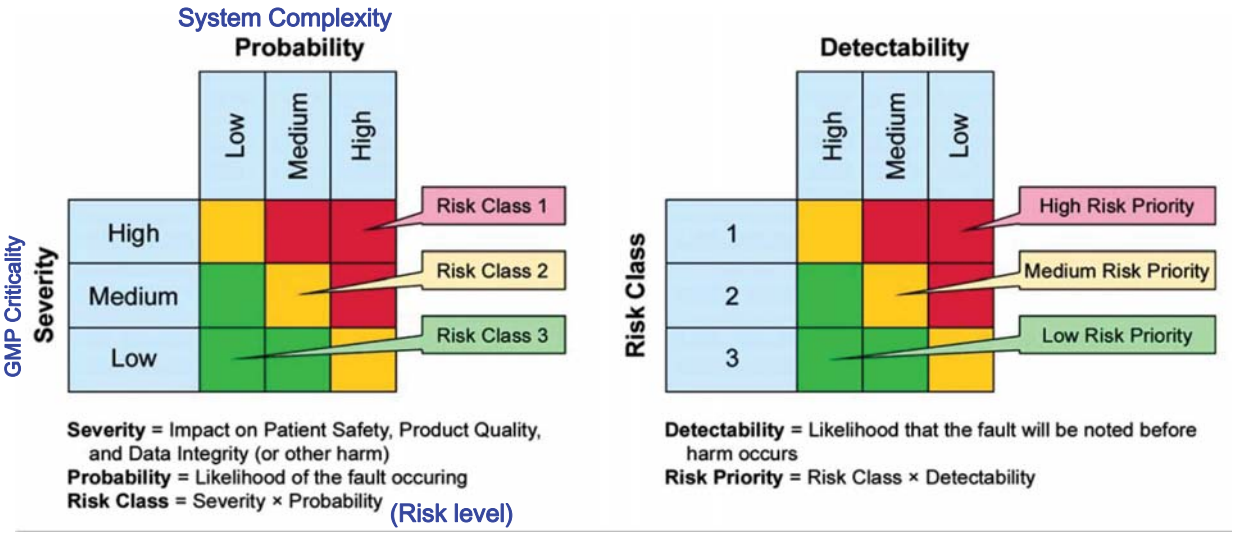
品質風險管理應用

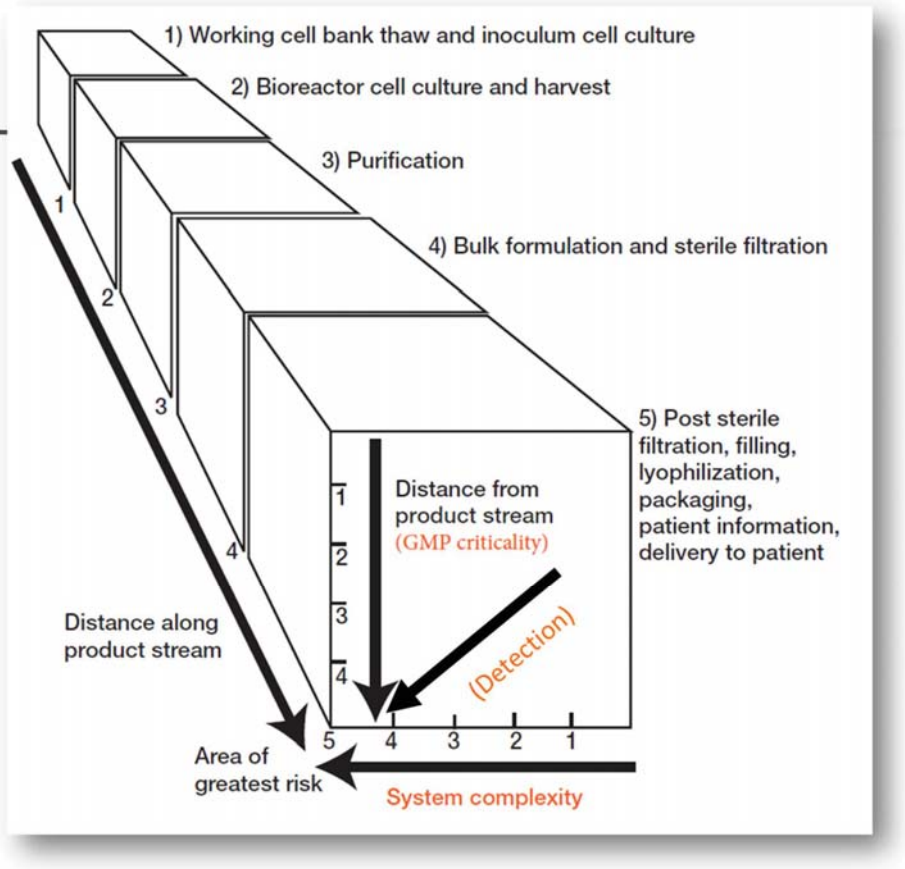
Risk assessment method
實用風險評估方法範例





Risk assessment method
實用風險評估方法範例





Inventory Register
公用設施和設備的風險登錄

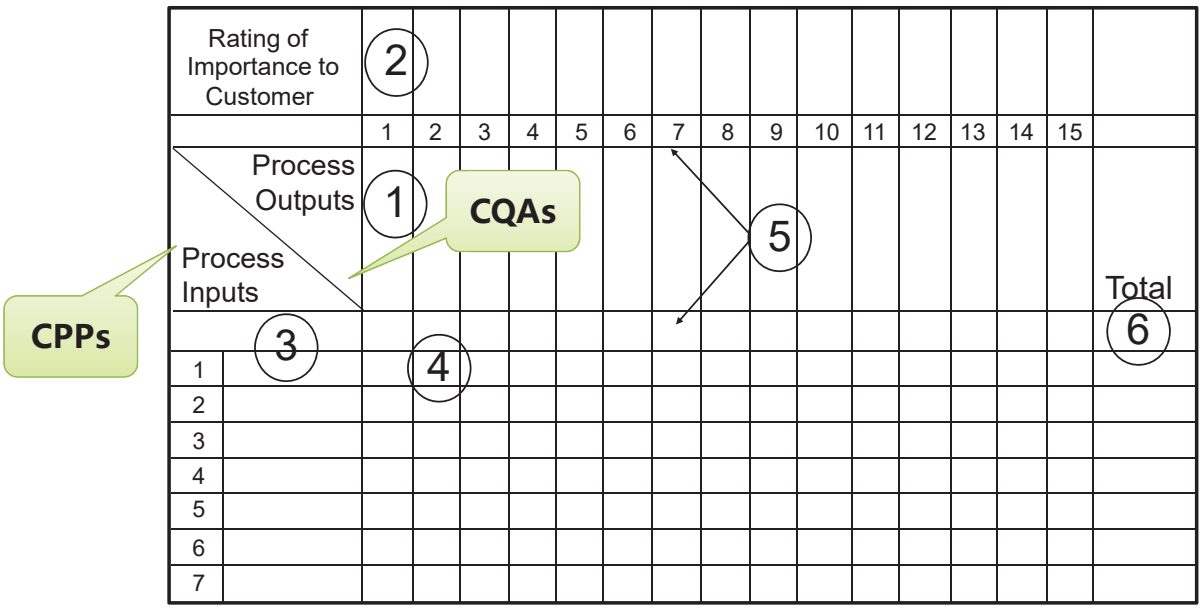
Equipment Inventory, QC Laboratory Example -Example — 10-Aug-15

System ID	System Description	Components Details (Description/ Manufacturer/ Model / Serial) - Subsystem	Component Software / Firmware Name / Versions	Software GAMP Category	Non-GMP (Y/N)	Risk Level	Risk Priority
QAA/QC/AA/01	AA Spectrometer	AA Spectrometer, Perkin Elmer, 4100, serial 1063	Unknown	3	N	High	High
		Autosampler, Perkin Elmer, AS-90, serial 4170	Firmware version 2	3			
		FIAS, Perkin Elmer, 400, serial 4716	Unknown	3			
		Furnace, Perkin Elmer, HGA-700, serial 8119	Firmware version 2	3			
		Furnace A/S, Perkin Elmer, AS-70, serial 3366	Firmware version 2	3			
		Furnace cooler system, Perkin Elmer, N/A, serial 3062	Firmware version 2	N/A			
		PC, Dell, Optiplex GX1, serial IN6DA	Microsoft Windows 2000, ver 1.01	1			
			AA Winlab, ver 3.51	4			
QAA/QC/GC/03	GC	Shimadzu GC, GC15A, serial 60270DN	Unknown	3	N	High	Low
		Shimadzu Intergrator, CR4A, serial 85070LP	Firmware version 3.3	3			
QAA/QC/LC/02	HPLC	HP pump, G1311A, serial DE72002618	Unknown	3	N	High	Medium
		HP autoinjector, G1329A, serial DE80301139	Firmware version 2	3			
		HP degasser, G1314A, serial JP73704078	Firmware version 3.1	3			
		HP column unit, G1316A, serial DE72003696	Firmware version 2	3			
		HP column cooler, G1330A, serial DE33301381	Firmware version 1.1	3			
		HP UV detector, G1322A, serial JP73007457	Firmware version 3.2	3			
		HP navigation unit, G1323A, serial, DE53305011	Unknown	3			
		PC:HP Vectra XA, serial FR72659138	PC firmware unknown	3			
			Windows NT Ver 4.0	1			
			HP Chemstation 3, Ver A.06.03	4			
		Printer: HP laserjet 4000, serial NLEW0909855	Unknown	3			
QAA/QC/UV/02	PE Lambda UV Spectrometer	PE Lambda 16, serial 60015	Unknown	3	N	Low	Low
		PC: Dell Optiplex GX1, R6J31	PC firmware unknown	3			
		Printer: Epsom stylus colour 440, serial A577260772	MS Windows 2000, ver 4.00.950	1			
			UV Winlab, ver 2.80.03	4			
QAA/QC/BL/01	Analytical Balance	Balance, Mettler, AE160, serial O65854	Firmware version 3	3			

原則上，生物製劑、無菌製劑風險風險度最大...

