Everlight Chemical

Better Chemistry Better Life

藥廠執行電腦數據完整性之經驗分享

醫藥事業處 資訊室
苗恒清
2018/11/22

Pharmaceuticals
醫 藥 事 業 處

Everlight Chemical

大綱

- **Data Integrity 問題檢視**
- **案例分享與改善**
- **分析儀器控管分享**

Data Integrity ALCOA & ALCOA+

ALCOA

Attributable
Legible
Contemporaneous
Original
Accurate

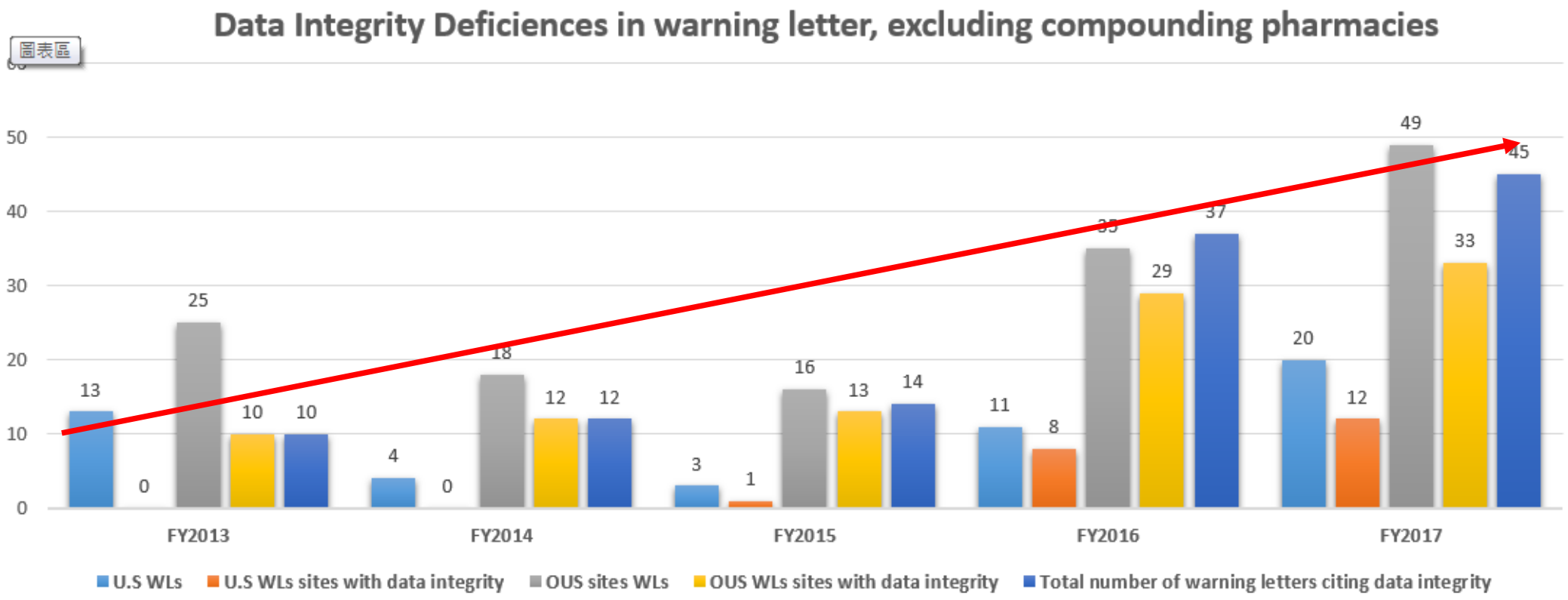
ALCOA+

Complete
Consistent
Enduring
Available

Data Integrity 相關規範需求

- 21 CFR Part 11
- MHRA
- EMA
- WHO
- PIC/S
- …

Data Integrity in WLs



Data source: B Unger, An Analysis of FDA FY2017 Drug GMP Warning Letters, Pharmaceutical Online, January 10, 2018.

Data Integrity 常見問題

- Is configuration of the instrument-associated software qualified and tested appropriately to meet predefined requirements? Where is this documented?
- Are passwords and log-ins shared or are they unique to each individual? Shared passwords prevent attributing specific actions to specific individuals. This includes actions such as logging into the system, collection of data, processing data, and modifying or deleting data.
- Are access privileges assigned appropriately? Is there a listing of who has what privilege and actions that may be taken by each?
- Are time/date stamps fixed, or can individuals alter them?
- Is electronic data, including critical metadata (audit trails) reviewed as part of laboratory data review, lot release, or OOS investigations? In the absence of audit trails and their review, it is impossible for the reviewer to determine whether data has been altered or deleted. Of particular importance is whether data was modified or deleted because it was an OOS result.

Data source: B Unger, Is GMP Quality System Auditing Fundamentally Flawed? A Data Integrity Alternative, Pharmaceutical Online, April 18, 2018.

Data Integrity 常見問題

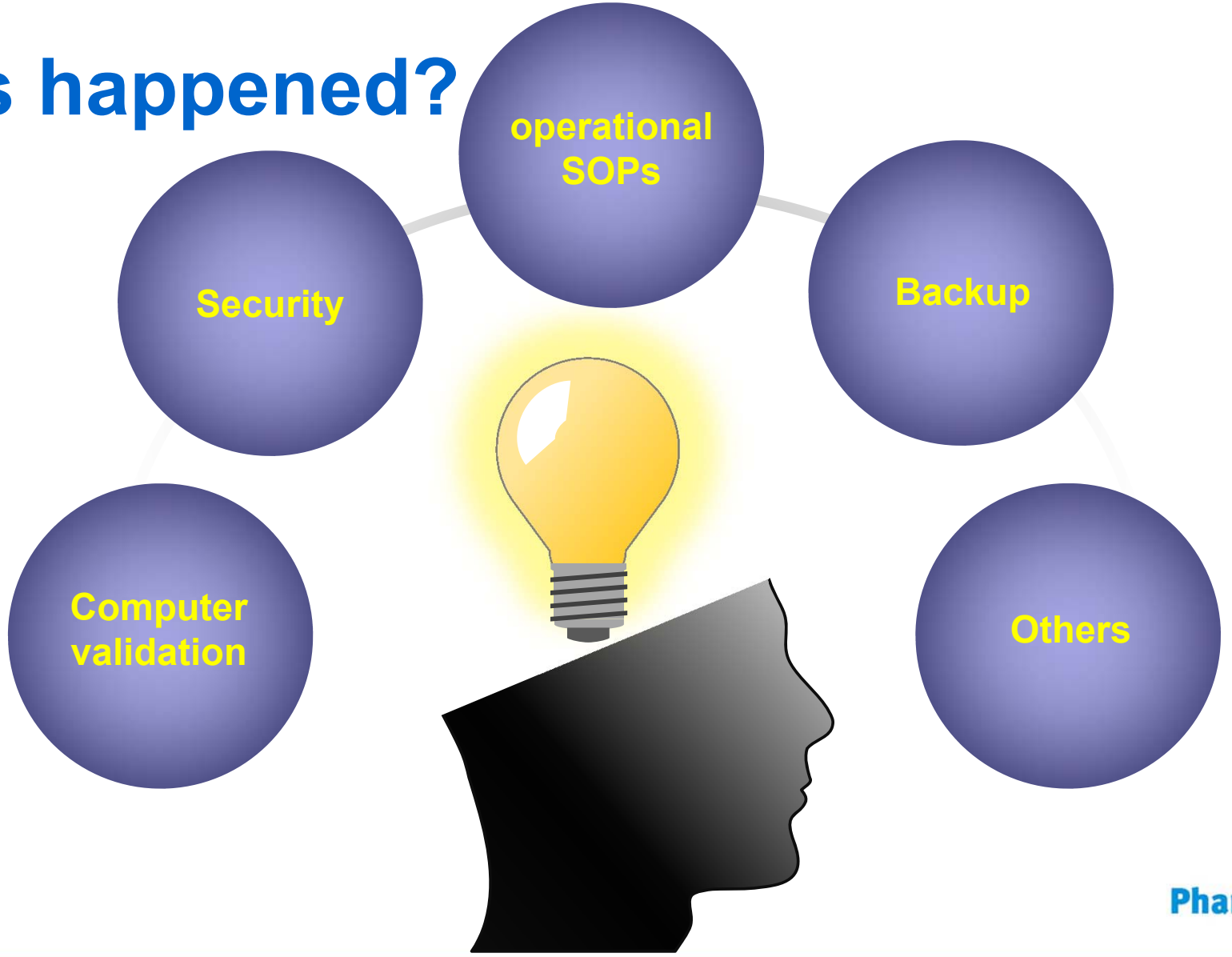
- How quickly can the audit trails be provided to an auditor? When it takes four staff members a half hour to locate them, it suggests the audit trails are not routinely evaluated.
- Is data periodically backed up to a secure server, or is it deleted to make space on existing hard drives? Is the backup automatic or manual? If the transfer is manual, how does the firm ensure that the transfer is complete and that data is not inadvertently deleted or altered in the process? Are these backups conducted according to a predefined schedule? If using automatic backup, has the process been validated, and is it routinely successful? If not, why not?
- Is data archived? Is the meta-data associated, or able to be associated, with the archived electronic record? Are the archived records protected against environmental factors such as fire and flood?
- Equally import to the laboratory instrument-associated computer systems are computerized controls applied on the floor in the manufacturing equipment. The manufacturing floor has received less attention from regulators in the past, but that is changing rapidly.

