電腦化系統確效 (CSV)：
生醫藥業數位轉型之阻力還是助力?

Rockwell Automation

VtR INCORPORATED
法德利科技股份有限公司

Pharma Day

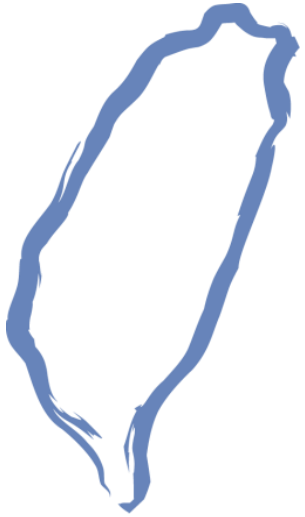
李佩力 Pei-Li Li, Ph.D.

法德利科技股份有限公司

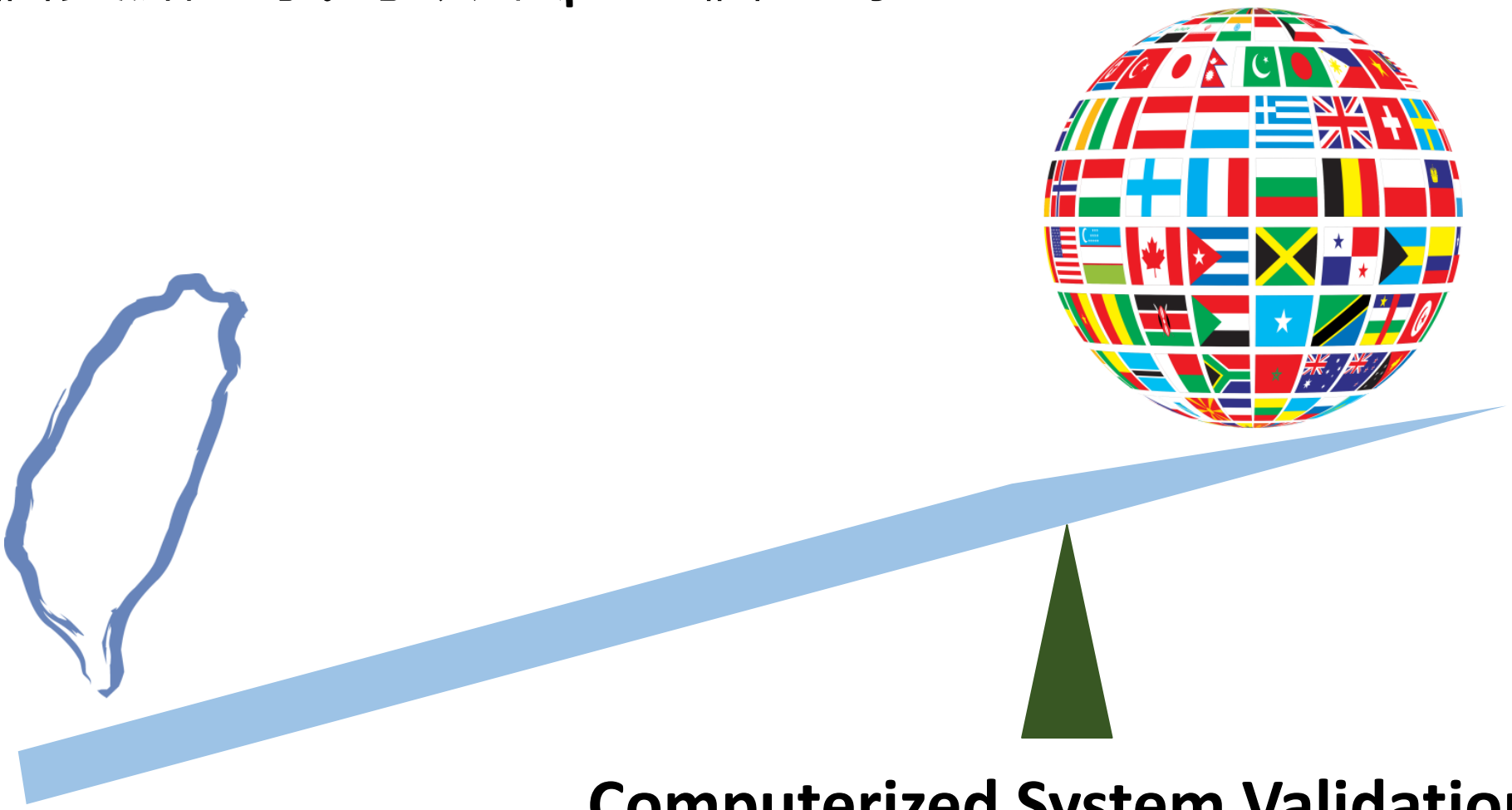
March 13, 2024

Agenda

- 藥廠資料庫之現況與數位化之挑戰
- 電腦系統確效1-2-3
- 確效實務分享
- 總結



給我一個支點，我可以舉起整個地球.

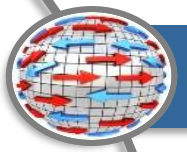


Computerized System Validation

藥廠進軍國際市場之挑戰

藥廠進軍國際市場之挑戰

競爭對手



全球化供應鏈

各國法規與合規壓力

專利期限

獲利空間

研發生產力無法提升

未優化的製程

促進法規協和與合作之國際組織

- ICH (established in 1990)
  - 全名：The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use

創始成員	政府機構	產業代表
歐盟	EC	EFPIA
美國	FDA	PhRMA
日本	PMDA	JPMA

  - 永久政府機構會員：Health Canada, Swissmedic
  - 政府機構會員：10 個國家組織，包含TFDA
  - 產業會員：BIO, GSCF, IGBA
  - 永久觀察員：IFPMA, WHO
  - 觀察員：22 個國家或組織

促進法規協和與合作之國際組織

- PIC/S (established in 1995)
  - 全名The Pharmaceutical Inspection Co-operation Scheme
  - 現有超過 50成員 (Health Authorities)，會員持續增加中，TFDA 於2013年1月加入。
  - PIC/S GMP Guide相當於歐盟GMP
- PIC/S 自2017 年起成為ICH 的觀察員組織，持續進行兩大組織間之合作。

您必須知道的與GMP相關的國際藥事法規

西藥藥品優良製造規範

（第一部、附則）

PIC/S：Guide to Good Manufactur

Practice for Medicinal Products

（Part I，Annexes）

西藥藥品優良製造規範

（第二部：原料藥）

為什麼藥廠資料管理數位化這麼難?