C&E Matrix Format
CPPs vs. CQAs

Cause and Effect Matrix



Cause-&-Effect Matrix Vaccine example

Process Parameters	Potency	Purity	Identity	Dose	pH	Moisture	Appearance (Lyo)	Appearance (Recon)	Recon Time	Endotoxin /LAL	Sterility	General Safety	Sub-Visible Particulates	Adsorption	Formulation Composition	Score
Raw Material (DS)	10	10	10	5	5	1	1	5	1	5	5	5	5	10	5	83
Raw Material (Buffer)	1	5	1	1	10	7	7	7	5	5	5	5	1	7	10	77
Raw Material (Vial/Stopper)	1	1	1	1	1	10	5	5	1	5	10	1	5	1	1	49
DS Thaw/ Handling	5	5	1	1	1	1	1	1	1	1	1	1	5	5	1	31
Formulation Compounding & Mixing	10	1	1	10	5	5	5	1	5	5	5	1	5	7	7	73
Filtration	5	5	1	5	1	1	1	1	1	1	10	1	7	5	1	46
Filling	7	1	1	10	1	1	5	1	5	5	5	1	7	5	1	56
Lyophilization	1	5	1	1	1	10	10	5	10	5	5	1	5	1	1	62
Capping	1	1	1	1	1	5	1	1	1	1	7	1	1	1	1	25
Visual Inspection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
	42	35	19	36	27	42	37	28	31	34	54	18	42	43	29	

Critical Process Variables "Relevance" matrix for cell culture example

EXAMPLE OF CRITICAL PROCESS VARIABLES / Process Steps & Unit Operations	Homogeneity / Uniformity	Shear	Temperature	pH	Viscosity	Osmolality	Conductivity	Sterility	BioBurden	Growth Rate	Cell Concentration	Product Concentration	Cell Culture By-product Proteins	Other By-products	Yield	Stability	Product Identity	Purity	Endotoxin	Viral Clearance	Composition of Process Stream
Solution Preparation:																					
Media	C		N	C		C		C	C							C	C			C	C
Buffer	C		N	C		C	C		C							C	C		C		C
Fermenter:																					
Cell Culture	C	C	C	C	N			C		C	C	C	C	C	C	C	C				C
(Microbial) Fermentation	C		C	C	N			C		C	C	C		C	C	C	C				C
Recovery:																					
Centrifugation		C	N		C				C		C		C	C	C						C
Cell Disruption	C		N	N	N				C		N			C	C						C
Microfiltration	C	C	N	N			C		C				C	C	C	C					C
Depth Filtration			N						C		N				C						N
Extraction	C		C	C					C			C		C	C	C		C			C
Refold	C	C	C	C			C		C			C		C	C	C		C			C
Expanded Bed Chromatography	C		N	C			C		C		N	C	C	C	C		C	C	C	N	C
Purification:																					
Ion Exchange Chromatography	C		N	C			C		C			C	C	C	C		C	C	C	N	C
Affinity Chromatography	C		N	C			C		C			C	C	C	C	C	C	C	C	N	C
Hydrophobic Interaction Chromatography	C		N	N			C		C			C	C	C	C		C	C	C	N	C
Size Exclusion Chromatography	C		N	N					C				C	C	C		C	C	C	N	C
High Pressure Liquid Chromatography	C		N	C	N		C		C			C	C	C	C	C	C	C	C	N	C
Precipitation	C	C	C	C	N		C		C			C	C	C	C		C	C	C	N	C
Chemical Treatment	C	N	C	C					C			C	C	C	C	C		C	C	C	C
Ultrafiltration / Diafiltration	C	C	N	N	N		C		C			C	C	C	C	C		C	C		C
Nanofiltration	C	N	N	N	N				C			C	C	C	C	C		C	C	C	C
Bulk in process:																					
Bulk Formulation / Bulk Fill	C		N	C			C		C			C	C	C	C	C	C	C	C	C	C
Sterilize-in-Place			C					C	C										C	N	
Clean-in-Place	C		C	N			C		C										N	N	C

LEGEND:

C — Typically a critical parameter

N — A design consideration, but not usually a critical parameter

Usually not a design consideration

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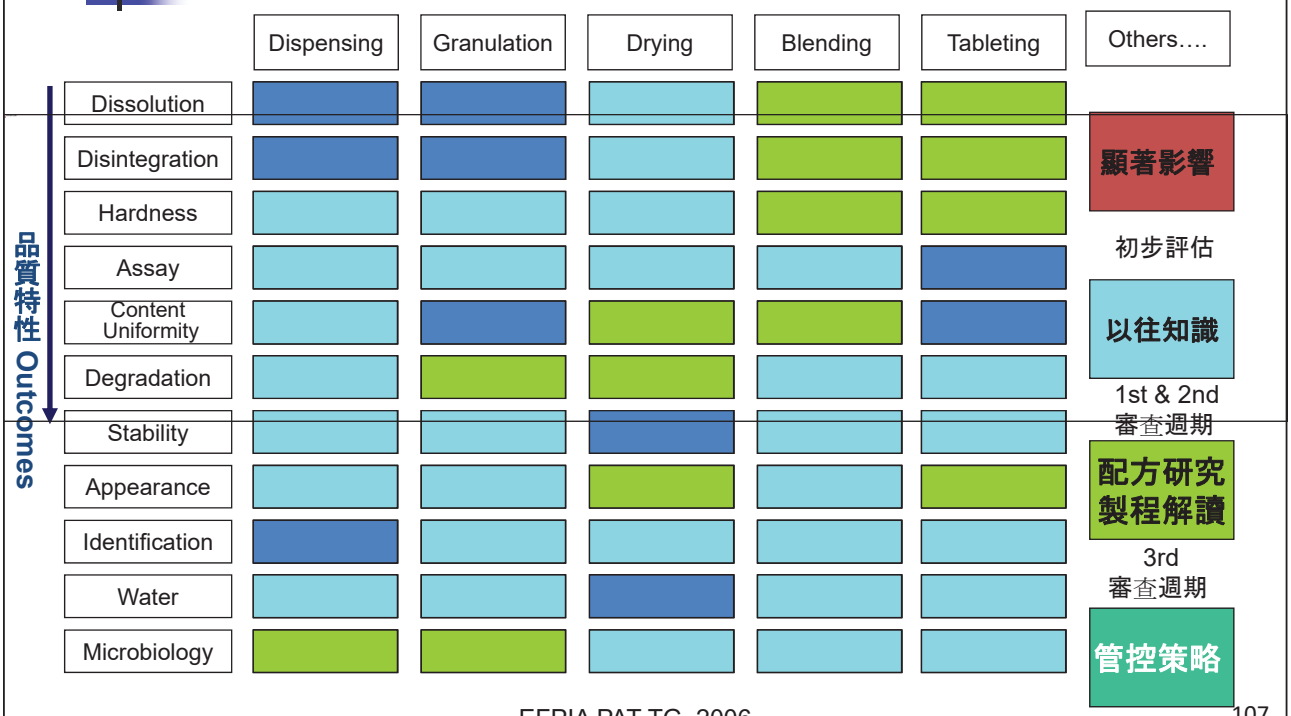
品質風險管理 – 聚焦於重要特性



