行政院及所屬各機關出國報告

出國報告（出國類別：研究-訓練）

參加第 14 屆經濟合作發展組織優良實驗室操作(OECD GLP)查核員訓練

服務機關：行政院農業委員會農業藥物毒物試驗所

姓名職稱：蔡韙任 研究員兼組長

派赴國家：南非-開普敦

出國期間：中華民國 **108** 年 **10** 月 **4~12** 日

報告日期：中華民國 **108** 年 **12** 月 **12** 日

摘要

經濟合作暨發展組織 (OECD)為推動 OECD 優良試驗室操作數據互相承認協定體系(GLP MAD)，從 1981 年開始要求會員國對於化學品試驗報告資料，需依照 OECD 測試準則(方法)及 OECD GLP 規範進行，進而在 1989 年起要求各會員國需依從 OECD GLP 建立一套查核與稽核的符合性評鑑體系，並從 1997 年起開放給非 OECD 會員國參加，可窺見實施此體系對產品需提報安全性資料在國際間互相認可的重要性。此次第 14 屆 OECD GLP 查核員訓練，於 2019 年 10 月 6 日至 10 日假南非開普敦舉辦，雖在較為偏遠的非洲，仍共有超過 24 個國家派人員參加。並由 OECD 邀請資深 GLP 查核員與專家擔任查核員訓練講師，聚焦於新興議題內容，包括數據完整性稽核之電子資料、試驗物質與參考物質的查核重點、公司的企業文化對符合性查核的影響、資訊科技資料的驗證與電子化歸檔的查核、及新興議題之 GLP 案例書面查核討論交流等，可見新興議題除了新的生技產品，如何能合宜於安全性評估與 GLP 的要求外，如何讓各會員國與學員學習到稽核資訊化攫取數據之資料與電腦化系統的過程，更是目前 OECD 對 GLP 符合性評鑑查核時的一大挑戰。

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一、目的

1. 讓會員國與非會員國的學員瞭解到對於主管之產品登記有需要涉及品質與安全性評估者 (如農藥、醫藥品、化工原料、動物用藥、食品添加物等)要求必須繳交符合優良實驗室操作 (GLP) 規範的試驗報告的重要性，以保障產品安全性的可追溯性。

2. 讓學員瞭解 GLP 規範對於試驗研究之計畫、執行、監控、記錄與報告等過程都有一定的作業條件要求及如何進行查核，以確認試驗報告符合 GLP 品質規範之要求，讓各國權責機關可信賴出口國的安全性試驗數據，並在「數據互相承認協定 (Mutual Acceptance of Data, MAD)」的架構下，各會員國與非會員國之間，只要符合 OECD GLP 規範與經權責單位認可實施的相關試驗研究報告資料，應被其他國家接受，如此則可避免重複試驗的浪費或減少實驗動物的使用量，並有利於產品的推廣及避免非關稅貿易障礙。

二、過程：

(一) 出國與查核訓練行程(附件一)：

日期	內容	備註
10 月 4-5 日	由台中至桃園國際機場，搭乘阿聯酋 EK0367 起飛，經杜拜轉機，搭乘阿聯酋 EK0770，於 10 月 5 日抵達南非開普敦。	起程與轉機
10 月 6 日	報到註冊(Registration)領取講義與課程準備及與會人員座談。	
10 月 7 日	開幕、課程目的與師資介紹、GLP 的發展歷史與 GLP 在全球所扮演的角色、OECD GLP 文件簡介、查核重點介紹、稽核案件的選擇、研究稽核及分組討論。	
10 月 8 日	試驗物與參考物質的查核、不符合 GLP 規範的確認及分組討論。	
10 月 9 日	資訊化系統在試驗體系、電腦化系統的查核、資訊化系統的驗證與電子化歸檔及分組討論。	
10 月 10 日	數據接受之權責單位與符合性監控單位角色與職責及	