電子化紙本記錄：還是紙本！

METHODS FOR INFORMATION CAPTURE AND SHARING

Paper Notebooks and Logs

Emails

Excel Spreadsheets

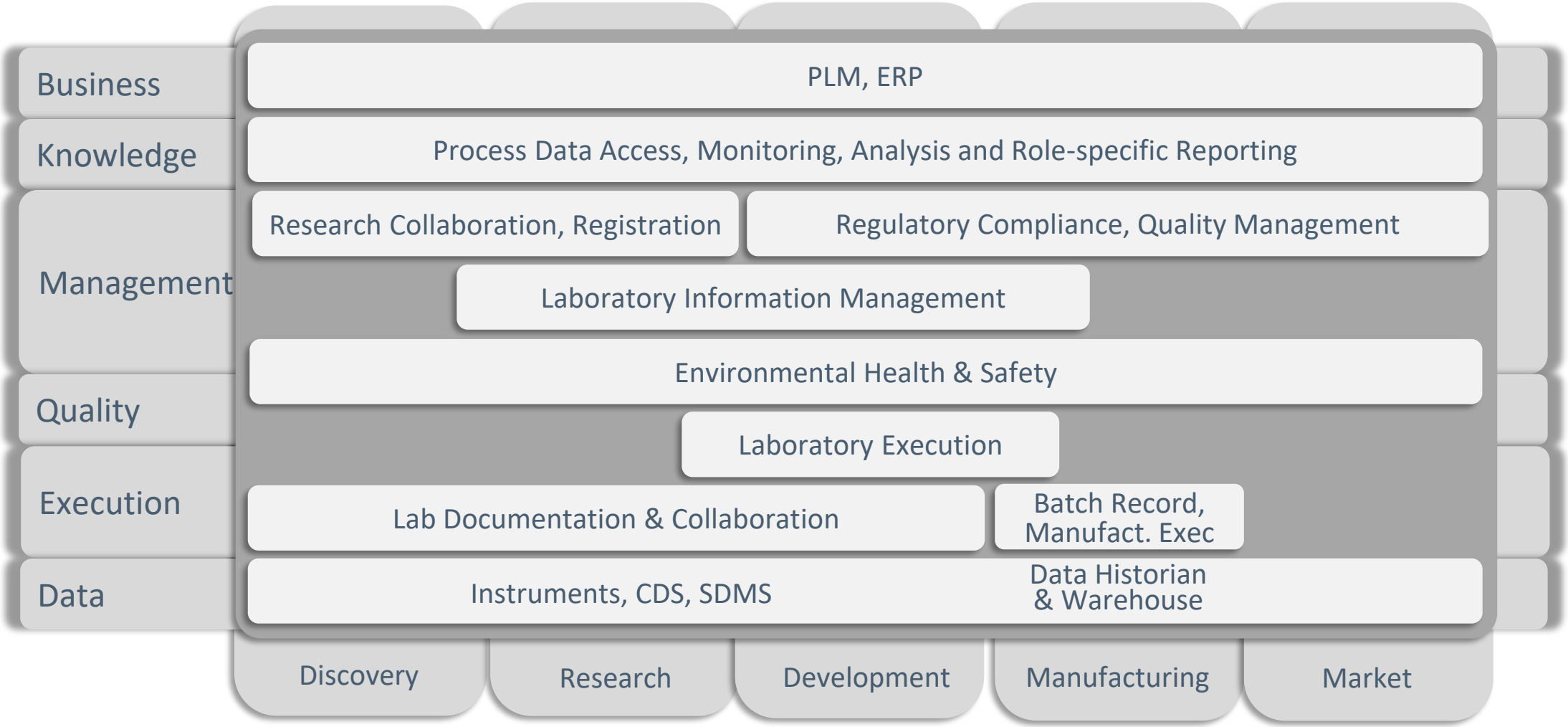
Documents

Instrument Data Files
Shared Local Drives

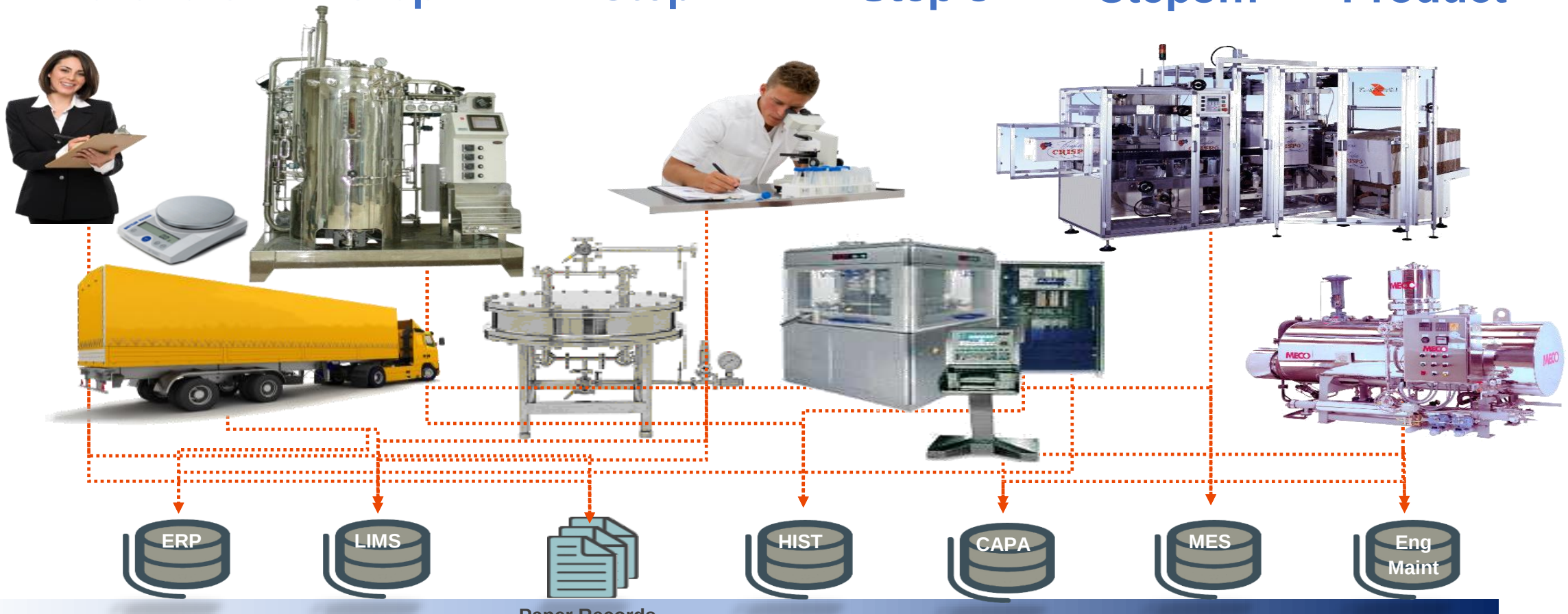
THERE ARE ISSUES

- 難以有系統性地搜尋
- 無法取得或分享資訊
- 非標準化格式與型式
- 手動剪貼
- 資料遺失與資安問題

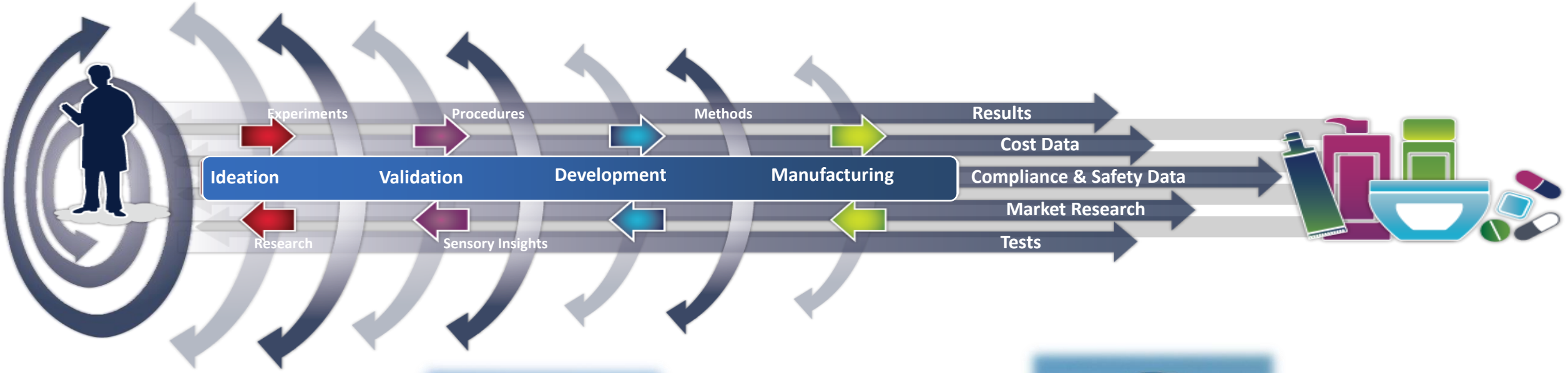
生技藥業資訊地圖

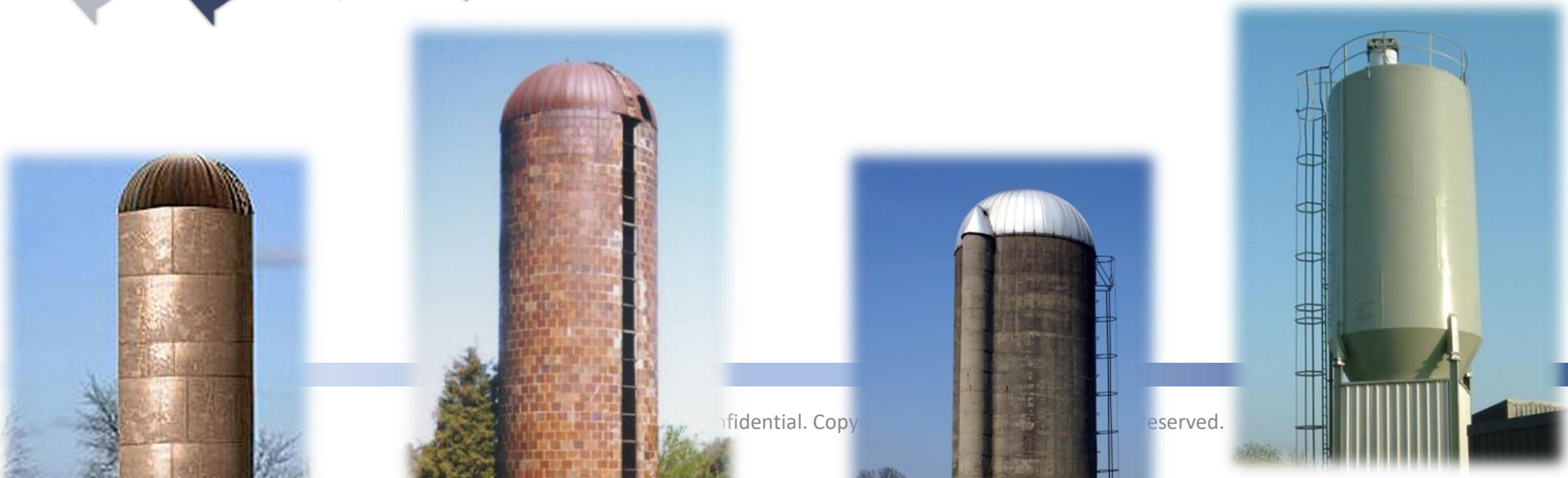


藥廠資訊收集過程



資料穀倉與壕溝 – 闇黑資料 (Dark Data)的形成





藥廠電子化環境：以實驗室資訊紀錄為例

Between Labs


Formulation


Process


Analytical


Contract

Within Groups


Method dev.


Method Val


Execution


QA/QC


Lab Manager

Paper Notebooks??

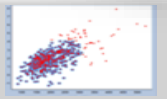
Laboratory Software


LIMS


CDS


SDMS


Reporting


Visualization

Instruments


HPLC


NMR


GCMS


LCMS


FT-IR

藥廠數位化之關鍵能力與優勢

知識管理
- Removal of paper processes
- Centralization of data
- Consistency and accuracy
- Accessibility
- Reporting/Dashboards

資源管理
- Reduction in administrative tasks
- Removal of process redundancies
- Review by Exception
- Capacity insight

數位化之藥廠資料環境

協同作戰
- Accelerated transfer
- Removal of latencies
- Connected workflows

品質與合規
- Reduction in human error
- Automated processes
- Standardized procedures
- Rule-driven execution

藥廠資料數位化之法規與合規

in-Pharma Technologist.com

Breaking News on Global Pharmaceutical Technology & Manufacturing

US FDA guidance looks to stem 'major problem' of data integrity

By Dan Stanton+, 18-Apr-2016

Related topics: QA/QC, APIs (active pharmaceutical ingredients), Regulations, Regulatory & Safety, Globalisation

The US FDA has issued draft guidance to address the recent torrent of data integrity problems at drug manufacturing sites.

The US Food and Drug Administration (FDA) is hoping to reduce the problem through draft guidance issued last week to help firms ensure data be reliable and accurate.

"FDA has increasingly observed cGMP violations involving data integrity during cGMP inspections," the document says. *"Ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health."*

Chinese API maker Zheijang Hisun Pharmaceuticals was hit with a warning last December , while a number of Indian drugmakers – seven firms between mid-2013 and mid-2014 - have also been hit due to data integrity problems. Facilities in Italy and the Czech Republic have also received warnings citing data integrity failings.