EFPIA PAT TG, 2006

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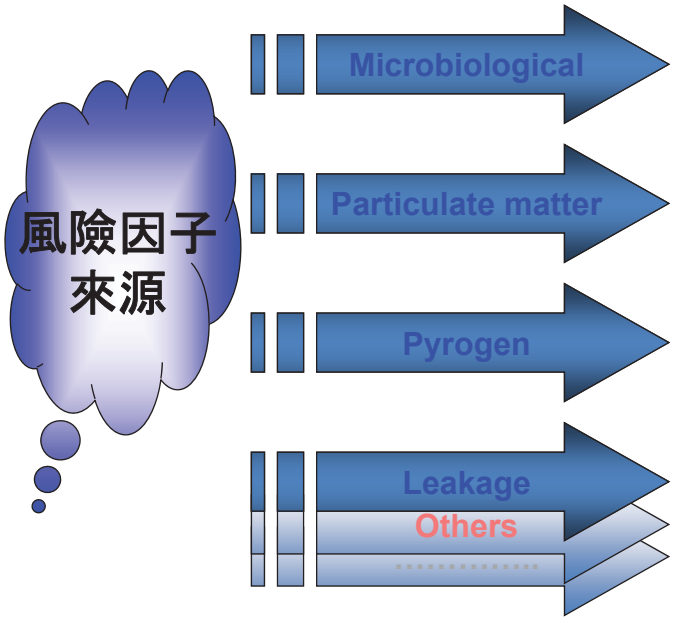
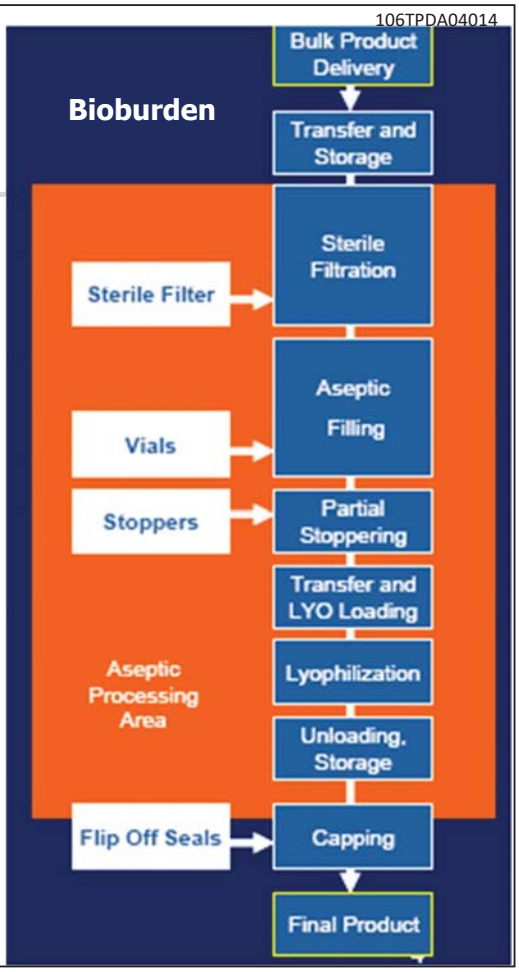
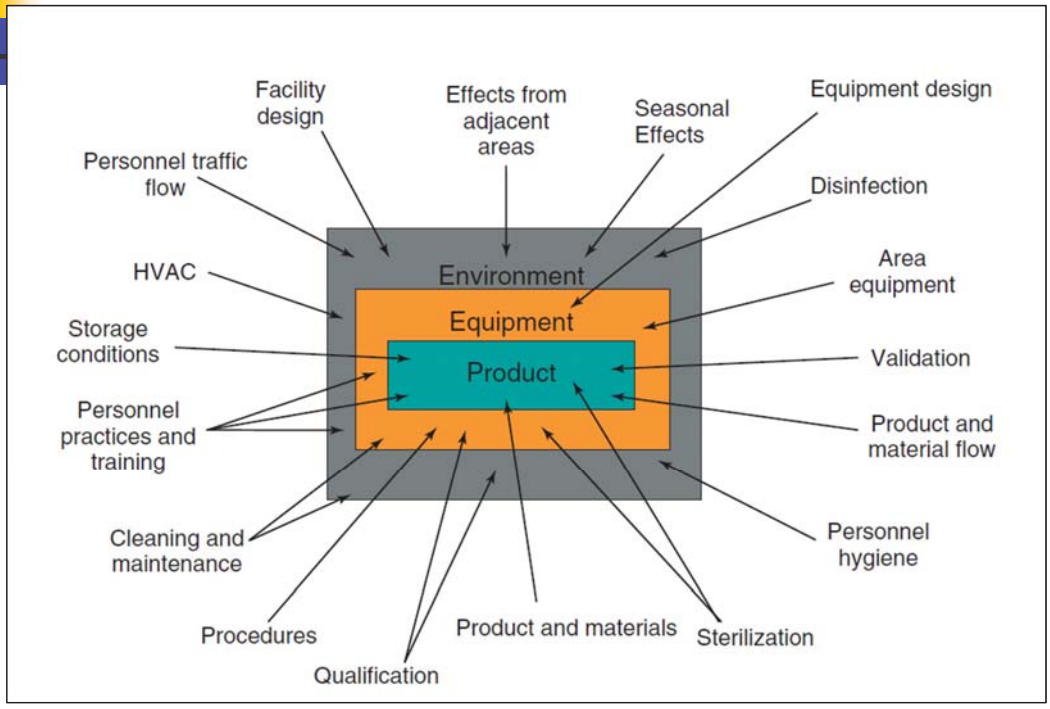
範例: 一般典型的無菌製程







Typical Impact of records example DI by QRM

Type of record	Typical Impact
Training/personnel record, job descriptions, incl. roles and responsibilities.	L-M
QA Audits and Investigations (including Deviations)	H
Equipment cleaning records	H
Calibration records	H
Planning documents	L
Validation documentation	L-M
Financial Disclosure by Clinical Investigators	L
Inspection Records	M

Type of record	Typical Impact
Environmental Monitoring records	M-H
SOPs	L-H
Material and finished product specifications	H
Distribution records	H
Clinical and Non- clinical studies and reports	H
Informed consent documentation	M
Investigational New Drug applications (INDs)	H
Disposition of investigational drug	H
New Drug Applications (NDAs)	H
Adverse Events (AEs) and Adverse Drug	H

Type of record	Typical Impact
Reactions (ADRs)	H
Bio-equivalency Study Reports	H
QC Analysis results	H
Batch records	H
Component, drug product container, closure, and labeling records	H
Sample management records	L
Patient information leaflets	H
Master production and control records	H
Complaint files	H

Data Integrity

“數據完整性，可靠性”

Data integrity global regulations under ICH Q9

	FDA	MHRA	WHO	PIC/S	EMA	PDA	ISPE
Scope 範圍	GMP	GxP (draft) GMP	GCP/GLP/ GMP	GMP/ GDP	GMP	GxP	GAMP GxP
Format 形式	Q&A Part 11	Guidance	Guidance	Guidance	Q&A	CoC	Guide

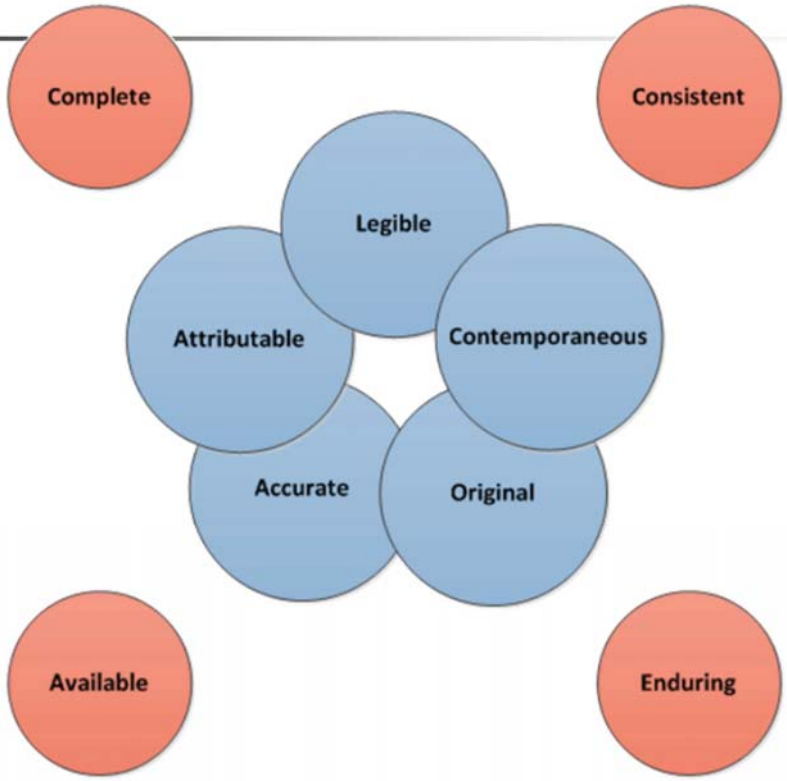
What is data?

- 數字、數值，也可以是文字、圖像、聲音等任何表現產品歷史的全部資料
- 通過對數據的審查、分析，可以用於科學研究、產品設計、品質查證等功能
- MHRA指南給予“數據”原則性的要求認爲，數據是由初始數據衍生或取得的資訊，且必須符合ALCOA 原則

What is data integrity?

- Data integrity refers to the completeness, consistency, and accuracy of data
  是指數據的完全性、一致性和準確性
- 應當具有 ALCOA
  - Attributable（可歸屬性）、Legible（清晰可辨性）、Contemporaneous（即時性）、Original（被記錄、原始性或真實有效副本）和 Accurate（準確性）