Data source: B Unger, Is GMP Quality System Auditing Fundamentally Flawed? A Data Integrity Alternative. Pharmaceutical Online, April 18, 2018.

Case Discussion: WL April, 2017 China

- Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.
  - ...your analysts manipulated the date/time settings on your high performance liquid chromatography (HPLC) systems. ….admitted to setting the clock back and repeating analyses for undocumented reasons.
  - Your firm reported only the passing results from repeat analyses. When test results are overwritten, the quality unit is presented with incomplete and inaccurate information about the quality of the drugs produced by your firm.
  - your firm's HPLC systems used for API testing had the audit trail feature disabled, …
  - The electronic raw data for the HPLC systems used for assay and impurities testing of API products is stored on the hard drive of the connected computers. There are no controls to prevent the deletion of this raw data.
  - The Computer Validation Plan (CVP) did not address the qualification of EXCEL files used for QC calculations … Not all electronic files used for calculations by QC data were qualified and controlled

What's happened?



Pharmaceuticals
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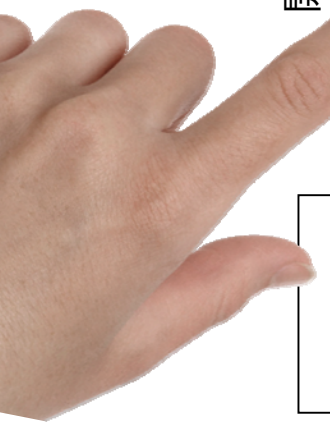
Thinking Objectives for Pharma IT

- Concept of Segregation of Duties
- Concept of Least Privilege
- Windows Administration (For all versions of Windows in Current Use)
  - Authentication
  - Users and Groups - Create & Administer
  - Windows Security & Permissions – Concepts, Administer
- Administration of Specific Applications
  - System / Vendor specific
  - Administer the application
  - Vendor-Recommended configurations to achieve objectives
  - Perform Backups & Restorations
- Networking
- …

Types of Remediation Activities

- **Controls**
  - Segregation of Duties, Technical & Procedural Controls, Configuration
- **Preservation of Data**
  - Backups & Handling of Data Post Backup
- **Analysis of Impact**
  - Data Integrity, Data Deletion, and Audit Trail Issues

改善流程



開始

問題分析
將觀查缺失歸類整理

設備盤點
調查設備現況

風險評估
根據不同風險建立改善策略

改善計畫
建立短期及中長期計畫

教育訓練
強化cGMP觀念

設施改善
硬體設備及環境改善

系統改善
軟體系統管理改善

流程改善
改善電腦系統確效及管理程序

持續運作

問題歸類-建立問題矩陣

CAPA #	Observation Description	Action	Observation System	Observation Source
CAPA01	XYZ-01:The Computer Validation Plan (CVP) …EXCEL files used for QC calculations	NA	Computers	FDA
CAPA02	XYZ-02:The electronic raw data for the HPLC systems …is stored on the hard drive	NA	Computers	FDA
CAPA03	XYZ-03:Your firm ..When test ..overwritten…	NA	Computers	FDA