The guidance consists of 18 questions and answers to assist drugmakers in ensuring the quality of their data, including how and when to limit access to the computer systems controlling data input.

Drug Shortages

Justin Neway from science-led processing optimisation firm Dassault Systèmes Biovia agreed data integrity has been a *"major problem"* for industry.

He told delegates at last week's Bioprocess International European Summit in Vienna, Austria *"the failure to prepare written processes mainly in foreign facilities"* has helped contribute to the growth in warning letters and contributed to drug

in-Pharma Technologist.com

Breaking News on Global Pharmaceutical Technology & Manufacturing

US FDA slams two Chinese API makers for quality systems and data issues

By Dan Stanton+, 29-Jun-2016

Related topics: Processing equipment, QA/QC, APIs (active pharmaceutical ingredients), Regulations, Ingredients

Quality system and data integrity issues have landed two Chinese API makers with US FDA warning letters.

Shanghai Desano Chemical Pharmaceutical received a warning letter earlier this month, after inspectors from the US Food and Drug Administration (FDA) found significant deviations from current good manufacturing practice (cGMP) at the firm's active pharmaceutical ingredient (API) facility in Pudong District, Shanghai in May 2015.

"Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture," the FDA stated.

The Agency told the firm to respond by providing an investigation into the extent of the inaccuracies in data records and reporting, and to include interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies.

The FDA also asked for a current risk assessment of the potential effects of the observed failures on the quality of your drugs from Desano.

"Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations."

in-Pharmatechnologist.com contacted Desano for further details but did not receive a reply by the time of going to press.

Chongqing Lummy Pharmaceutical

A warning letter was also sent to fellow API maker Chongqing Lummy Pharmaceutical for deviations from cGMP seen during an FDA inspection at its Chongqing facility.