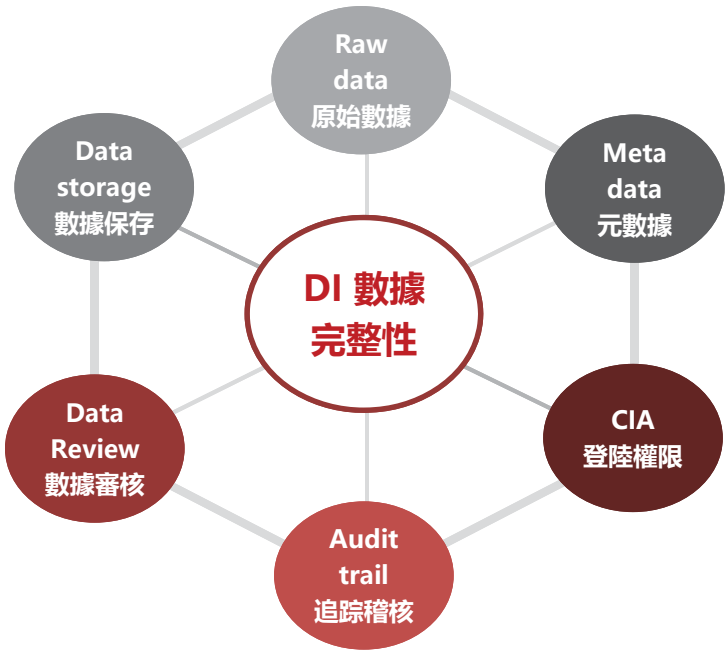
ALCOA & ALCOA+



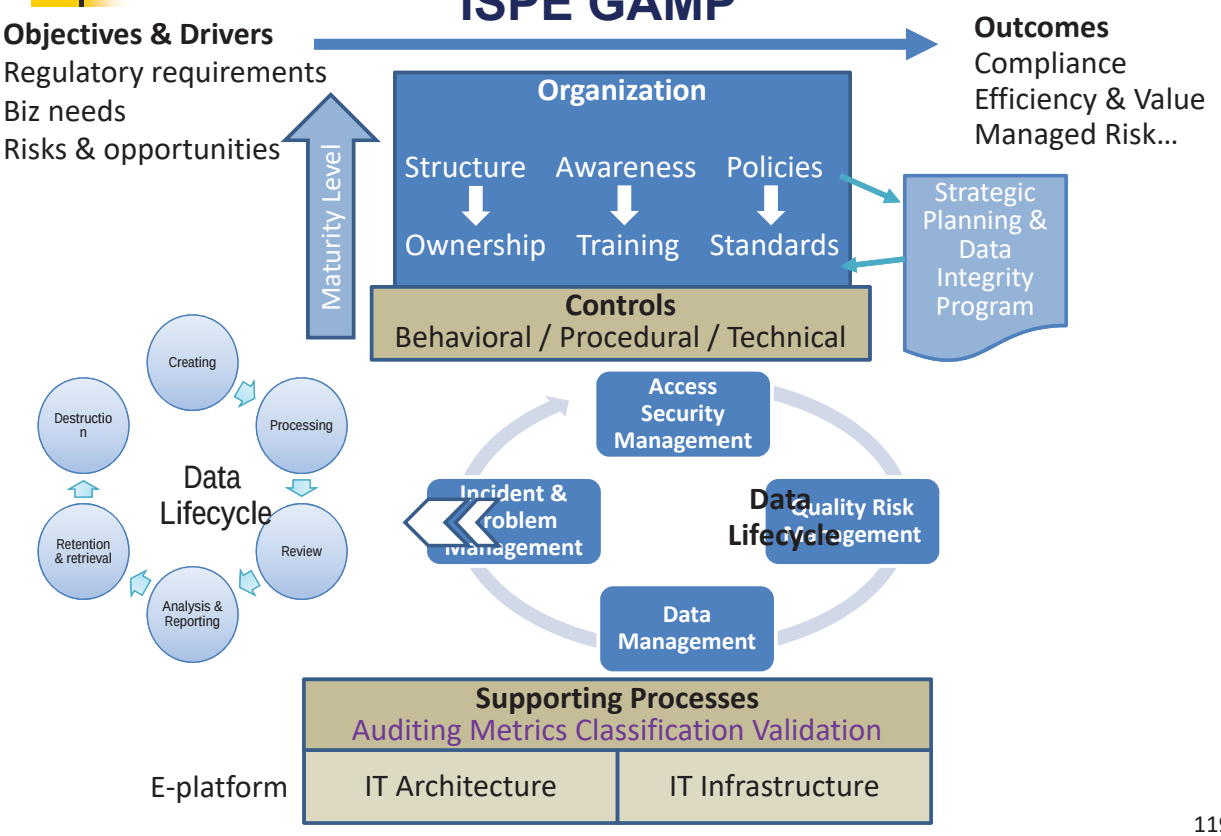
Data management principle ALCOA & ALCOA+

基本原則	A	Attributable	可歸屬的	記錄可追溯
	L	Legible	清晰的、可見的	清晰可見
	C	Contemporaneous	同步、及時	與操作同步生成 / 輸入
	O	Original	原始的	第一手數據，未經改變的，真實副本
	C	Accurate	準確的	與實際操作相一致的，無主觀造假或客觀 輸入錯誤
管理基本原則	C	Complete	完整的	無遺漏
	C	Consistent	一致的	與實際生成邏輯順序一致，現實的記錄人 同實際操作者一致
	E	Enduring	長久的	原始數據長久保持，不易剔除、遺失
	A	Available	可獲取的	數據在審核是可獲取，不被隱藏

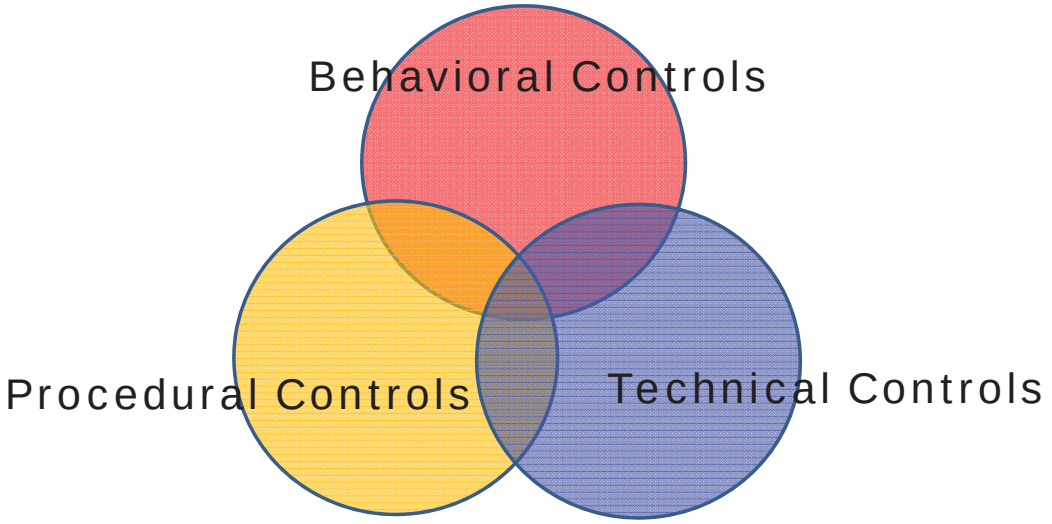
法規要求-DI 基本要素



Data Governance Framework
ISPE GAMP



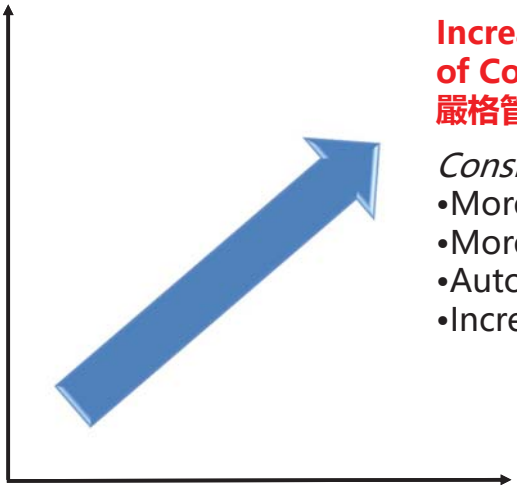
Data Governance Control



Relationship between Impact, Risk, and Rigor of Controls

Increasing Impact
衝擊增加

Increased effect on:
- Patient safety
- Product safety
- GxP compliance



Increased Rigor of Control required
嚴格管控要求增加

Consider:
- More controls
- More frequent controls
- Automatic controls
- Increased internal audits

Increasing Risk 風險增加

Increased Potential for:
- Loss of record
- Corruption of record
- Wrong record
- Lack of detection

影響 DI 的系統因素

- 論理行為準則 CoC/CoE Policies
- 品質文化 Culture
- 品質管理系統 ICH Q9/Q10 – QRM/PQS
- 品質度量 Quality Metrics
- 資源配置 Resource Allocation
- 內部問題解決 Effective Problem Solving
- 訓練 OJT - Abilities

Some important DI terms

- Archive
- Audit trail
- ALCOA
- Back-up
- Computerized system
- Control strategy
- Data
- Data Governance
- Data Integrity
- Data Lifecycle
- Meta-data
- True copy
- CIA
- Test into compliance data
- Dynamic record
- Static record
- Data exclude
- Data transfer/migration
- Data Processing
- Exception report
- Electronic signatures
- Data Review
- User access/system administrator
- Flat file
- CAPA
- Good data and record management practices

DI some highlight topics

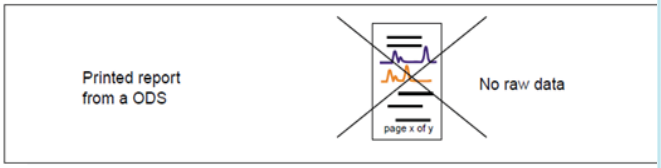
- **Raw data**
  - 以原始生成的格式（即，紙本或電子形式）或以“真實副本”進行保留的原始記錄與文件
- **Flat file**
  - 設備中的電子記錄，電子記錄又細分爲兩種形式，沒有相對結構的文件（Flat File）和數據庫文件（Database File）

DI some highlight topics

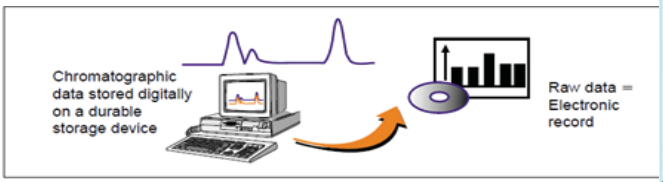
- **Meta Data**
  - 超數據、中介數據、元數據、數據定義、後設數據、 以及數據包等
  - Data about data
  - 「有關資料的資料」或「描述資料的資料」- 如描述 data 屬性 property 資訊，以支持如指示存儲位置、歷史數據，資源查找，文件記錄等功能
  - E.g. data 3.5 和 meta data，提供內容爲 NaCl, Lot1234 ，3.5mg，J Smith 01/07/2017 meta data 是組成原始記錄的不可分割的部分，沒有meta data，Data 本身就沒有了意義
  - E.g. Audit trail is on of “meta data”

“Data” Understanding!

With some devices, the real record is a hard copy.



The printed copy of an electronic record is no longer considered raw data. The “typewriter excuse” is no longer accepted.