	相互合作，及品保的基本風險。	
10 月 11-12 日	由開會地點開普敦至南非開普敦國際機場，搭乘阿聯酋 EK0773 起飛，經杜拜轉機，搭乘阿聯酋 EK0366，於 10 月 12 日抵達桃園國際機場。	回程與轉機

(二) 訓練日期與地點：

第 14 屆 OECD GLP 查核員訓練，於 2019 年 10 月 6 日至 10 日假南非開普敦舉辦，雖在較為偏遠的非洲，仍共有超過 24 個國家派 61 位人員參加(附件二)，並以經濟合作暨發展組織優良實驗室操作規範與符合性監控系列之共通文件(附件三)做為訓練與講解之教材。

(三) 訓練內容：

1. OECD 推動 GLP MAD 扮演的角色

OECD 致力於推動優良試驗室操作數據互相承認協定體系(GLP MAD)，截至目前已有 36 個會員國與 6 個非會員國及重要夥伴，進而達成無論會員國與否的全面性相互認可 GLP 資料，一方面讓安全試驗報告符合 GLP 規範，使試驗總結報告維持一定的品質外，並可減少重複進行農藥毒理安全相關試驗，每年可省下約 2 億 7 百萬歐元及減少約 3 萬多隻(32702)實驗動物的使用量。

2. GLP 研究的稽核重點(附件四)

(1) 除了事前規劃外，查核員尚須具備傾聽能力、專業知識、溫和態度、組織能力、盡速建立融洽關係及適時顯現同理心，及查核後要評估其預防與矯正措施，必要時要再補充相關佐證資料，並確認是否滿足需改善的問題，評估偏離是單一事件還是系統性問題，有無適當的預防措施及期限內可完成。

(2) 資料的品質及真實性

GLP 的符合性稽核的目標，就是重建整個實驗的現況，藉由核對總結報告與計畫書、SOP、原始數據及其他歸檔的資料文件或樣品，做為查核依據。

(3) 多試驗點研究與稽核

01. 無論有多少個試驗地點，其概念上仍是一個計畫書(SP)，一個研究主持人(SD)及一份總結報告(FR)。

02. 在稽核時須特別注意是試驗單位還是委託者選擇試驗的地點，若是委託者應注意其與 SD 及主研究人員(PI)的溝通紀錄。另外尚須注意所有試驗地點與 PI 要有明確地列入在 SP，如何確認 PI 同意執行的文件、樣品或試驗物如何在各試驗點接收或傳送的計畫及 SP 有無指名誰當品保人員(QA)去稽核各 PI 所應負的責任。

03. 試驗材料臨時儲存情況及在試驗單位(TF)及試驗地點(TS)間運送，其接收的品質與量情況。

04. 對於試驗點所衍生的偏離，應先讓 PI 知道然後是 SD。

05. 品保稽核活動，在試驗點品保須將查核結果同時給 SD，品保總管及管理階層[PI 及試驗地點的管理階層(TSM)]。

(4) 品保稽核報告在多點試驗的特性

01. 針對 PI：要有 phase report，GLP 符合性聲明及品保聲明。

02. 針對 SD：要包含 PI 的 phase report，可當成附件及 GLP 符合性聲明的相關所有範圍。

03. 針對 QA 品保聲明：QA 在各試驗點的查核活動均須在品保聲明中敘述或以附件形式說明在各試驗點的品保查核情形。

04. 針對檔管：各原始資料可歸檔各試驗點或送回試驗單位。但如果試驗點分屬不同區域或國家，則所有的原始資料應歸檔於試驗單位。

3. 電腦化系統在 GLP 試驗體系的查核重點(附件五)

電腦化系統在 OECD GLP 的規範中，越來越被重視，目前在其 GLP 共通性文件(附件三)其中編號 17 文件就特別加以說明，包括電腦化系統驗證的 GLP 規範要求、電腦化驗證的流程、電腦化系統驗證狀態保持的要求、電腦化需注意的安全事項及電子化紀錄與歸檔。