PHARMACOMPASS
Grow Your Pharma Business Digitally

SEARCH for Companies, APIs, Drugs, to find S

Newsletter | Log in | Market Place | ☆ Manufacturers |

Data integrity concerns uncovered in India, China and Taiwan

Created: 21 Oct 2015 View: 1752

Last week, while key decision makers of the pharmaceutical industry were busy attending CPhI Madrid, the Canadian regulator – Health Canada – and the US Food and Drug Administration (FDA) issued compliance alerts to companies based in India, China and Taiwan.

Data integrity concerns uncovered in India, China and Taiwan

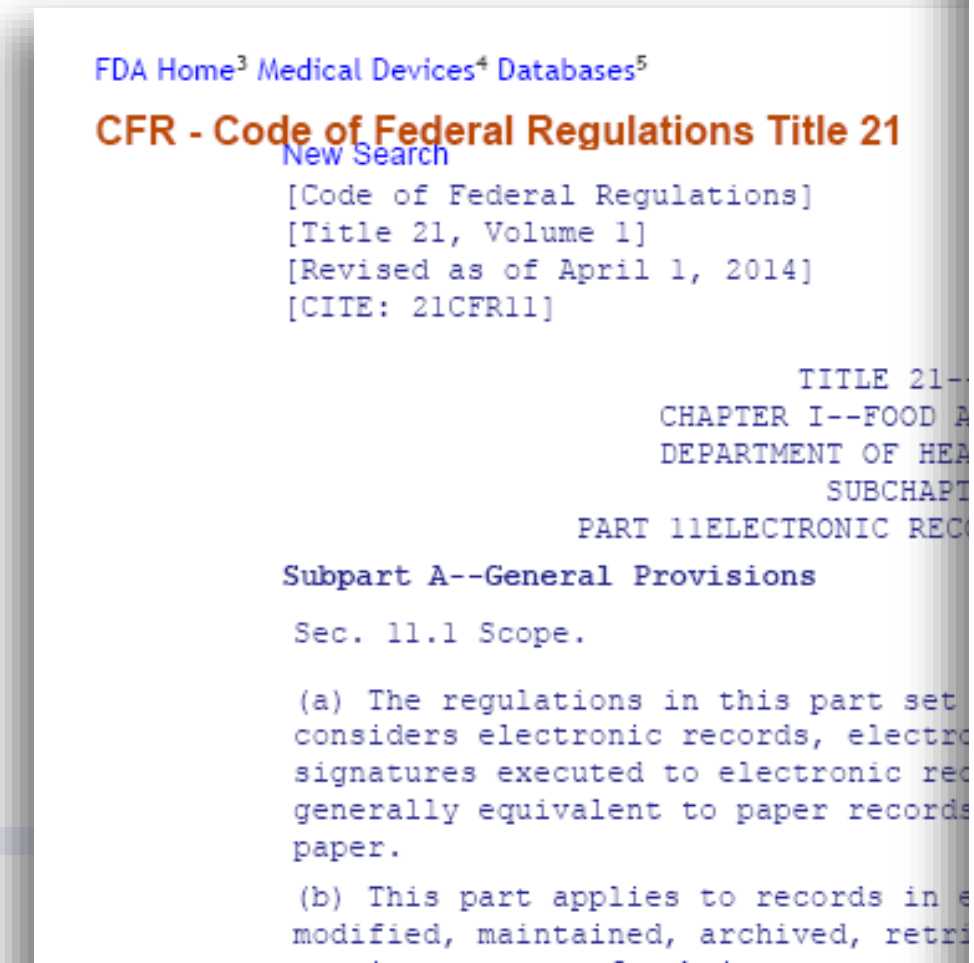
Created: 21 Oct 2015 View: 1752

This week, we once again review this unprecedented wave of regulatory action against pharmaceutical manufacturers, and its

藥廠資料電子化所需面臨的法規

- US and virtually all industries in the whole world:
  - **21 CFR Part 11**: Electronic Records; Electronic Signatures – 電子記錄與電子簽章
- Taiwan and PIC/S members, virtually the whole world:
  - **PIC/S GMP Annex 11**: Computerized Systems – 電腦化系統統一規範
  - **PIC/S GMP Annex 15**: Qualification and Validation – 驗證與確效規範
- The above and "**All Predicate Rules**": Part 210, 211; ICH Q7, Q9; PIC/S GMP Ch. 4, 5, 6, etc.

21 CFR Part 11



FDA Home[3] Medical Devices[4] Databases[5]

CFR - Code of Federal Regulations Title 21

New Search

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2014]
[CITE: 21CFR11]