With chromatography data systems, the raw data typically is an electronic record

記錄=原始數據+元數據
Record=Raw data + Meta data
原始數據=原始的二進位制符號
結果數據(process data)=計算的結果
元數據=用於計算的過程參數

元數據：

- **過程參數**
- **區域，反應係數**
- **計算**
- **校準數據**
- **其他資訊**

一個可信的電子記錄結果由原始數據和與其有關聯的元數據組成

DI some highlight topics

- **Data life cycle**
  - 數據產生、處理、審查、分析和報告、傳遞、儲存和恢復及持續監控直至銷毀的過程的所有階段應該有一個有計劃的方法來評估、監控和管理數據和在某種程度上與病患安全、產品品質的潛在影響和/或貫穿於數據生命週期的所有階段做的決策的可靠性相適應的那些數據的風險 (WHO)
  - 數據生命週期的各個階段，包括數據的初始生成和記錄、處理、使用、保存，備份、歸檔和銷毀
- **Data governance**
  - 不論這些數據產生形式如何，爲確保在整個生命周期內數據的記錄、處理、保留和使用均完整、一致和準確所采取措施的總和，e.g. ISPE

DI some highlight topics

- **Archiving**
  - 歸檔是保護記錄不能被進一步改變或刪除和在整個需要的記錄保留時間內在專門的數據管理人員的管控下儲存這些記錄的過程
  - 應包含歸檔記錄，如關聯的元數據和電子簽名
- **Audit trail (…one of meta data)**
  - 指安全的、電腦生成的、時間標記的電子記錄，允許重建有關創建、修改或刪除電子記錄的事件過程 – 人事時地物(5W)，應適時審查 or 備查
  - 歐盟對工廠完成全面audit trail系統的升級期望是 2017 年底前
- **CAPA and Chang Control**

系統	潛在DI風險	風險源	CAPA提議	CAPA負責人	有效性評估
…	…	…	…	…	…

DI some highlight topics

- **Dynamic record vs. Static record**
  - 靜態用於表示固定數據文件，例如紙本記錄或電子圖像，動態指記錄形式允許用戶和記錄內容之間存在互動
  - 動態格式的記錄，例如電子記錄，允許在用戶和記錄內容之間建立互動的關係例如，在數據庫格式中的電子記錄允許用戶去追踪、分析趨勢和查詢數據；作爲電子記錄保持的色譜記錄允許用戶再處理這些數據和放大基準線以便更清晰地查看積分
  - 靜態格式的記錄，例如紙本或PDF記錄，是一個固定的和在用戶和記錄內容之間允許少量或沒有互動的格式，例如一旦列印或轉換成靜態PDF，色譜記錄就失去再處理或查看更多基準線細節資訊的能力
- **True copy**
  - 真實副本是數據的原始記錄的副本，被證明可以確認它是一個額外和完整的副本可以代表原始記錄的全部的內容和意思，包括如果是電子記錄適用的所有的元數據和原始記錄格式
- **Record**
  - QMS 空白表格管控，連號管控-log book

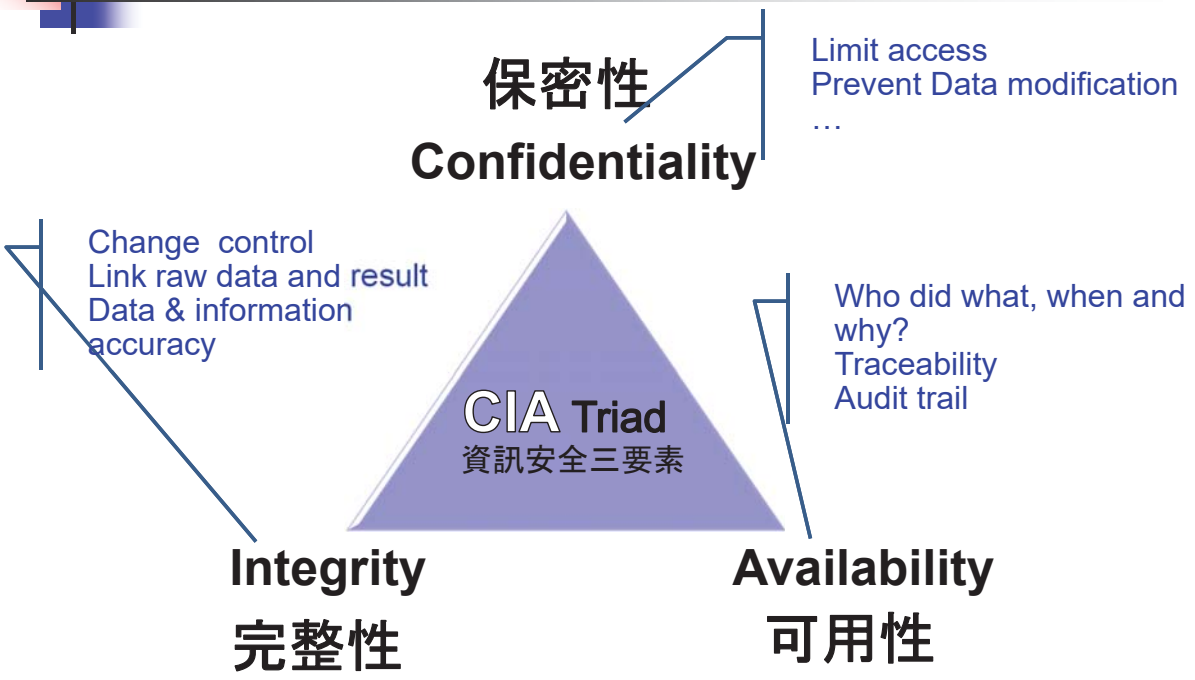
DI some highlight topics

- **Hybrid approach**
  - 指的是在原始電子記錄和紙本記錄包括應該審核和保留的全部記錄集組合使用的地方使用電腦化系統
  - 混合方法例如在使用電腦化儀器系統的實驗室分析的地方產生原始的電子記錄然後列印出結果的匯總
  - 混合方法需要一個在記錄保留周期內所有包括紙本和電子記錄類型之間的安全連接
  - 在混合方法使用的地方，應該有對電子文件，例如範本，可能列印的表格和主文件的適當管控
- **Test into compliance**
  - 不符合CGMP的符合性導向檢驗，實現特定結果或克服不可接受結果爲目的的取樣和檢驗取得的數據 (FDA OOS)

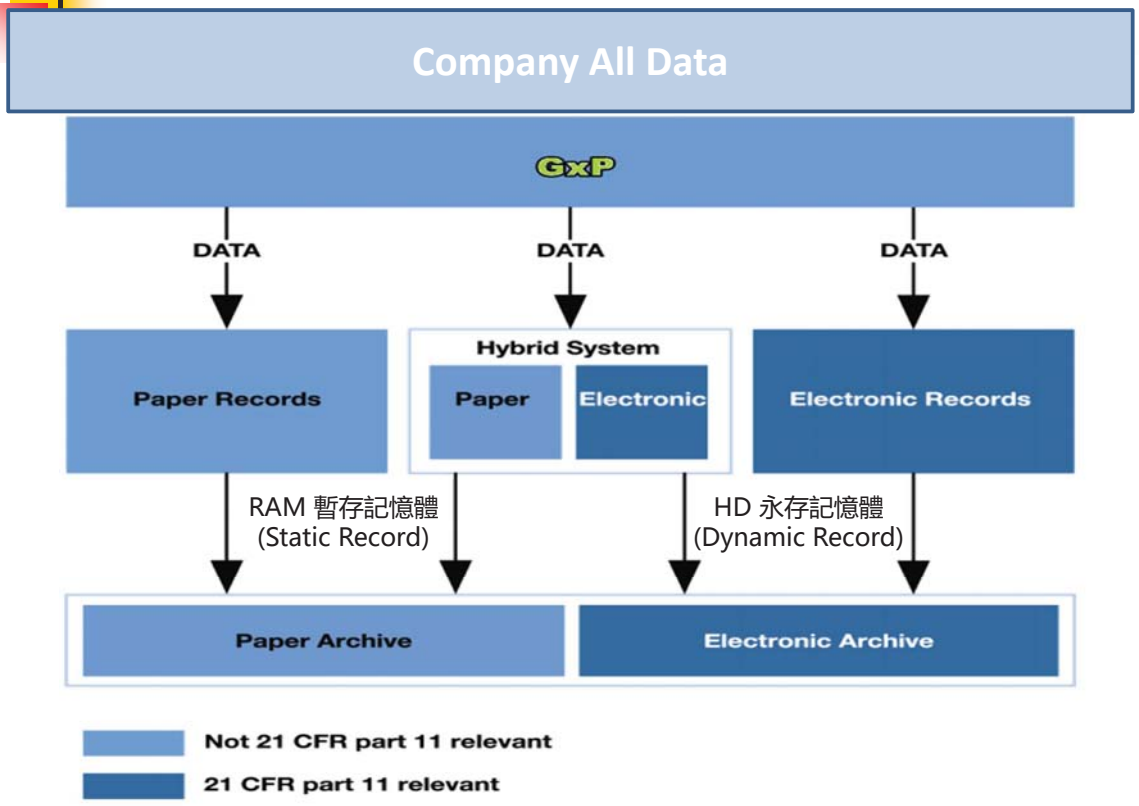
DI some highlight topics

- **Back-up**
  - 用來指在整個記錄保存期間安全地保存的原始數據的真實有效副本
- **Wrongful Act**
  - 不法行爲-Whistle policy
- **Data exclude**
  - **若要從放行標準決策制定過程中排除CGMP數據，必須有一個有效的、存檔的、科學上的排除理由 (FDA OOS)**
- **Data processing**
- **Data transfer and migration**
- **CIA**
- **CSV**
- **ERES –part 11**