問題歸類-建立問題矩陣

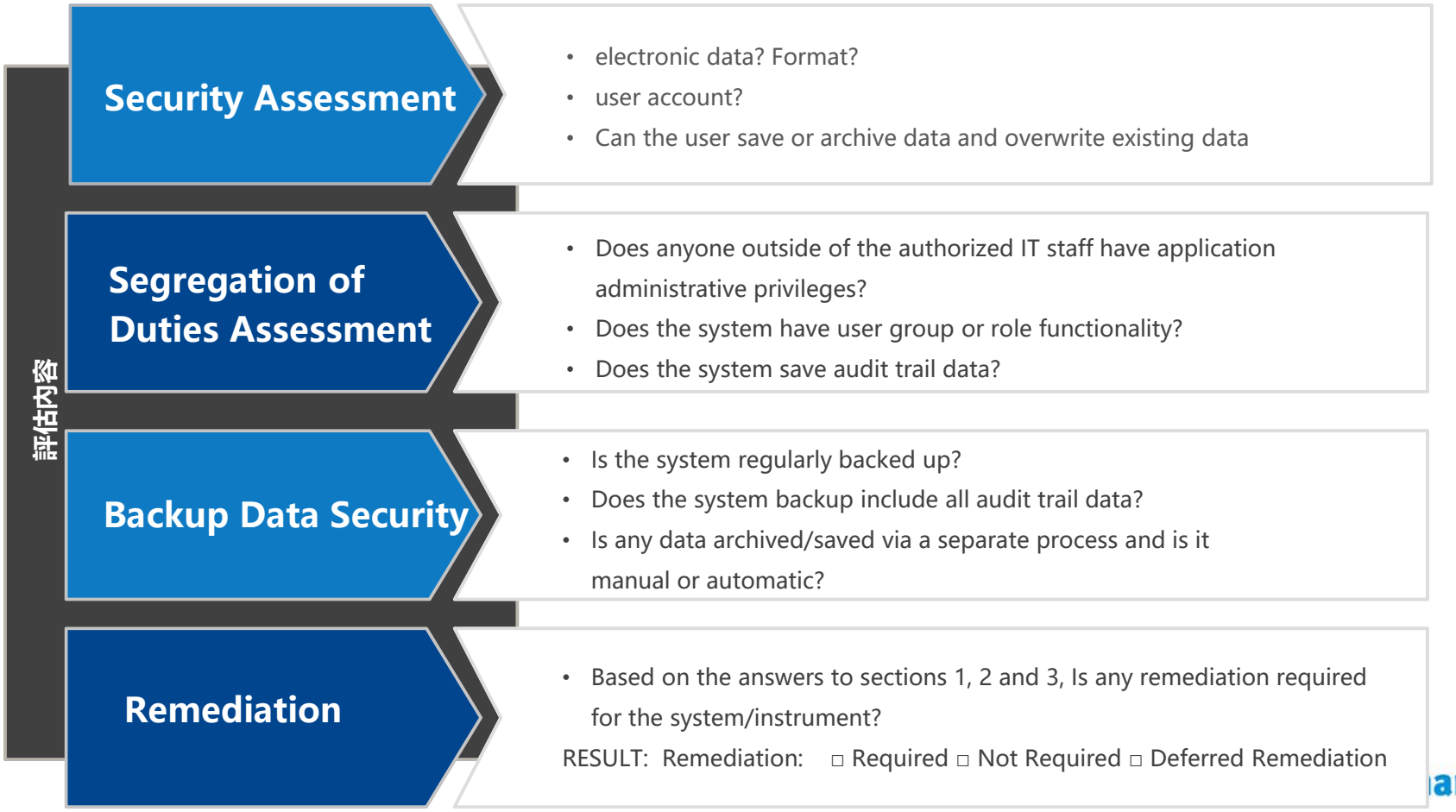
CAPA Tittle	FDA CAPA	Complete
Spreadsheet validation	CAPA01	NA
Computer validation procedures	CAPA03	NA
Backup and Archive	CAPA02	NA
Infrastructure Qualification	CAPA06	NA
….	….	..

設備電腦盤點

System ID	ECIC ID	Application	Location	AUDITDA	PCMAKE	PCMODEL
Malvern Mastersizer	103-MASTERSIZER	Malvern Mastersizer Particle sizer	M 103	2016/3/7	ASUSTeK Computer INC.	BM5275(BM5375.BM5675)
Agilent OpenLab	API-QC01	AGILENT OpenLab (Server)	M 120	2016/3/4	HP	ProLiant ML350p Gen8
Agilent OpenLab	API-QC02	AGILENT OpenLab	M 120	2016/3/4	Hewlett-Packard	HP Compaq Elite 8300 MT
Agilent OpenLab	API-QC03	AGILENT OpenLab	U 409	2016/3/3	Hewlett-Packard	HP Z420 Workstation
Agilent OpenLab	API-QC04	AGILENT OpenLab	M 120	2016/3/4	ASUSTeK COMPUTER INC.	BM6AD_BM1AD_BP1AD
Agilent OpenLab	API-QC05	AGILENT OpenLab	M 120	2016/3/4	ASUSTeK COMPUTER INC.	BM6AD_BM1AD_BP1AD
Agilent OpenLab	API-QC06	AGILENT OpenLab	M 120	2016/3/4	HP	ProLiant ML350p Gen8
EMP3QC1	EMP3SVR	Empower server	M 121	2016/3/4	Dell Inc.	PowerEdge T630
EMP3QC1	API-QC14	Empower 3 Client	U 409	2016/3/4	Dell Inc.	OptiPlex 9020
EMP3QC1	API-QC17	Empower 3 Client	M 121	2016/3/3	Dell Inc.	OptiPlex 780
EMP3QC1	API-QC18	Empower 3 Client	M 121	2016/3/3	Dell Inc.	OptiPlex 9020
EMP3QC1	API-QC19	Empower 3 Client	U 409	2016/3/3	Dell Inc.	OptiPlex 780
EMP3QC1	API-QC20	Empower 3 Client	M 121	2016/3/3	Dell Inc.	OptiPlex 990

目的:清楚的了解每一台設備電腦的組態(使用的系統、放置位置、電腦編號、廠牌、型號....)

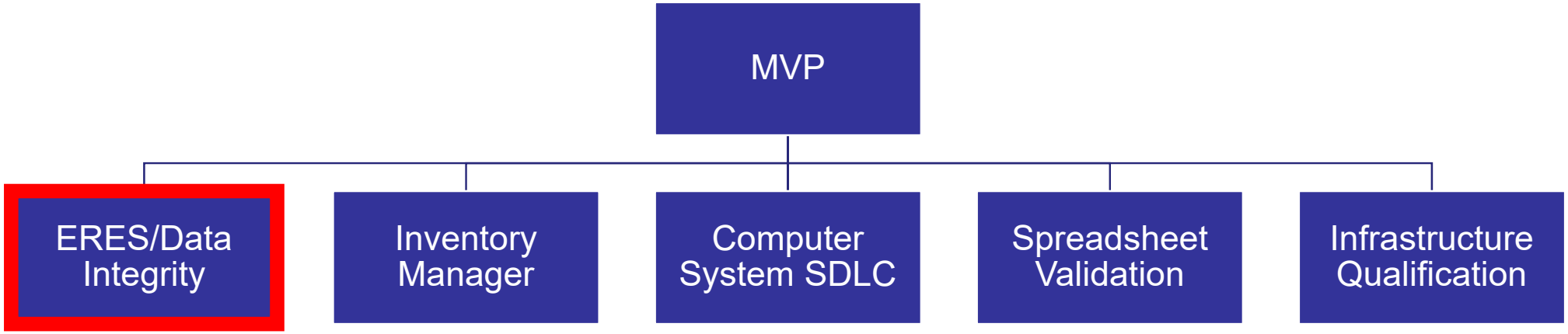
Computer System Security, SOD, Backup Assessment



試算表盤點

Owner	成品品號/finished product code	Filename workbook	Usage (worksheet)	controlled? (Y=Yes, N=No)	Verified Status (Y=Yes N=No)	Verification Date (03/25/2016 - 03/23/2017)	validated? (Y=Yes, N=No)	Validation Date	Priority	Re-Validation Date	Comments
QC	電子計算驗證	A001	(1) Purity	Y	Y	2016/04/29	N	NA	3	2018 Q2	
QC	電子計算驗證	A001-IPC001	(1) IPC-01, (3) IPC-03	Y	Y	2016/04/29	N	NA	3	2018 Q2	
QC	電子計算驗證	A001-IPC02	(2) IPC-02	Y	Y	2016/05/09	N	NA	3	2018 Q2	
QC	電子計算驗證	A002	(1) Assay, (2) Impurity,	Y	Y	2016/04/29	N	NA	3	2018 Q2	
QC	電子計算驗證	A001-IPC015	(1) Purity	Y	Y	2016/05/09	5N	NA	3	2018 Q2	
QC	電子計算驗證	A005	(1) Purity	Y	Y	2016/04/29	N	NA	3	2018 Q2	
QC	電子計算驗證	N003	(1) Impurity, (2) Assay---滴定,	Y	Y	2016/04/29	N	NA	3	2018 Q2	