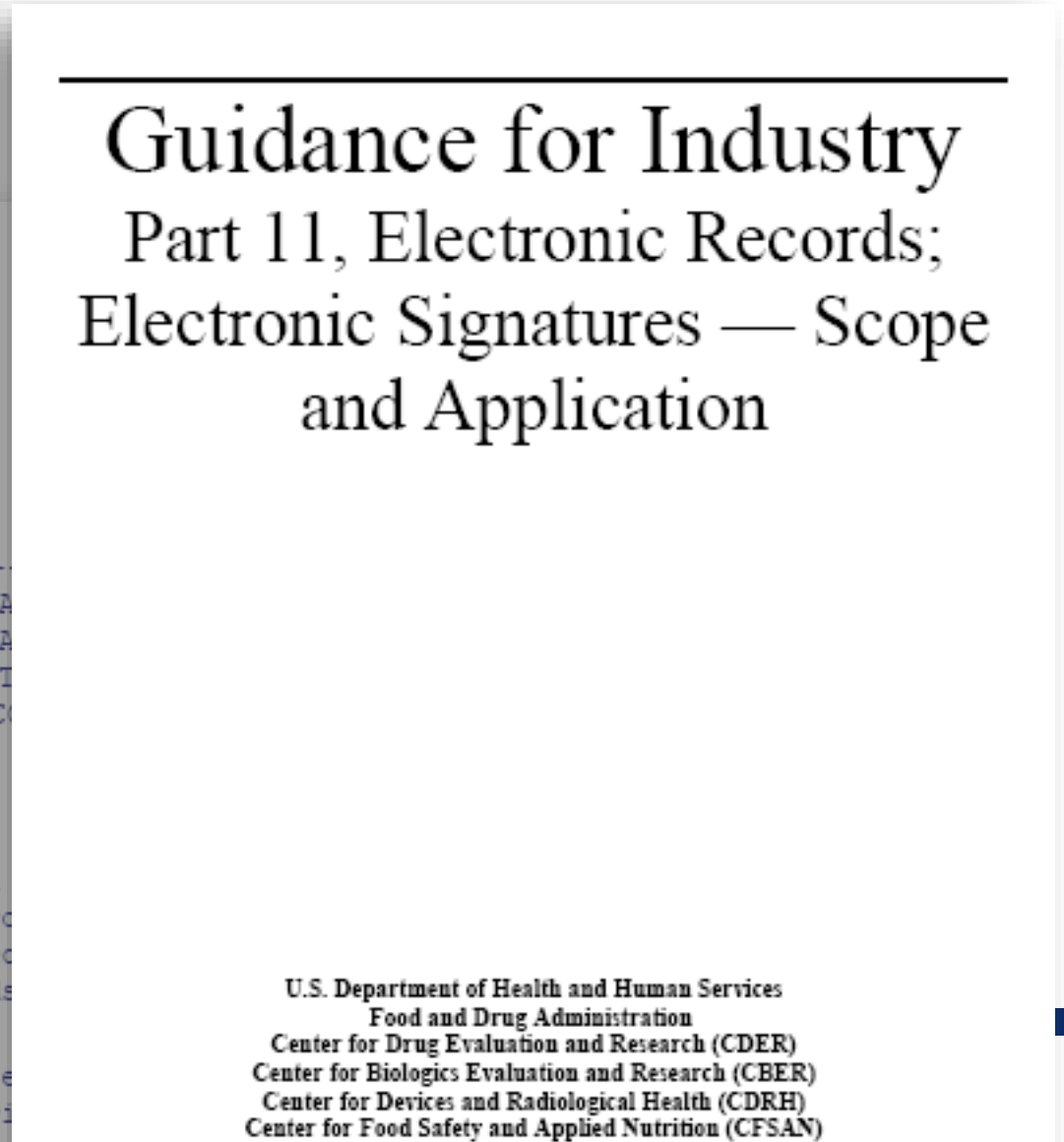
TITLE 21--
CHAPTER I--FOOD A
DEPARTMENT OF HEA
SUBCHAPT
PART 11ELECTRONIC REC

Subpart A--General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set
considers electronic records, electro
signatures executed to electronic rec
generally equivalent to paper records
paper.

(b) This part applies to records in e
modified, maintained, archived, retri



Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)

PIC/S GMP Annex 11

西藥藥品優良製造規範

（第一部、附則）

PIC/S：Guide to Good Manufacturing Practice for Medicinal Products

（Part I、Annexes）

附則 11　電腦化系統（COMPUTERISED SYSTEMS）

原則（PRINCIPLE）	
本附則適用於作為GMP管理活動使用之電腦化系統，電腦化系統是一套軟體與硬體組件，共同應用以完成某些功能。	This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfill certain functionalities.
該應用軟體應進行確效；資訊技術之基礎設施應該加以驗證。	The application should be validated; IT infrastructure should be qualified.
電腦化系統取代手工作業時，不得有降低產品品質、製程管制或品質保證之結果。不應增加該流程的整體風險。	Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.
概述（GENERAL）	
1. *風險管理（Risk Management）*	
在考慮病人安全性、數據完整性與產品品質下，風險管理應應用於電腦化系統的整個生命週期。作為風險管理系統之一部分，確效與數據完整性管制的程度之決定，應基於已證明其合理性並文件化之電腦化系統的風險評估。	Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.
2. *組織與人事（Personnel）*	

PIC/S GMP Annex 15

西藥藥品優良製造規範

（第一部、附則）

PIC/S：Guide to Good Manufactur

Practice for Medicinal Products

（Part I、Annexes）

附則 15 驗證與確效（QUALIFICATION AND VALIDATION）

原則（PRINCIPLE）	
本附則是描述驗證與確效的原則，該原則可適用於藥品製造所使用的廠房設施、設備、公用設施與製程，對 PIC/S GMP 第二部沒有導入追加的要求，也可作為原料藥的補充選用指引。在產品與製程的整個生命週期中，製藥廠透過驗證與確效管制其特殊操作的關鍵層面是 GMP 的要求。對可能影響產品品質之廠房設施、設備、公用設施與製程等的任何計畫性變更，應予正式文件化，並且評估其對於已確效之狀態或管制策略的影響。使用於藥品之製造的電腦化系統也應當依照附則 11 的要求予以確效。在 ICH Q8、Q9、Q10 與 Q11 所呈現的相關概念與指引也應當納入考慮。	This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products

合規與生產力/競爭力提升之兩難

系統各自獨立未整合且未完整確效，合規風險拉高

為了符合法規與查廠需求產生大量紙本紀錄

為了處理紙本紀錄而降低研發效率與生產力

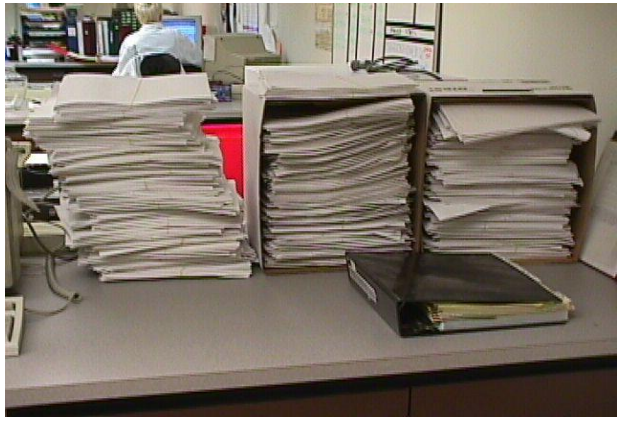
為了提升生產力與競爭力而引進資訊系統，推行無紙化

願景

Before

After

現實

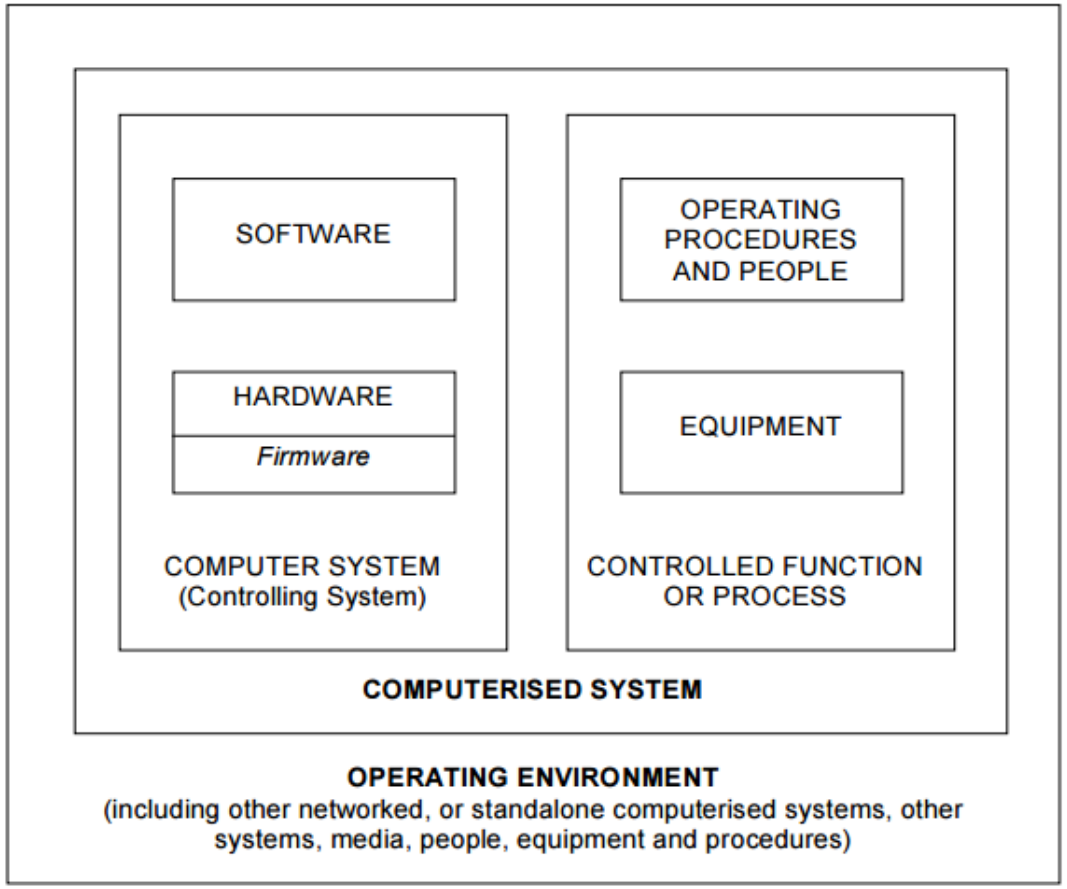


電腦化系統確效 1-2-3

電腦確效之二、三事 (及五、六、七、八...)