CSV ERES - 21 CFR Part 11 Compliance Assurance - CIA

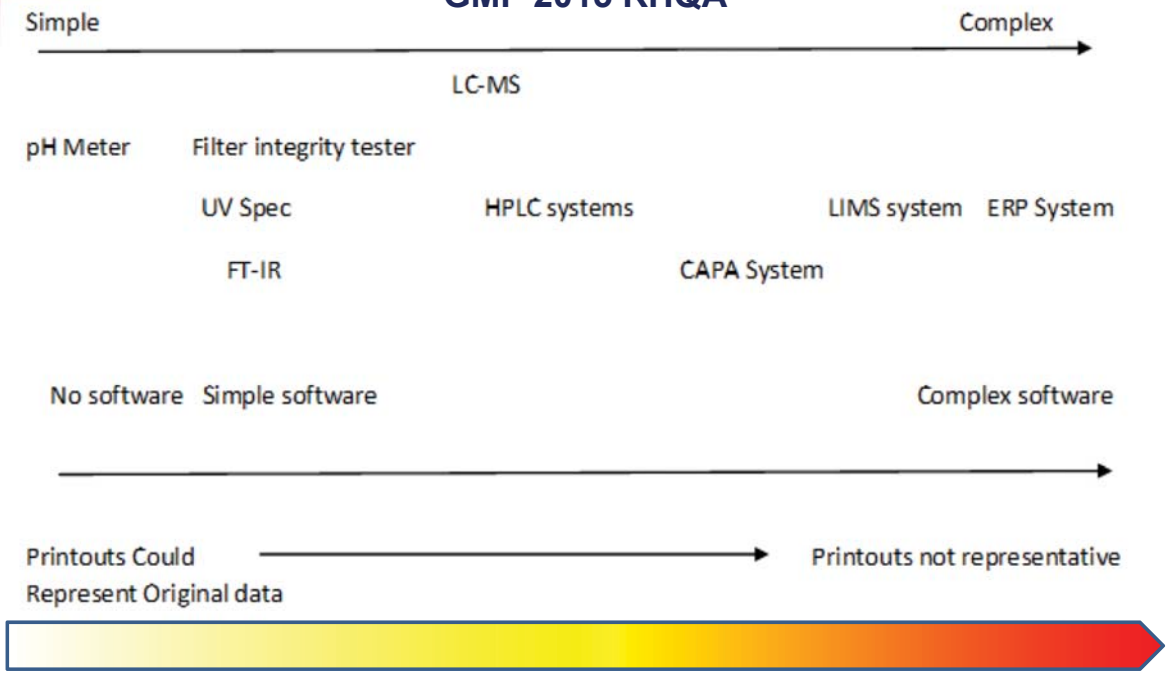


Paper vs. Electronic



ERES - 21 CFR Part 11- Definition

Simple machine (left) to complex system (right), and relevance of printouts as 'original data' based on ICHQ9 GMP 2015 RHQA



Data Form Paper electronic

Simple machine (left) to complex system (right), and relevance of printouts as 'original data' based on ICHQ9 GxP 2016 MHRA Draft

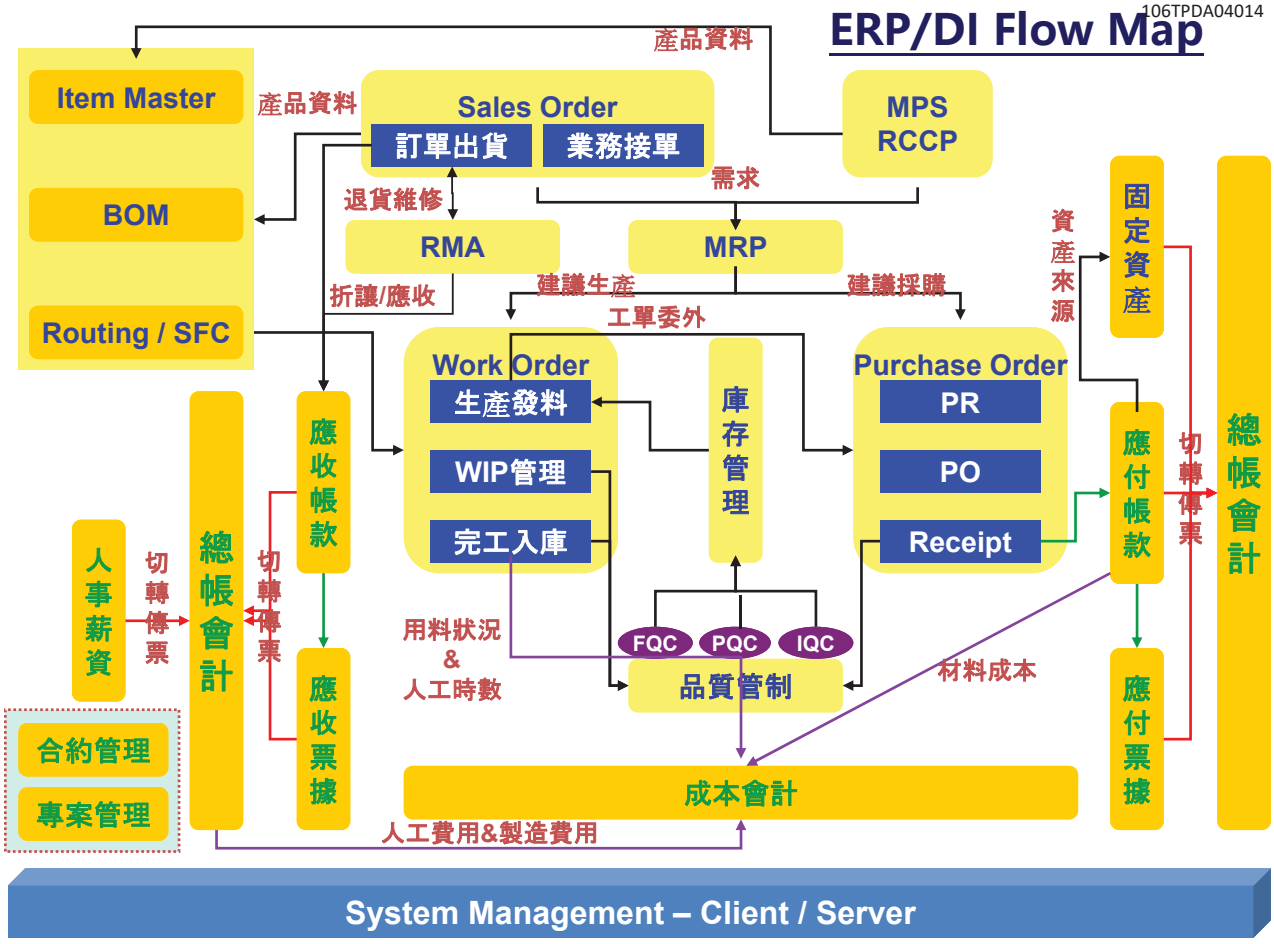
System complexity	Simple system					Complex system
	pH meter	Filter integrity test			Interactive response technology	Enterprise resource planner
		UV spec	HPLC systems	LC-MS-MS	LIMS	
	Balance	FTIR		Pharmacovigilance database		Bespoke systems
		ECG machines	Electronic trial master file		Clinical database	
		Spreadsheet			Statistical analysis tools	
	Min/Max thermometers	Data loggers	Building management system			
Software	No software	Simple software				Complex software
Printouts	Printouts may represent original data	Printouts not representative of original data				