(1) 電腦化系統的驗證流程

電腦化系統的生命週期，包括從啟用、確認、軟硬體安裝、操作、測試、變更控制及驗證整個過程在使數據呈現出可溯性及提高效率。

(2) 驗證流程需訂定 SOP

建立電腦化系統驗證的 SOP，使得整個體系從開發、測試、操作及維護均能符合 GLP 要求，SOP 訂定重點包括驗證的要求文件，設置環境的安全性、變更管制、定期審核、系統的備份與維護及教育訓練。

(3) 風險評估

電腦化系統要先列出需求的清單，那一種類型、要用在何種用途，尤其是商品化的物件，在使用時是否會因軟硬體而造成數據異常、密碼設定之安全性、有無防火牆，這些也要符合 GLP 原則有一定評估流程並需留下紀錄說明具體風險、解決策略及預防措施。

(4) 供應商與使用者

電腦化系統在選擇供應商時，須審慎評估供應商可提供使用者(用戶端)的系統能力、安全性能力、問題解決能力及瞭解其以往的服務情形，在使用者端要清楚提出系統要做什麼，尤其是要符合該實驗室的需求。

(5) 驗證報告

電腦化系統應真實及準確的反映驗證過程及驗證結果，如同品保稽核應總結驗證活動及在驗證過程中沒完成的驗證計畫或偏離事項，最後應有使用聲明，由管理階層核准使用該電腦化系統。

(6) 其他注意事項

01. 應注意電腦化系統保有驗證狀態的管理及相關的 SOP。
02. 應注意電腦化系統環境設施的安全性、管控的安全性、數據的安全性及備份安全性。
03. 確保電子化簽名的程序，包括登錄、修改、建立的日期和時間均有適當的紀錄與保存。

(7) 電腦化系統的稽核

01. 應先列出電腦化系統清單，並確認選擇使用的系統。

02. 是否為研究人員所需要的，針對認可的測試項目要有驗證計畫、進行驗證報告及報表產出等程序書。

03. 電腦驗證報告的稽核：藉由驗證計畫規格需求，產出的報表，重新重構報告內容的產出過程。

04. 稽核重點

A. 確認是否為其原始數據的定義，電腦系統使用的訓練紀錄及相關的SOP(操作維護及資料備份)，核對其登錄過程、連結確認變更管制及檔案歸檔。

B. 變更管制

i. 維持電腦系統週期性的驗證體系，包括策略評估變更的責任過程、核可、軟體升級或更新重新驗證之文件。

ii. 風險管控系統性驗證的說明資料，確實性及全部或部分重驗證。

(8) 電腦化系統稽核的技巧

01. 問一些理所當然的問題

02. 以查核員的知識觀點去運作

03. 如果有疑問試著去詢問同仁或有經驗的專家

04. 使用查核表但保留彈性

05. 從簡單再到複雜的電腦化或資訊化系統

06. 從查核中學習

07. 偏離單開出前應 110%的確認與判定後

(9) 電腦化系統的結論

電腦化系統應用在毒理試驗體系為一國際趨勢，為加快國內與本所 GLP 符合性的運作，任何涉及電腦化系統應儘快思索如何清楚的讓電腦化系統完成驗證過程及保持驗證體系的完整，才能因應未來對 GLP 品質的符合性要求。

三、重要心得：

1. 經濟合作暨發展組織 (OECD)為推動 OECD GLP MAD 體系，從 1981 年開始要求會員國對於化學品試驗報告資料，需依照 OECD 測試準則(方法)及 OECD GLP 規範進行，進而在 1989 年起要求各會員國需依從 OECD GLP 建立一套查核與稽核的符合性評鑑體系，並從 1997 年起開放給非 OECD 會員國參加，可窺見實施此體系對產品需提報安全性資料在國際間互相認可的重要性。