- What is Validation?
- Why Validate?
- Why is It Important to Validate
- What is included in a Risk-Based Validation?
- FDA Warning Letter Related to Computer System Validation

什麼是電腦化系統?



This term covers a broad range of systems, including:

- clinical trials data management
- laboratory information management
- automated manufacturing equipment
- automated laboratory equipment
- warehousing and distribution
- blood processing management
- document management

Ref: GOOD PRACTICES FOR COMPUTERISED SYSTEMS IN REGULATED "GXP" ENVIRONMENTS
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

什麼是確效?

- Establishing **documented evidence** which provides a **high degree of assurance** that a specific process will **consistently** produce a product meeting its **predetermined specifications** and quality attributes.
  - FDA Guidelines on General Principles of Process Validation, May 1987.
  - Ref: http://www.fda-consultant.com/provalid.html
- FDA considers software validation to be "**confirmation by examination** and provision of objective evidence that software specifications conform to **user needs and intended uses**, and that the particular requirements implemented through software can be **consistently** fulfilled."
  - FDA General Principles of Software Validation, January 11, 2002
  - Ref: http://www.fda.gov/RegulatoryInformation/Guidances/ucm085281.htm

電腦化系統為何要做確效?

- Failure in Medical Device Software
  - The FDA's analysis of 3140 medical device recalls conducted between 1992 and 1998 reveals that **242 of them (7.7%) are attributable to software failures**.
  - Software validation and other related good software engineering practices discussed in this guidance are a principal means of avoiding such defects and resultant recalls.

Ref: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm

電腦化系統為何要做確效?

Computer systems are becoming more and more complex!

- System Design Challenge
  - Data Storage Design
  - Security Design
  - Network Control & Monitor Design
- Deployment Challenge
  - Physical Network
  - Database Server / Application Server
  - Security
  - Load Balancing
- Dynamic Configuration Challenge
  - Network Connectivity Configuration
  - Security Configuration
  - Application Configuration
  - Data Service Configuration

確效為何重要?

- In the pharmaceutical industry, there are two key reasons why validation is extremely important:
  - **Regulatory Requirements**
    - FDA regulations mandate the need to validate. Failing a FDA audit can result in FDA Inspectional Observations (483s) and warning letters. Failure to take corrective action in a timely manner can result in facility shutdowns, consent decrees, and significant financial penalties.

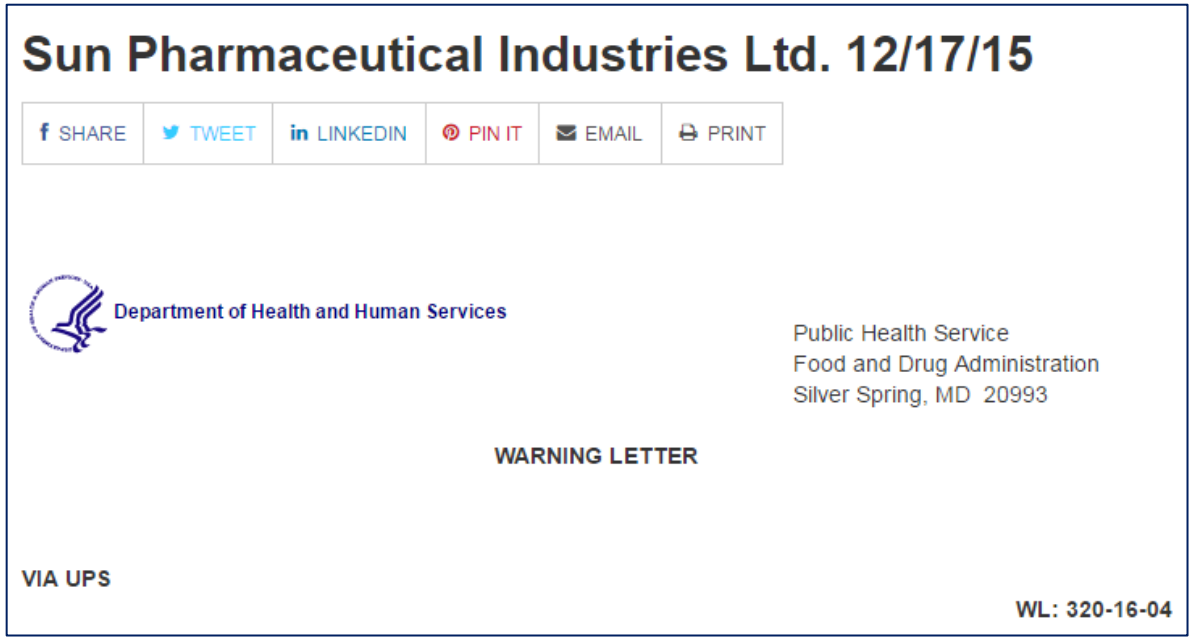
確效為何重要?

- **Business Cost and Impacts**
  - Validation helps prevent software problems from reaching production environments. Mission-critical software applications and processes in the pharmaceutical industry can cause serious consequences if they have functional or data integrity issues.

Between May 25, 2023, the date of the FDA warning letter to iRhythm, and June 27th, iRhythm stock fell almost 25%.

Source: *iRhythm Technologies Inc (IRTC) Stock Price & News*. https://www.google.com/finance/quote/IRTC:NASDAQ?sa=X&sqi=2&ved=2ahUKEwjrtfOu36eAAxU5pIkEHWBaCM8Q3ecFegQIIhAX&window=6M. Google Finance; 26 July 2023.

FDA Warning Letter Related to Computer System Validation



Sun Pharmaceutical Industries Ltd. 12/17/15

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Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