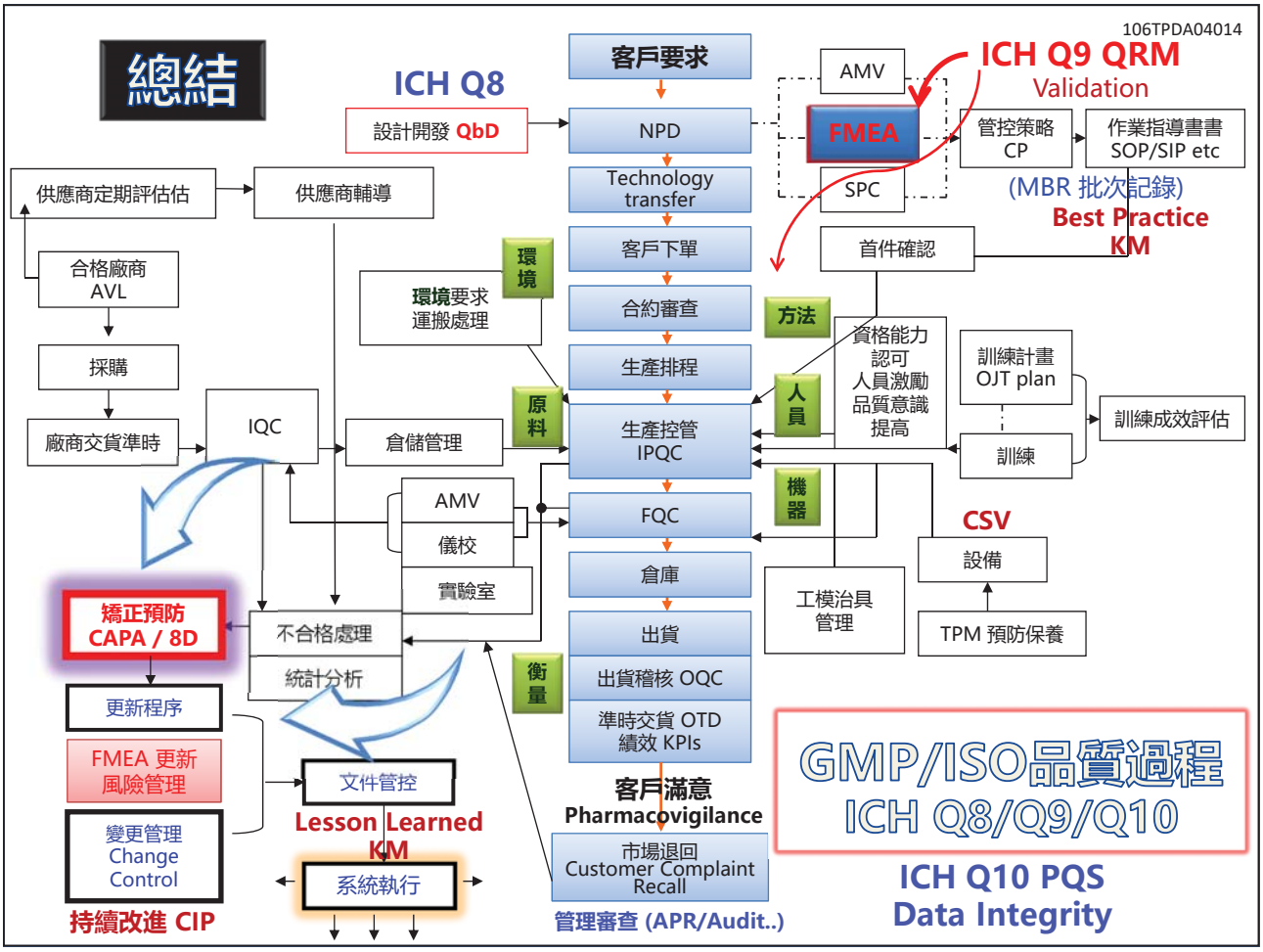
Data Form Paper electronic

DI for Paper-based system

- Templates Control 範本控管
- Blank form Control 空白表單控管
- Batch Record distribution 生產記錄發放
- Record Use 記錄使用
- Record Filling-out 記錄填寫
- Record Modification 記錄修改
- Record Verification 記錄確認
- Record Storage 記錄保持
- Directed Print-out 直接列印文件
- True Copy 真實副本
- Limitations of remote review 匯總數據遠程檢查的限制性
- Archiving 文件保存
- Decommission/Disposal 文件銷毀

ERP/DI Flow Map





106TPDA04014

Thank you for your attention!

Annex

參考資料

Data integrity expectations (ALCOA) in the existing EU GMP correlation -EMA

	Basic Requirements for Medicinal Products (Part I): Chapter 4[1] / Chapter 6[2]	Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 6[3] / Chapter 5[4]	Annex 11 (Computerized System)
A Attributable (data can be assigned to the individual performing the task)	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]
L Legible (data can be read by eye or electronically and retained in a permanent format)	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]
C Contemporaneous (data is created at the time the activity is performed)	[4.8]	[6.14]	[12.4], [14]
O Original (data is in the same format as it was initially generated, or as a 'verified copy', which retains content and meaning)	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]
A Accurate (data is true / reflective of the activity or measurement performed)	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"], [5], [6], [10], [11]

[1]Chapter 4 (Part I): Documentation
[2]Chapter 6 (Part I): Quality Control
[3]Chapter 5 (Part II): Process equipment (Computerized system)
[4]Chapter 6 (Part II): Process equipment

Data integrity expectations (ALCOA) in the existing PIC/S GMP correlation

ALCOA principle	PIC/S Guide to GMP for Medicinal products, PE009 (Part I):	PIC/S Guide to GMP for Medicinal products, PE009 (Part II):	Annex 11 (Computerized Systems)	PIC/S Guide to GDP for Medicinal products, PE011:
Attributable	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]	[4.2.4], [4.2.5]
Legible	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]	[4.2.3], [4.2.9]
Contemporaneous	[4.8]	[6.14]	[12.4], [14]	[4.1], [4.2.9]
Original	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]	[4.2.5]
Accurate	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"] [5], [6], [10], [11]	[4.2.3]

WHO ALCOA+ Expectations

	Paper record	electronic paper
A Attributable	• 姓名的首寫字母； • 完整的手寫簽名； • 個人印章； • 日期和，當需要時，時間	• 與用戶創建、修改或刪除數據的行爲相鏈接的唯一的用戶登錄； • 唯一的電子簽名（生物識別或非生物識別）； • 應該獲取用戶ID和日期和時間標記的追踪稽核； • 簽名，必須是安全和永久性連接至被簽的記錄
L Legible, traceable and permanent	• 使用永久性的不會褪色的墨水； • 不能使用鉛筆或其可擦除的方式記錄； • 修改記錄時使用單橫線劃掉然後簽名、日期和記錄修改原因（例如相當於紙本記錄的追踪稽核）； • 不能使用不透明的塗改液或者其他模糊記錄的方式； • 管控有封面的用連續的頁碼編號的記錄本的發放（例如允許人員刪除缺失或忽略的頁碼）； • 管控有連續頁碼編號的空白表格的複印件的發放（例如允許人員爲所有發放的表格記數）； • 獨立的指定的檔案保管人員將紙本記錄歸檔進安全管控的紙本檔案室內(檔案管理員這個術語是用於品質管控、GLP和GCP設置中的那些人員在GMP設置中這個角色通常分派給品質保證部門的具體個人)； • 在紙張/墨水不可避免使用的地方保護其不會隨著時間褪色	• 根據需要設計和配置電腦系統和書面標準操作程序（SOP）來執行在活動的同時和進行下一步系列事件前數據的保存（例如要有管控來禁止在臨時內存中產生和處理和刪除數據和在系列中下一步驟之前在永久內存中替換在活動時出錯的數據）； • 使用安全的、有時間標記的追踪稽核來獨立地記錄操作人員行爲和追溯行爲至登錄的個人； • 限制訪問的配置設置增强了安全許可（例如系統管理員角色可以用於潛在地關閉追踪稽核或幫助覆蓋或刪除數據），僅僅給與電子記錄的內容的那些職責不相關的人員 • 需要時用配置設置和SOP來使其失去和禁止覆蓋數據的能力，包括禁止初始和中間處理數據的覆寫； • 以嚴格管控配置和數據注釋工具的使用的方式來防止數據在顯示和列印中被模糊化； • 經過確效的電子數據備份以確保災難恢復； • 經過確效的由獨立的指定的檔案保管人員將電子記錄歸檔到安全管控的電子記錄檔案室內

WHO ALCOA+ Expectations

	Paper record	electronic paper
C Contemporaneous	• 書面程序和訓練和審核和稽核和自查管控來確保人員在活動的同時直接在正式管控的文件中記錄數據輸入和資訊（例如試驗室記錄本、批記錄、案例報告表格等）； • 需要程序來規定在紙本記錄中記錄活動以及活動的日期（如果活動是時間敏感的也要記錄時間） • 良好的文件設計，其鼓勵良好的行爲規範：文件應該適當設計和應該確保要記錄的活動在空白表格/文件有足够的空間記錄 • 日期記錄和活動的時間使用同步的時間來源（廠房和電腦化系統的時鐘）其不能被未經授權的人員修改在可能的地方，手工活動的記錄的日期和時間應該自動進行	• 爲了確保步驟或事件在其執行的同時的持久記錄，確保在步驟或事件完成和進行下一步步驟或事件前記錄在臨時內存中的數據提交到持久媒介中的配置設定、SOP和管控； • 不能被人員調整的安全的系統時間/日期標記； • 程序和維護項目確保時間/日期標記與GxP操作同步； • 允許一個活動相對另一活動的定時識別的管控（如時區管控） • 系統在活動的同時對於用戶的可用性
O Review of original records	• 書面的程序和訓練和審核和和稽核和自查管控確保人員實施對原始數據充分的審核和批準，包括用來記錄同步獲取的資訊的紙張； • 數據審核程序應該描述相關元數據的審核例如用於審核的書面程序應要求員工評估對在紙本記錄上的原始資訊做出的修改（例如用劃掉或數據糾正記錄的修改）以確保這些修改被適當記錄幷有證據證明，需要時調查 • 數據審核的文件對於紙本記錄這個通常通過在紙本記錄上簽名的方式表明已經審核過了在記錄批準是獨立過程的地方這個也應該同樣地簽名數據審核的書面程序應該闡明審核和批準簽名的意義是爲了確保相關人員理解他們作爲審核者和批準者的職責是爲了保證提交審核和批準的紙本記錄的完整性、準確性、一致性和符合已建立的標準 • 程序應該描述如果數據審核發現錯誤或遺漏需要採取的行動程序應該幫助用符合GxP的方式對數據做出改正或說明，前提是原始記錄的可見性和改正可以用追踪稽核追踪到，同時使用ALCOA原則	• 書面的程序和訓練和審核和稽核和檢查管控確保員工對原始電子記錄執行充分的審核和批準，包括電子數據的人工可讀原始記錄 • 數據審核程序應該描述原始電子數據和相關元數據的審核例如用於審核的書面程序應該要求員工評估在電子記錄中對原始資訊做出的修改（例如在追踪稽核或歷史字段中記錄的或在其他有意義的元數據中發現的修改）以確保這些修改已經被適當記錄幷有證據證明，需要時調查 • 數據審核的文件對於電子記錄，這個通常通過電子簽署電子數據集來表面已經審核和批準了數據審核的書面程序應該闡明審核和批準簽名的意義是爲了確保相關人員理解他們作爲審核者和批準者的責任是爲了保證提交審核和批準的電子數據和元數據的完整性、準確性、一致性和符合已建立的標準 • 程序應該描述如果數據審核發現錯誤或遺漏應該採取的行動程序應該幫助用符合GxP的方式來對數據進行改正或說明，前提是原始記錄的可見性和改正可以用追踪稽核追踪到，同時使用ALCOA原則