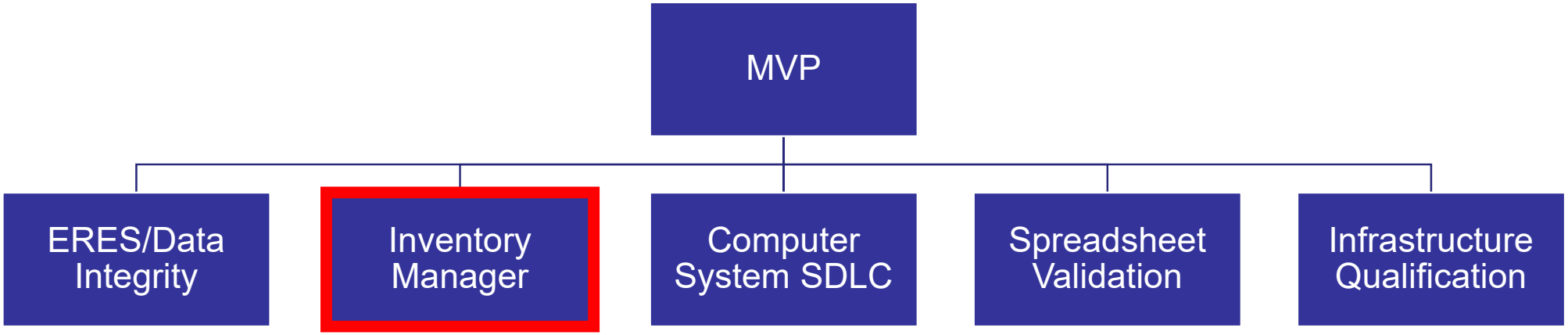
SOP Architecture



ERES/Data Integrity

- **Electronic Records & Electronic Signatures/Data Integrity**
  - Electronic Signatures
  - User Account、Password
  - Data Entry
  - Audit Trails
  - Roles and Permissions
  - …..

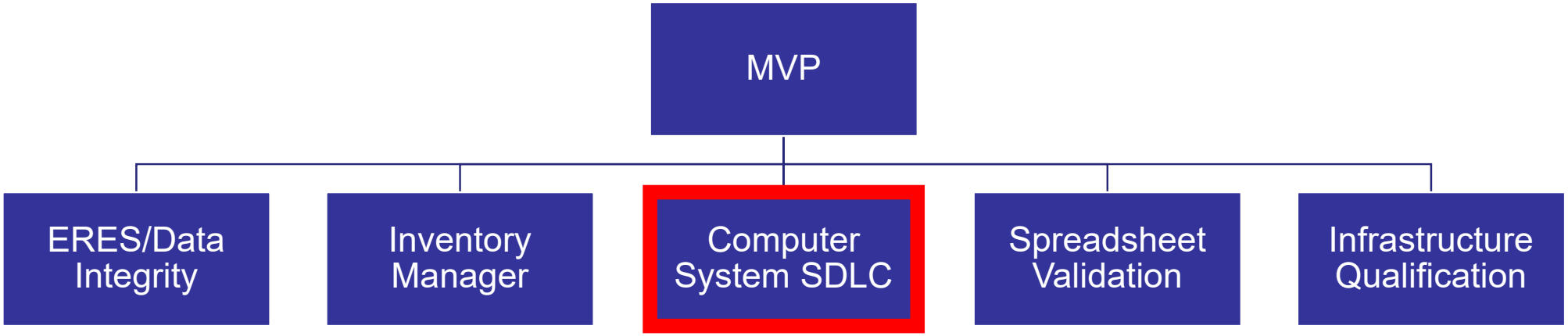
SOP Architecture



Inventory Manager

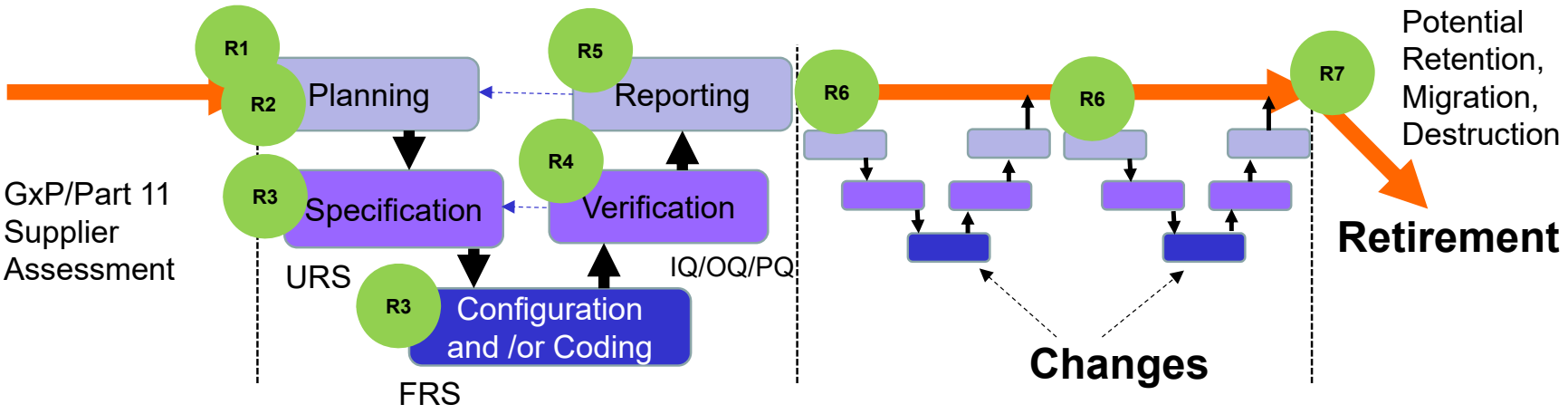
- 實體電腦庫存管理
  - 作業系統OS
  - 單位Department
  - 保管人Custodian
  - 類型（工作站、伺服器）Type (Server, Workstation)
  - 位置Location
  - 組態Configuration (CPU, RAM, HD/SSD, Graphics Card, MAC)
  - 狀態（使用中、維修中、報廢）Status (Alive, Maintenance, Retired)
  - …
- 電腦系統庫存管理
  - 軟體名稱Software Name
  - 軟體發行商Software Manufacturer
  - 軟體版本Software versions
  - 授權類型（如企業版、單點版、單機版）License Type (i.e. enterprise, site, single)
  - 軟體使用單位Software Owner Department – Department that purchased the software
  - 購買日期Purchase Date
  - GMP（軟體是否做GMP用途）GMP (i.e. YES/NO if software is used for GMP purposes)
  - GxP風險程度（高、中、低）GxP Criticality (High, Medium, or Low)
  - …

SOP Architecture



Computer System SDLC

- Computer System Development Life Cycle (SDLC)