VIA UPS

WL: 320-16-04

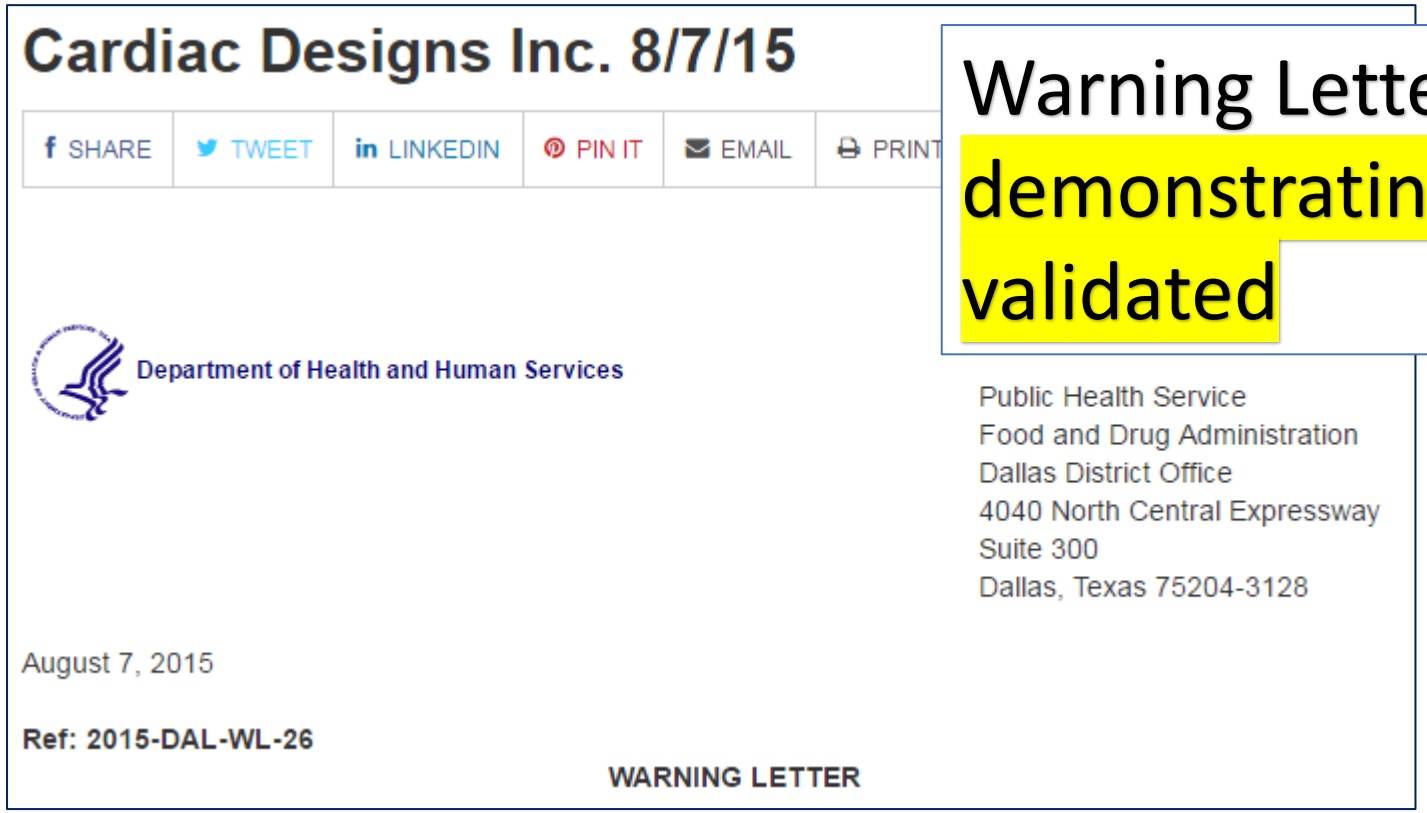
Warning Letter: Lack of Audit Trails and other deficient computerized system controls

Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b)).

You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters."

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm478393.htm

FDA Warning Letter Related to Computer System Validation



Cardiac Designs Inc. 8/7/15

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Dallas District Office
4040 North Central Expressway
Suite 300
Dallas, Texas 75204-3128

August 7, 2015

Ref: 2015-DAL-WL-26

WARNING LETTER

Warning Letter: No records demonstrating the software was validated

"Failure to establish and maintain design validation procedures to ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions, as required by 21 CFR 820.30(g).

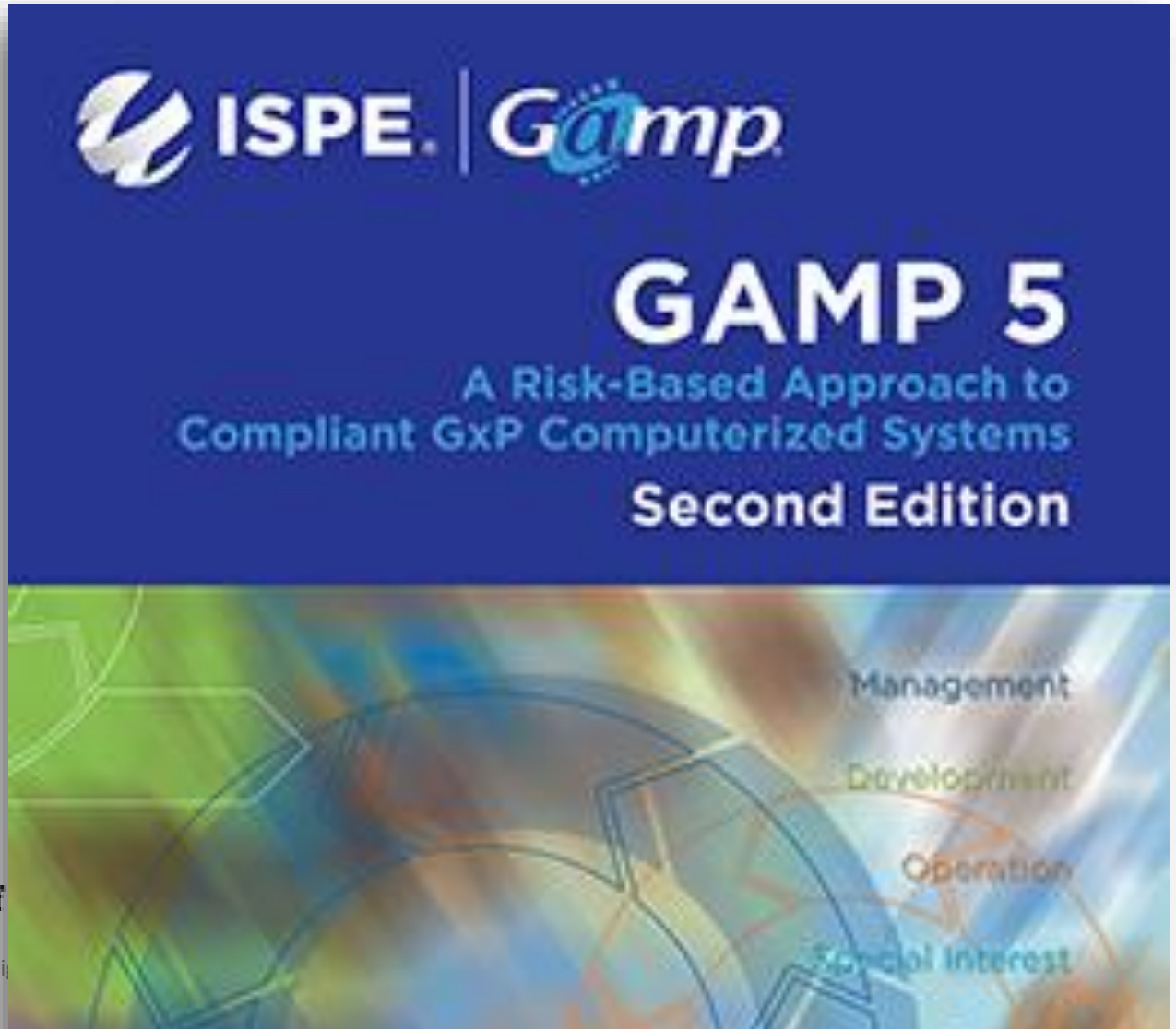
電腦系統確效服務之方法論與指導準則

電腦系統確效之 “Bible” (Gold Standard)