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WHO ALCOA+ Expectations

	Paper record	electronic paper
O Retention of original records or true copies	• 紙本記錄管控和安全的存放區域，包括檔案室； • 指定的獨立於GxP操作的紙本檔案管理員是GLP指南的要求；在其他GXP中歸檔GXP記錄的角色和職責應該規定和監控（一般應該是品質保證職能部門的職責或一個獨立的文件管控部門） • 允許迅速檢索的記錄的索引； • 基於風險評估適當間隔時間的定期測試來確認檢索歸檔的紙本或靜態格式記錄的能力； • 如果原始紙本記錄已經作爲真實副本複製成了縮微平片或縮微膠片來歸檔，當需要時應提供合適的讀取設備，例如縮微平片或縮微膠片讀取器 • 必要時規定包括以下步驟的原始紙本記錄轉換成真實副本的過程的書面程序、訓練、審核、稽核和自查： a) 製作原始紙本記錄的副本，根據需要保存原始記錄格式，靜態格式（如照片副本、PDF）； b) 副本需要與原始記錄比較來確定副本是否保留了原始記錄的全部內容和意思，包括了元數據，在副本中沒有數據丟失如果副本要符合原始紙本記錄的真實副本的要求，記錄格式保留的方式與記錄的意思一樣重要 c) 確認者用安全鏈接至副本的方式確認，顯示這是一個真實副本或提供相等同的證書	• 儲存在其他地方作爲發生引起原始電子數據丟失的災難防護的原始電子數據的日常備份副本； • 電子記錄的管控的安全的儲存區域，包括檔案室； • 指定的電子檔案管理員，例如哪些在GLP指南中要求的，檔案管理員應獨立於GxP操作（指定人員應該經過執行他們職責的適當的確認幷有相關經驗和適當訓練）； • 允許迅速檢索的索引； • 5定期測試以確認從儲存位置檢索到歸檔電子數據的能力從儲存位置檢索到歸檔數據的能力應在電子檔案室確效期間測試確效了從儲存位置檢索歸檔數據的能力後應該定期再確認，包括從第三方存儲的檢索 • 提供合適的讀取設備例如軟件、操作系統和虛擬化環境等以便在需要時查看歸檔的電子數據； • 必要時規定包括以下步驟的原始電子記錄轉換成真實副本的過程的書面程序、訓練、審核、稽核和自查： a) 製作原始電子數據集的副本，根據需要保存原始記錄格式，動態格式（如使用已確效的備份過程對電子數據和元數據的全部數據集的歸檔副本）； b) 第二人確認者或技術確認過程（例如技術散列）來確認備份成功，憑藉做出的電子備份副本對原始電子數據集的比較來確認副本保留了原始記錄的全部內容和意思（例如包括了所有數據和元數據，在副本中沒有數據丟失，任何動態記錄格式與記錄的意思一樣重要，譯碼被保存，文件在已確效的備份過程的實施過程中沒有被損壞）； c) 如果副本符合作爲原始記錄的真實副本的要求，確認者或技術確認過程應該將確認以安全鏈接到副本上的方式記錄，證明這是一個真實副本

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WHO ALCOA+ Expectations

	Paper record	electronic paper
A Accurate	• 可產生列印條的設備的確認、校驗和維護，例如天平和pH儀器； • 產生、處理、維護、分發或歸檔電子記錄的電腦化系統的確效； • 當在電腦化系統中間/內部轉移(數據)時必須確效系統來確保其完整性； • 分析方法的確效； • 生產製程的確效； • GxP記錄的審核； • 異常、可疑結果和OOS結果的調查； • 和品質管理體系中許多其他風險管理管控 應用於數據生命周期的這些管控的例子於下列 保證準確的GxP記錄的詳細風險管理考量 • 經過授權的人員輸入關鍵數據進電腦（例如主要過程公式的輸入）要求對手動輸入的數據的準確性進行額外檢查這個檢查可以由第二個經過授權的人或通過經過確效的電子方法通過獨立的確認和放行使用來進行例如，爲了檢測和管理與關鍵數據相關的風險需要由第二個人例如品質部門人員來確認程序：在電子表格中輸入計算公式；在LIMS中輸入主數據例如用於在分析報告單中標記OOS值的品質標準範圍的字段；如果需要，其他關鍵主數據；另外，一旦經過確認，當可行和適用時這些關鍵數據字段將被鎖定以避免進一步的修改，僅僅通過正式的變更管控流程才能修改 • 數據獲取過程的有效性是確保產生高品質數據的基礎 • 用到標準詞典、辭海和表格（如單位和刻度）的地方應該受控 • 在系統之間轉移數據的過程應該確效 • 數據從系統移進和移出需要明確的計劃的測試和管控 • 時間可能不是對所有活動都關鍵當活動是對時間關鍵時，列印的記錄應該顯示時間/日期標記 • 例如:爲了確保在天平列印出的紙條中記錄的稱量樣品的準確性，天平在使用前應該適當地校準和維護另外在天平上同步和鎖定元數據設定將確保在天平列印紙條上準確記錄時間/日期	

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106TPDA04014

ICH Q8, Q9, Q10 Guidelines work together at different stages of the product lifecycle

結合ICH Q8/Q9/Q10於不同階段產品生命週期

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Formulation Development Activities

Pharmaceutical Development 藥品開發 → Technology Transfer 技術轉移 → Commercial Manufacturing 商業化生產 → Product Discontinuation 產品終止

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Quality Target Product Profile (QTPP)	• Clinical and non-clinical studies on drug substance: bioavailability, PK/PD, and safety	• Informal and/or formal risk assessment to evaluate patient needs and potential medication risks	• Knowledge Management / Prior Knowledge (relevant information to support the understanding, risk assessment and scope of DOE) - Laboratory note book documentation - Development report - Etc…
Pre-Formulation Studies	• Characterization of drug substance (physical properties) • Chemical stability of drug substance, degradation and potential formulation interactions • Development of analytical tests	• Determine failure modes and risk factors for drug substance physical and chemical stability	
Formulation Screening	• Excipient compatibility • Dissolution method development • Screening DOEs	• Determine failure modes and risk factors for excipient interactions	
Formulation Optimization and Selection	• Excipient and drug substance material property & characterization • DOEs for excipient amounts • Stability of drug product and storage conditions • Develop IVIVC relationships	• Opportunities for formal risk assessment	

Process Development Activities

Pharmaceutical Development 藥品開發 → Technology Transfer 技術轉移 → Commercial Manufacturing 商業化生產 → Product Discontinuation 產品終止

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Process Screening	• Exploration of unit operations • Characterization of process intermediates	• Determine failure modes, risk factors for unit operations and rank risk	• Batch records and operational guidelines for manufacturing • Tech Transfer report • Identification and selection of suppliers that meet raw material needs
Process Development and Optimization (Lab Scale)	• DOEs for process parameters and interactions with material attributes • Development of Design Space • Operational ranges for scale-independent parameters • understanding of critical process operations	• Screening risk assessment to determine potential parameters impacting product quality (e.g., Ishikawa) • Determine critical process steps, process parameters and material attributes (e.g., FMEA) • Potential issues of scale	
Process Development and Optimization (Pilot Scale)	• Pilot to verify lab scale knowledge • DOE and modeling effects of scale • Development of design space • Development of on-line measurement technologies	• Development of control strategy to control risks incl. for scale up	

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Technology Transfer

ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
• Gain product and process knowledge • Knowledge supports transfer between development and manufacturing to achieve product realization	• Forms the basis for the manufacturing process • Improves effectiveness of control strategy • Contributes to processes validation and ongoing continual improvement	• Advance understanding through scale-up activities • Provide preliminary indication of process performance and successful integration into manufacturing • Gain knowledge from transfer and scale up activities to enhance the basis for the control strategy

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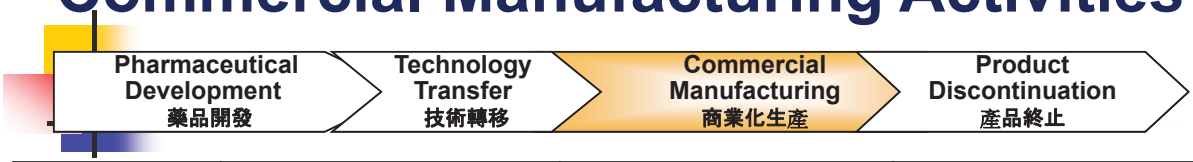
Commercial Manufacturing Activities



	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Commercial Scale Manufacturing for Drug Product	• Definition of commercial process design • Commercial scale runs to verify process design, with additional sampling to verify understanding • Implementation of on-line measurement technologies	• Development of a control strategy for commercial manufacturing, including in-process controls, end-product testing, raw material controls and change control • Check procedures in the PQS regarding risk from Process specific procedure (e.g., sampling plans, design space and model verification, change control for movement within design space)	• Process-specific operating procedures (e.g. sampling plans, design space etc.) • Documentation to support on-line testing methods • Validation to demonstrate process and analytical method reproducibility • Storage of development reports, risk assessments
Continual Process Verification and Continual Improvement	• On-going analysis and trending of process data, (multivariate SPC, etc.) • Evaluation of process changes and associated effect on intermediates and products	• Manage risks of process or material attribute change (including changes within or outside of design space) • Review risks in audits/inspections and implement risk-based CAPAs	• Procedures on process monitoring and action limits • Change control procedures including how and when to do risk assessment for process changes and evaluation of the change • Maintenance and update of knowledge management

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Recent FDA Warning Letter Trends

- Failure to maintain complete data derived from all laboratory tests
  - Deletion of raw data
  - Changes to raw data
  - Incomplete raw data
  - Inauthentic records
  - “Unofficial” or “trial” testing
- Failure to record activities at the time they are performed
  - Critical laboratory information documented days after the testing was performed
  - Belated entry of cleaning information
  - Belated entry of sample identification
  - Lots released prior to proper approvals

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Recent FDA Warning Letter Trends

- Failure to prepare or maintain written production, control, or distribution records
  - Incomplete records
  - Discarded original paper records
  - “Unofficial” visual inspection records
  - Manufacturing data recorded on scratch paper
  - Falsified batch records and training documents
- Failure to record activities at the time they are performed
  - Critical laboratory information documented days after the testing was performed
  - Belated entry of cleaning information
  - Belated entry of sample identification
  - Lots released prior to proper approval

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