2. 此次第 14 屆 OECD GLP 查核員訓練，於 2019 年 10 月 6 日至 10 日假南非開普敦舉辦，雖在較為偏遠的非洲，仍共有超過 24 個國家計 61 位人員參加此訓練與研習，各國與會學員有試驗單位、主管機關與監督機構，可見各國對提升 GLP 具備管理與技術的查核能力之重視。並由 OECD 今年邀請資深 GLP 查核員與專家擔任查核員訓練講師，計有來自英國、澳洲、瑞士、美國、南非、比利時、日本、馬來西亞、丹麥、奧地利、芬蘭、紐西蘭及法國等，更可看出 OECD 積極在國際間推動此項符合性評鑑體系的努力。

3. 本次 OECD GLP 查核員訓練主要聚焦於新興議題內容，包括數據完整性稽核之電子資料、試驗物質與參考物質的查核重點、公司的企業文化對符合性查核的影響、資訊科技資料的驗證與電子化歸檔的查核、及新興議題之 GLP 案例書面查核討論交流等，可見新興議題除了新的生技產品，如何能合宜於安全性評估與 GLP 的要求外，如何讓各會員國與學員學習到稽核資訊化攫取數據之資料與電腦化系統的過程，更是目 OECD 對 GLP 符合性評鑑查核時的一大挑戰。

四、結論：

此次參加 OECD GLP 查核員訓練後，分析 OECD GLP 規範國際趨勢與未來發展及課程聚焦議題，由各國積極派代表參加訓練課程，讓試驗單位、主管機關與監督機構學員都具備管理與技術實力，並提升學員對資訊數位化數據之查核能力，為國際聯合查訪 (Mutual Joint Visit)預作準備，就是要讓 OECD GLP MAD 體系進一步全球化與納入更多的非會員國，達成避免重複試驗，有利於產品的推廣及試驗研究報告互相承認甚為重要。

五、建議事項：

1. 國內應積極培養國際間互相認可之符合性規範的查核人員，才能掌握國際間對

新興科技崛起的因應策略與驗證系統，以稽核日趨龐大的電腦自動資訊管理系統的試驗資料，厚植 OECD GLP 查核能力與提升我國在國際能見度，期使保有我國相關產業在國際之競爭力。

2. 國內研發的生物製劑農藥產品若要更有國際競爭力，熟悉符合性的 GLP 監控體系是必要的，此次研習透過案例與 GLP 資深專家研討，瞭解到國際間藉由查核內涵互相討論及研習產品符合性的 GLP 監控體系，並介紹共識文件讓與會人員有一致性的標準參考，才能取得國際間對 GLP 規範的信任及合作，化解國際間的貿易障礙。

3. 由於 OECD GLP MAD 程序必須透過各國聯合查訪與稽核試驗報告數據才能獲得相互認可資格，因此提升國人的英語能力或國內從小學實行雙語政策，整體上才能有利於國人在國際場合與國際聯合查訪間進行良好的溝通。

附件一、第 14 屆 OECD GLP 查核員訓練課程 (主辦單位提供的文件)