R1 - Initial risk assessment

R2 - Risk-based decisions during planning

R3 - Functional risk assessment

R4 - Risk-based decisions during test planning

R5 - Risk-base decision during planning of operational active

R6 - Functional risk assessments in change control

R7 - Risk-based decisions when planning system retirement

Data source: GAMP 5 A Risk-Based Approach to Compliant GxP Computerized Systems

Computer System SDLC

Concept Phase

GxP/Part 11

Supplier Assessment

Project Phase

Val Plan

URS/FRS

Detailed Risk Assessment

System Design

IQ/OQ/PQ

Traceability Matrix

Summary Report

Operational Phase

Operation Maintenance

Help Desk

Backup/ Disaster Recovery

Logical and Physical Security

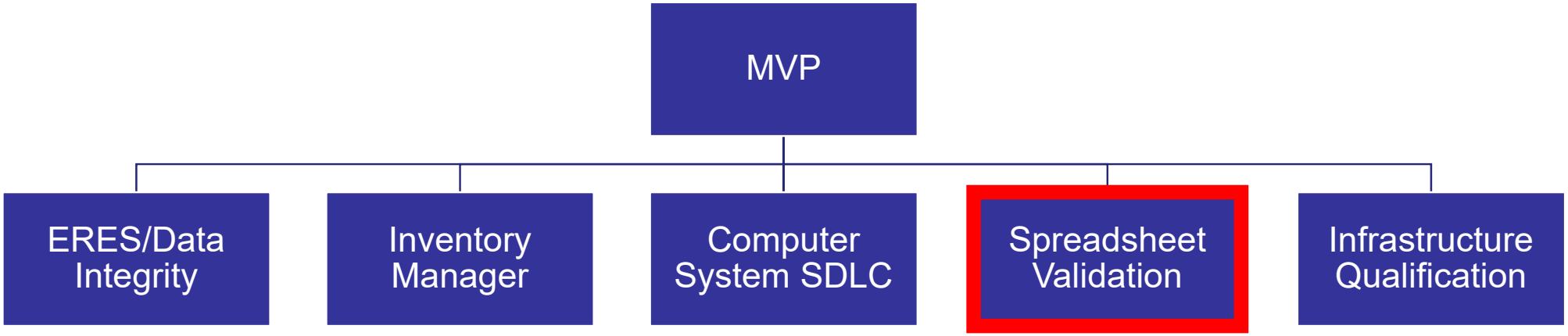
Retirement Phases

System Retirement

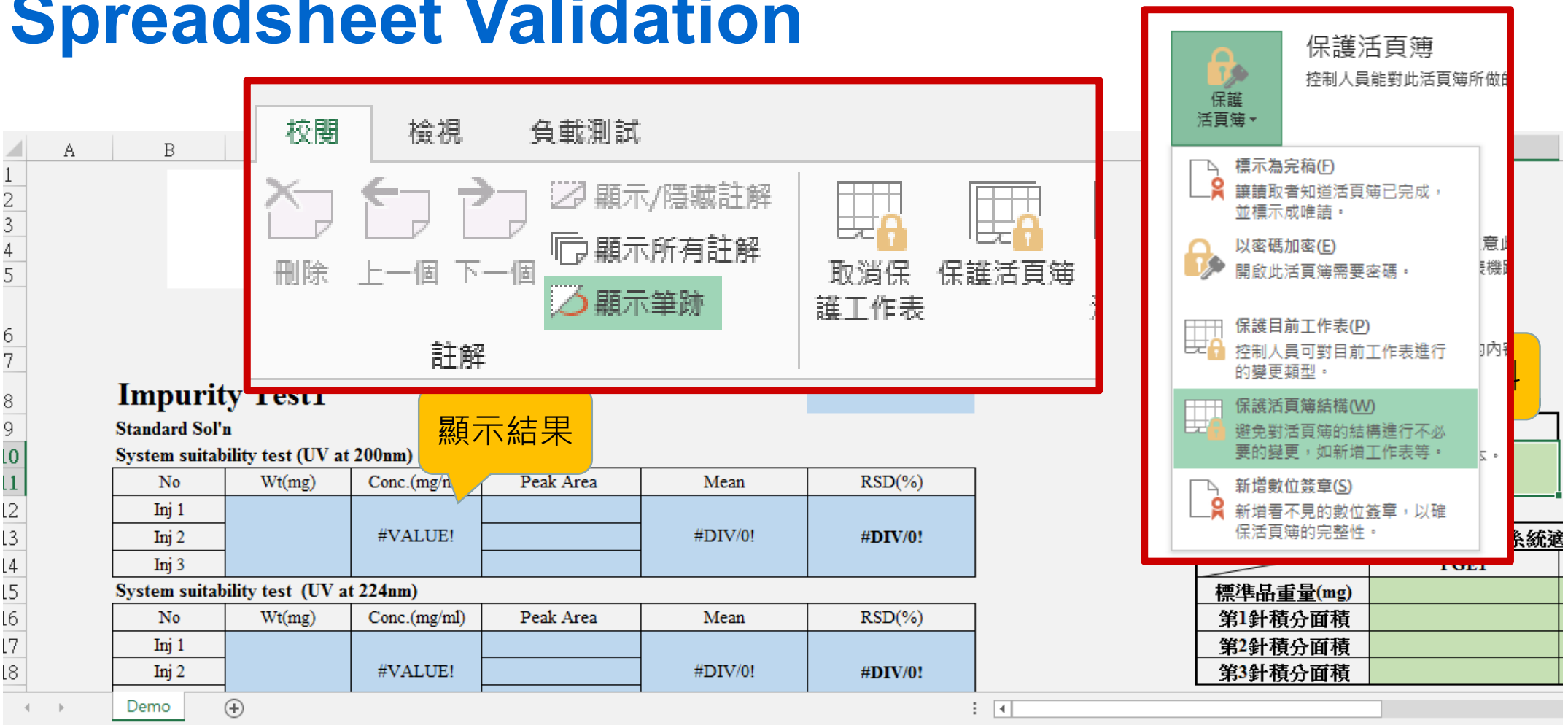
Example - validation documents and activities for types of changes

Activity	Change Control	GxP Assessment	URS	Design Specs	VP	IQ	OQ	PQ	T M	Val summary report	SOPs	Training	Maintenance log	Help Desk
New system	×	×	×	×	×	×	×	×	×	×	×	×		
Upgrade software (minor)	×			update	×	×		×	×	×				
Upgrade software (major)	×		upda te	update	×	×	×	×	×	×	update	×		
modify roles	X		upda te								update	×		