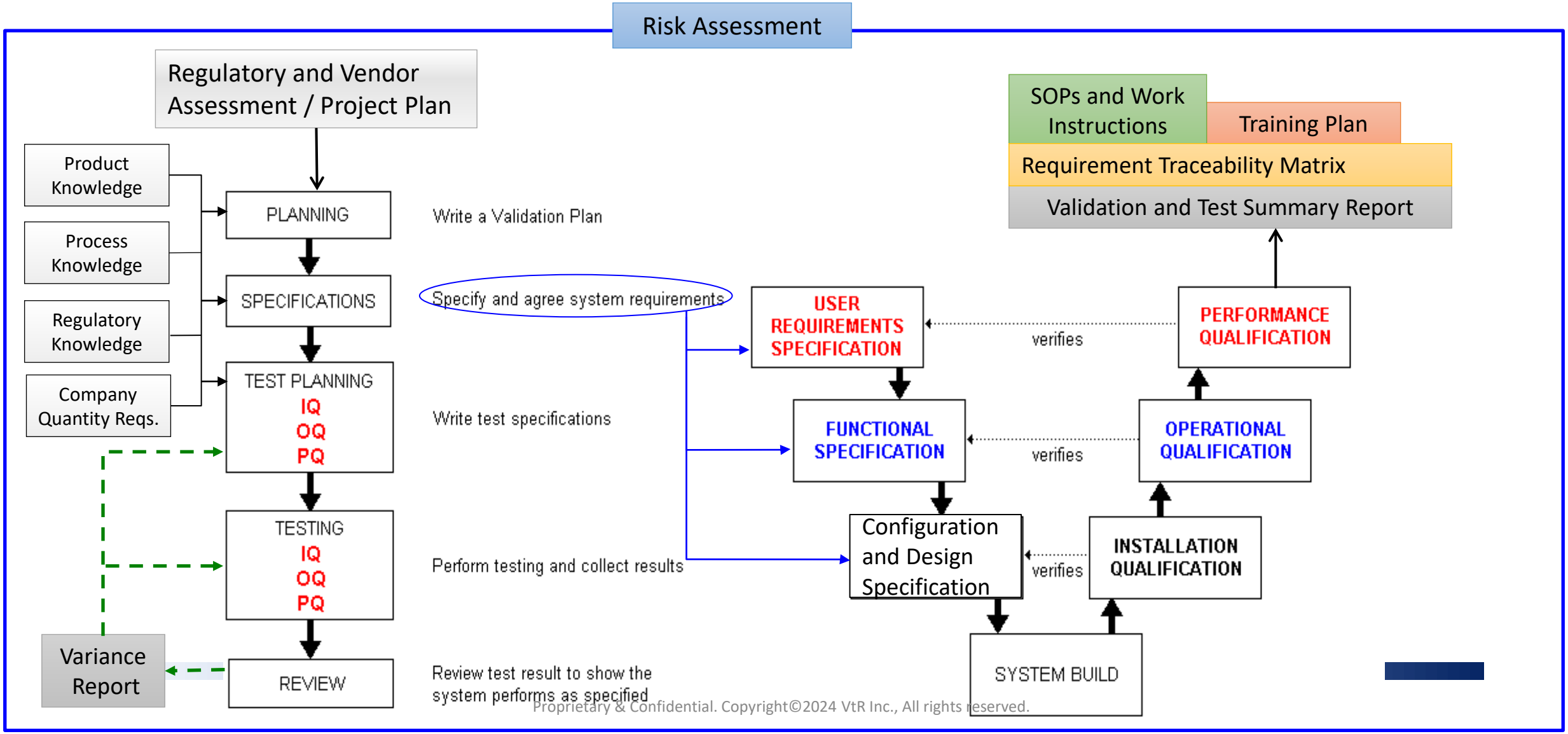
General Principles of Software Validation; Final Guidance for Industry and FDA Staff

Document issued on: January 11, 2002

This document supersedes the draft document, "General Principles of Software Validation, Version 1.1, dated June 9, 1997.



Validation Process & V-Model



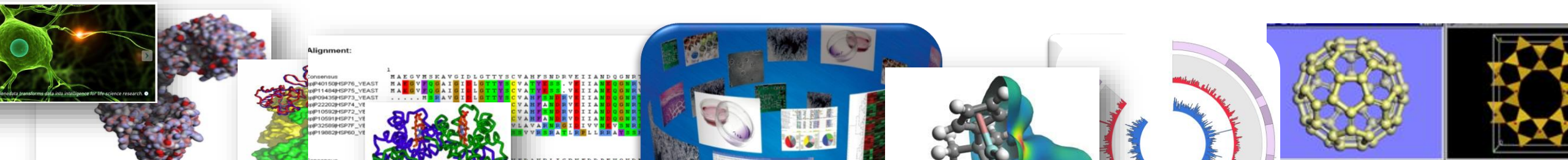
化阻力為助力：現代藥廠數位化之契機

電腦系統確效 FAQ

- 我打算導入的這個系統合規嗎？到底需不需要確效？
- 我何時需要作電腦系統確效？
- 我如何作電腦系統確效？
- 誰能幫我作電腦系統確效？
- 我難道不能花錢買一個 **“FDA 認證/許可”** 的電腦系統，然後自動/馬上就合規了嗎？

法德利科技 科學資訊事業

- 法德利科技是國內少數提供完整**高端科學資訊服務**的在地團隊。
- 法德利服務以科技產業為主，包含生技藥業、醫療服務業、電子半導體產業、能源石化業等，提供從R、D、Q、到M (**研究、發展、品質、製造**)一貫之資訊解決方案。
- 法德利的產品及服務項目涵括**生物資訊**、**化學資訊**、**生命科學**、**奈米與材料科學**、**電子化臨床與實驗室管理**、**製程監控分析**、及**企業品質管理系統**等。
- 法德利除提供先進之軟體及資料庫外，更包含安裝調校、合規**電腦系統確效**(CSV)、委託研究、系統客製開發、使用者教育訓練等服務，客戶遍及產、官、學、研各界。



產業資訊與合規之完整解決方案

符合法規之電子系統確效與整合實驗研究成果之資訊解決方案

實驗室合規管理系統
電腦系統確效服務
系統整合維護與硬體資源提供

Unified Solutions

合規的文檔及品質管理解決方案

企業品質管理系統
電腦系統確效服務
電子送件提交系統
系統整合維護與硬體資源提供

製程、化學品配方之研發解決方案

生命科學研究產品
委託研究
實驗室合規管理系統
系統整合維護與硬體資源提供

法德利 服務產品

- 法德利科技以超越原廠及業界標準之服務品質，提供完整及在地化之資訊與合規解決方案
- 主要服務項目：
  - 科學資訊相關軟硬體系統建置與整合
  - **依循ISPE GAMP®5標準，為法德利或第三方軟體系統導入進行完整電腦系統確效服務以符合FDA及PIC/S GMP規範**
  - 法規與合規諮詢服務
  - 特殊軟體系統之客製開發
  - 生命科學與材料科學委託研究與諮詢服務
  - 標準及客製化之軟體教育訓練

總結

結語

- 市場全球化是現今藥廠必走的趨勢。
- 為因應各國法規及提高競爭力，現有之紙本資料庫必須數位化
- 數位資料庫系統必須強調數位連續性，避免產生資料「穀倉」或「孤島」，以發揮數位化之最大效益。
- 任何在GMP環境下使用之電子資料系統，必須符合Part 11 及 Annex 11、15、以及該資料原有相關法規之規範。
- 電腦系統導入時之完整確效是符合GMP規範之關鍵步驟，該系統才能發揮最大效益並且合規。
- 法德利是藥廠電腦系統合規的好夥伴！

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