SOP Architecture

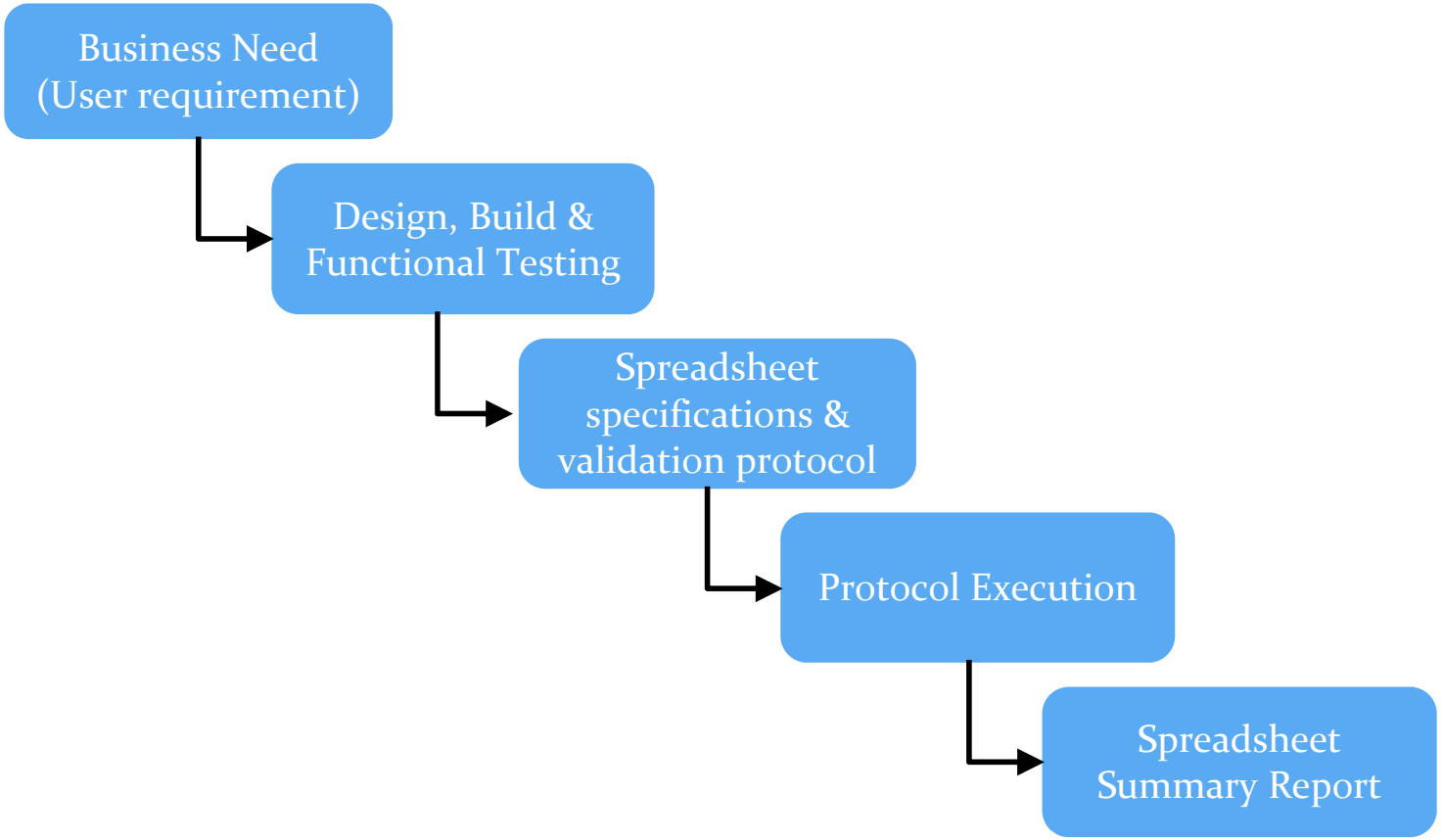


Spreadsheet Validation

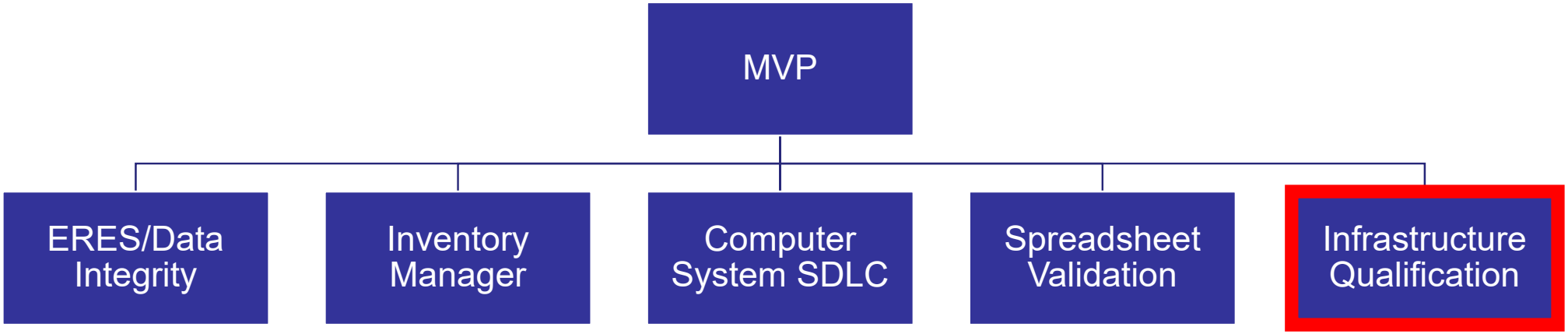


Pharmaceuticals
醫藥事業處

試算表系統設計流程

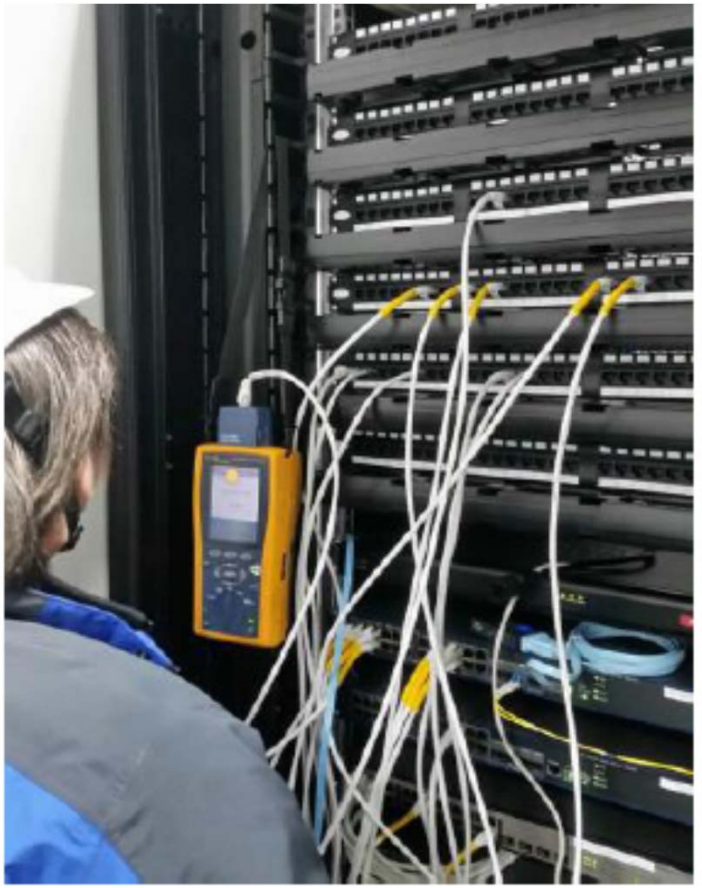

Business Need
(User requirement)
Design, Build &
Functional Testing
Spreadsheet
specifications &
validation protocol
Protocol Execution
Spreadsheet
Summary Report

SOP Architecture



Infrastructure Qualification

- **IT Infrastructure**
  - **AD**
  - **VM Ware**
  - **NAS**
  - **NTP**
  - **DHCP**
  - **Printer Server**
  - **Environment Control**
  - **Fire Suppression System**



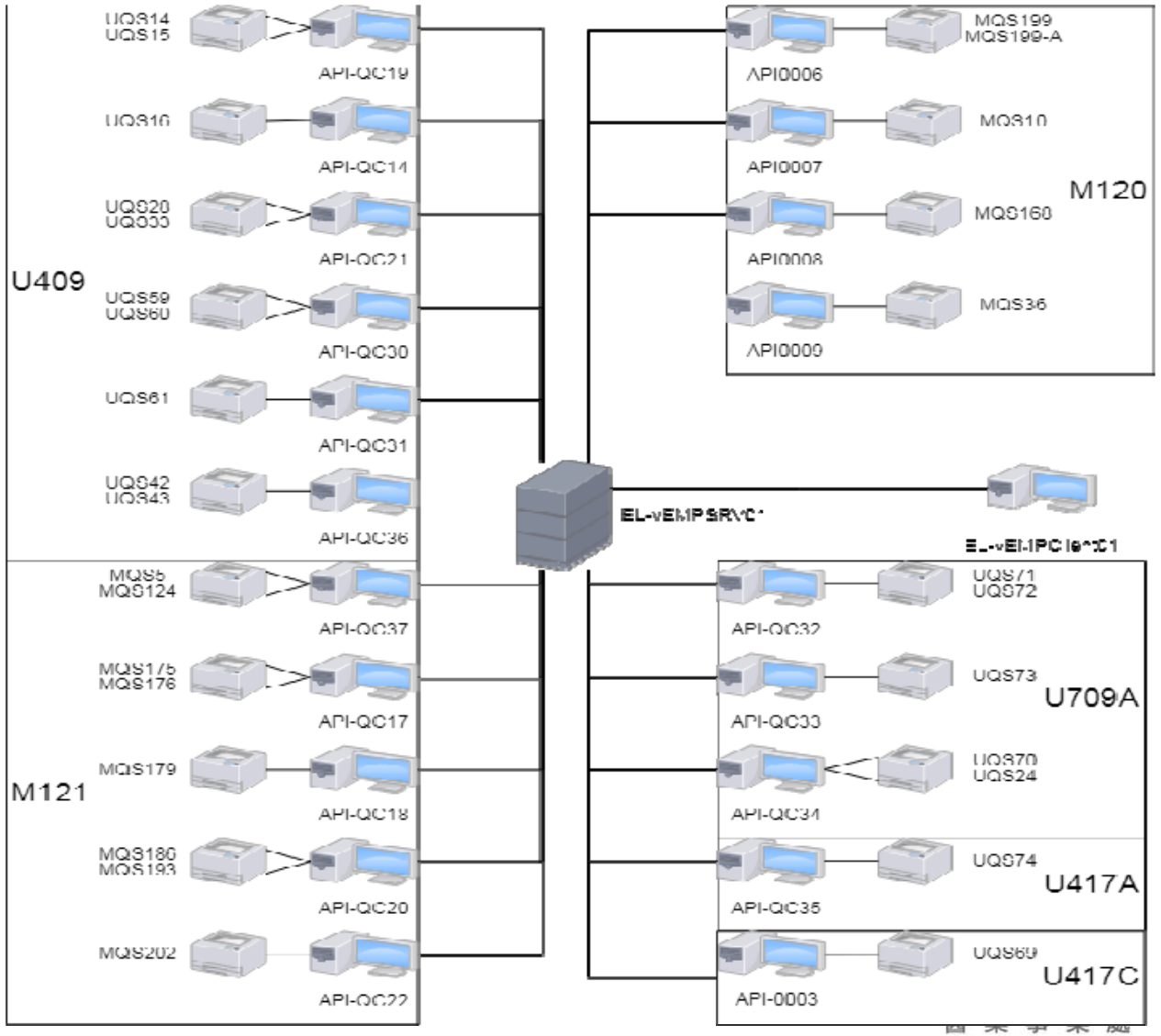
分析儀器控管分享

- 系統圖
- 職責分隔
- 作業區分隔
- 資料封裝
- 稽核審查
- 總結

系統架構圖

管理重點

1.確認資料來源。
2.未來擴充規畫。



Segregation of duties

管理重點

1.必免球員兼裁判
2.確定人員職責
3.依照作業流程決定角色功能

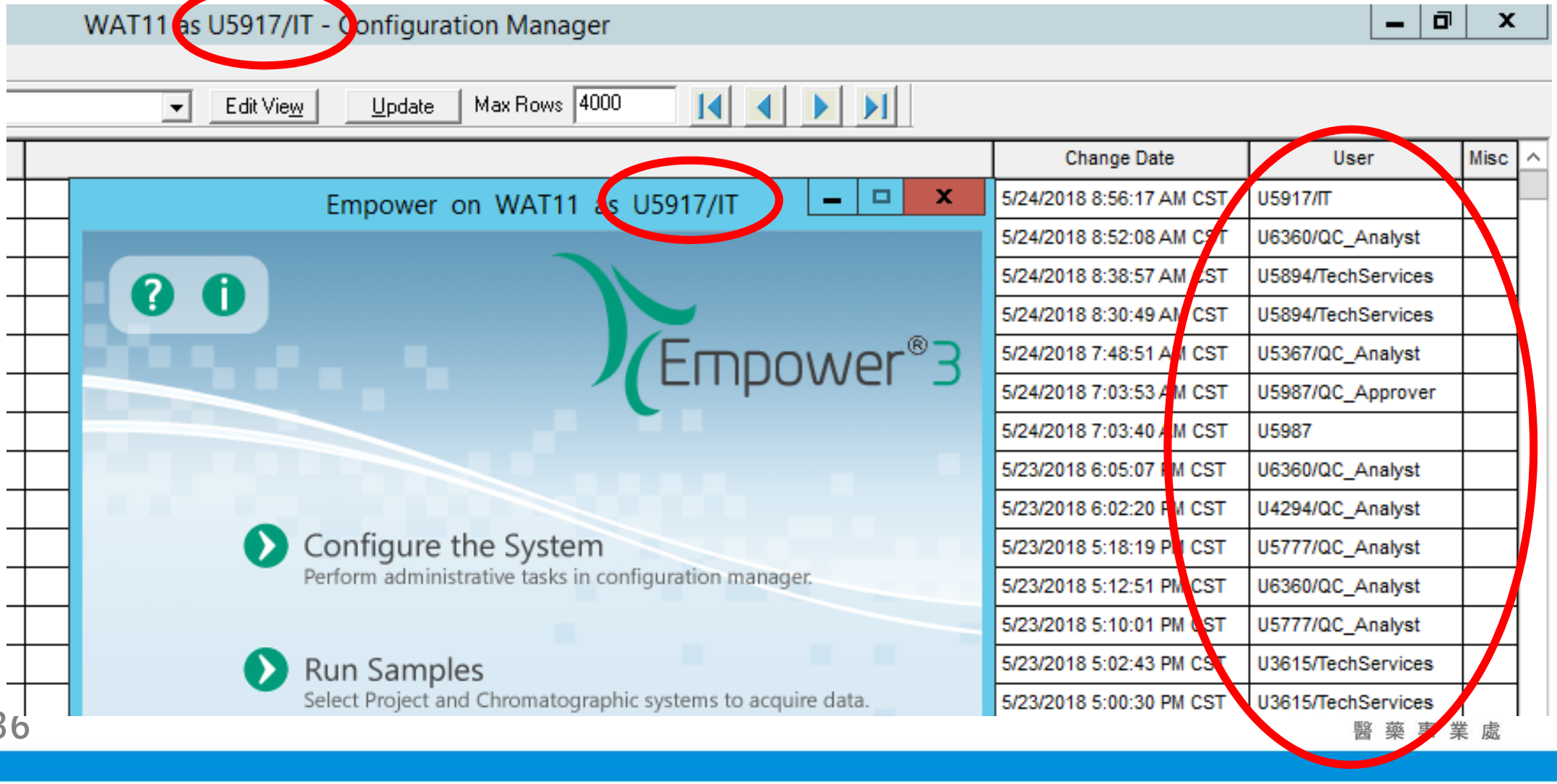
權限	管理者	分析師
Lock Projects	O	O
Unlock Projects	O	X
Alter Users	O	X
Sign Off 1	X	O
Sign Off 2	O	X
Save Processing Methods	X	O
Modify Integration Parameters	X	O
Modify Component Times	X	O
Acquire Samples	X	O

權限類別

QC_Analyst	QC_Manager	QC_Approver	QA_Reviewer
對象：品管單位執行檢測人員。 功能：僅能執行檢測、第一層電子簽核。	對象：品管單位資料管理者。 功能：不能執行檢測與電子簽核。主要負責協助管理資料，如變更專案位置、專案容量等。	對象：品管單位資料核准者。 功能：不能執行檢測，但能執行第二層電子簽核。	對象：品保單位資料審查者。 功能：審查電子資料與報告。

QA_Auditor	TechService	Vendor	IT	Administrator
對象：保單位執行內部稽核人員。 功能：審查系統稽核記錄。	對象：研發單位。 功能：執行方法開發。	對象：原廠廠商。 功能：一般儀器保養、檢修。依據工作內容可請更多權限。	對象：資訊單位。 功能：協助管理人員、權限、群組與其他系統設定維護。	對象：系統管理者。 功能：擁有受管制的功能與跨群組瀏覽的權限。

驗證登入者身分


WAT11 as U5917/IT - Configuration Manager
Edit View
Update
Max Rows
4000
Empower on WAT11 as U5917/IT
Empower®3
Configure the System
Perform administrative tasks in configuration manager.
Run Samples
Select Project and Chromatographic systems to acquire data.
Change Date
User
Misc
5/24/2018 8:56:17 AM CST U5917/IT
5/24/2018 8:52:08 AM CST U6360/QC_Analyst
5/24/2018 8:38:57 AM CST U5894/TechServices
5/24/2018 8:30:49 AM CST U5894/TechServices
5/24/2018 7:48:51 AM CST U5367/QC_Analyst
5/24/2018 7:03:53 AM CST U5987/QC_Approver
5/24/2018 7:03:40 AM CST U5987
5/23/2018 6:05:07 PM CST U6360/QC_Analyst
5/23/2018 6:02:20 PM CST U4294/QC_Analyst
5/23/2018 5:18:19 PM CST U5777/QC_Analyst
5/23/2018 5:12:51 PM CST U6360/QC_Analyst
5/23/2018 5:10:01 PM CST U5777/QC_Analyst
5/23/2018 5:02:43 PM CST U3615/TechServices
5/23/2018 5:00:30 PM CST U3615/TechServices

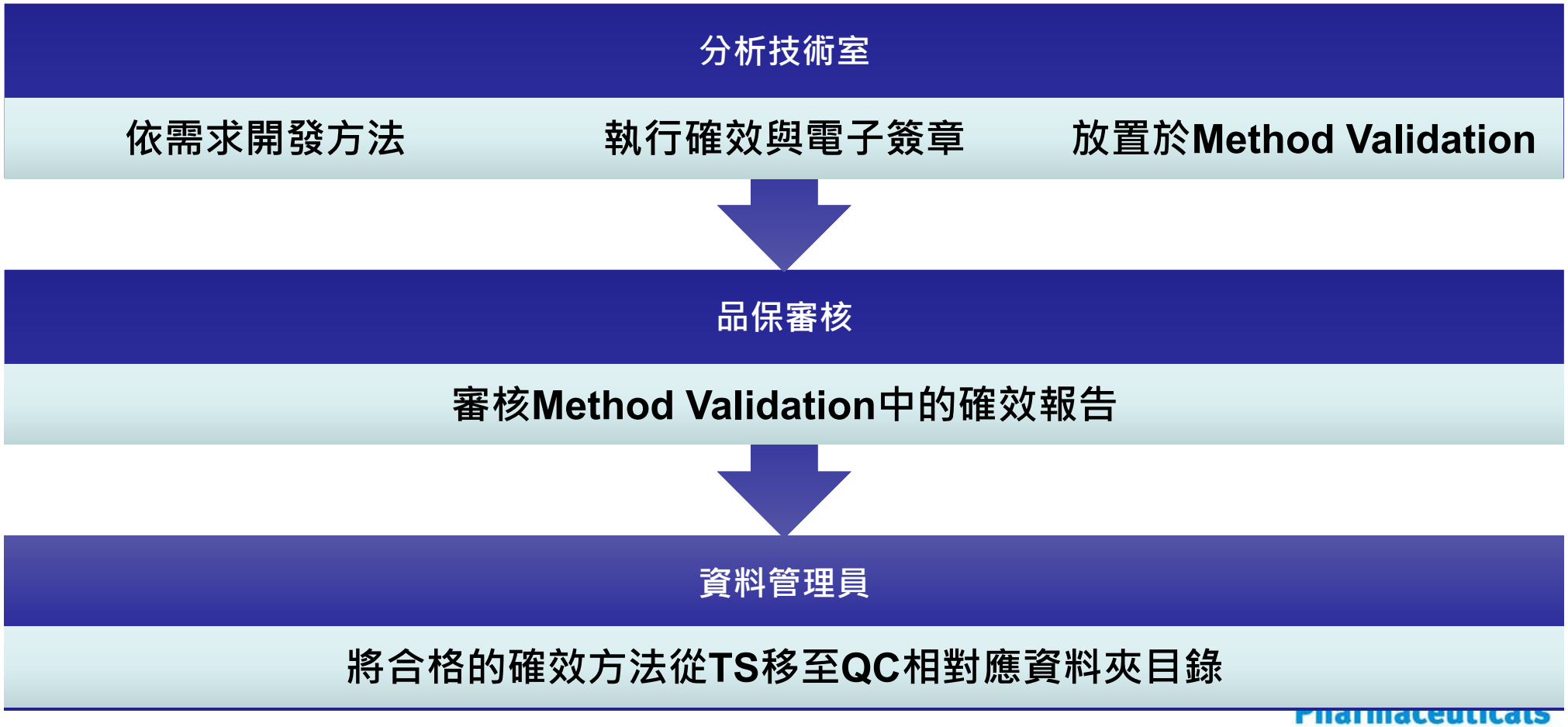
Project Access Control

管理重點

1.資安管理
2.避免誤用

群組名稱	群組負責人
IT	U1668
Lab_Manager	U2742
QA_Auditor	U4878
QA_Reviewer	U1731
QC1	U4637
QC2	U3463
RD1	U3549
TechService	U3615
Vaildation	U5917
Vendor	Vendor A

分析方法開發、確效與轉移



Data Archive

- 管理重點
  - 減少線上系統資料負載量。(機房效能)
  - 宣告所有封裝的資料的唯一性與真實性。(外部查廠)

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Thank you and Questions!

Pharmaceuticals
醫藥事業處

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