日期：10. 7-10, 2019

地點: Lagoon Beach Hotel, Milnerton, Cape Town

Sunday 6 October 2019		
Registration		16h00 – 18h00
Cocktail Reception		19h00 – 21h00
Day 1 (7th October 2019) Monday (Chair: Rob Jaspers)		
Title	**Speaker**	**Time**
Registration		08h00 – 09h00
Inaugural Session • Welcome Greetings • Opening Remarks & Welcome/Inaugural Address • Course objectives	Shadrack Phophi (South Africa) - Ron Josias (SANAS CEO) - Tshenge Demana (**the dti**) - Richard Sigma (OECD Secretariat) - Christoph Moor (GLP WG Chair) Shadrack Phophi (South Africa)	09h00 – 09h30
History and development of GLP GLP in International Context	Richard Sigman (OECD Secretariat)	09h30 – 10h00
Overview of OECD GLP documents	Shadrack Phophi (South Africa)	10h00 – 10h30
Tea/Coffee Break		**10h30 – 11h00**
Introduction to inspection process	Martin Reed (UK)	11h00 – 11h30
How to select studies for a study audit?	Elizabeth Moane (Australia)	11h30 – 12h00
Auditing of GLP Study (Including multi-studies)	Christoph Moor (Switzerland)	12h00 – 12h30
Data Integrity (Including electronic data)	Charles Bonapace (US – FDA)	12H30 – 13H10
Lunch Break		**13h10 – 14h00**
Workshop I - How to select studies for a study audit? - Auditing a GLP study/Data integrity		14h00 – 15h00
Tea/Coffee Break		**15h00 – 15h30**
Workshop I - How to select studies for a study audit? - Auditing a GLP study/Data integrity		15h30 – 16h30
Discussion on workshop I	Feedback presentation by groups	16h30 – 17h30
Question & Answer Session	All	17h30 – 18h00
Day 2 (8th October 2019) Tuesday (Chair: Christoph Moor)		
Inspection of Test and Reference Items	Fariza Wan Abdullah (Malaysia)	08h30 – 09h00
How to understand new requirements in document No. 19?	Kenji Nakano (Japan)	09h00 – 09h30
Non-compliance process: Making non-compliance decision and typical examples of non-compliance decisions	Guido Jacobs (Belgium)	09h30 – 10h10

Tea/Coffee Break		**10h10 – 10h40**
Workshop II - Test and reference items - Non-compliance decision		10h40 – 13h10
Lunch Break & Photo Shoot		**13h10 – 14h00**
Sightseeing (Optional Tour) Welcoming dinner at the Durbanville Hills Wine Estate		13h30 – 18h00 19h00 – 21h00
Day 3 (9th October 2019) Wednesday (Chair: Fariza Wan Abdullah)		
Discussion on Workshop II	Feedback presentation by Groups	08h30 – 09h30
IT systems in the test facility	Lene Bjerring Bork (Denmark)	09h30 – 10h00
Inspecting the computerised system	Martin Baeten (Belgium)	10h00 – 10h30
Tea/Coffee Break		**10h30 – 11h00**
IT validation & Electronic archiving	Ronald Bauwer (Austria)	11h00 – 11h50
Commercial/outsourced archiving	Paula Korhola (Finland)	11h50 – 12h20
Lunch Break		**12h30 – 13h30**
Workshop III – Computerised system / IT		13h30 – 16h00
Tea/Coffee Break		**16h00 – 16h30**
Discussion on workshop III	Feedback presentation by groups	16h30 – 17h30
Question & Answer Session	All	17h30 – 18h00
Day 4 (10th October 2019) Thursday (Chair: Martijn Baeten)		
The Receiving Authorities: - role and responsibilities - cooperation with Receiving Authorities	R Jaspers (Netherlands)	08h30 – 09h30
Claiming compliance with principles of GLP	Celine Dugué (France)	09h30 – 10h00
Tea/Coffee Break		**10h30 – 10h30**
Risk-based quality assurance programme	Martin Reed (UK)	10H30 – 11H00
Question & Answer Session	All	11H00 – 12H00
Course Evaluation/Closing remarks/Certificate Handover	Shadrack Phophi (South Africa) Richard Sigma (OECD) Mpho Phaloane (South Africa)	12H00 – 13H00
End of Training		**13h00**
Lunch Break		**13h00 – 14h00**

附件二、參加 OECD GLP 查核員訓練課程國家與人員 (主辦單位提供的文件)

Participants for Groups and Subgroups

Group	Team	No.	Red Group		Orange Group		Blue Group		Lime Group	
GROUPS	Team 1 (Subgroup A)	1	John Ndalamo *	South Africa	Kgwaredi Ledwaba***	South Africa	Lebogang Motsoeneng**	South Africa	Ekta Kapoor*	India
		2	Kyungtae Kim**	South Korea	Ori Elad**	Israel	Kyung -Hwa Park*	South Korea	Anele Bougart***	South Africa
		3	Tsai Wei-Ren*	Chinese Taipei	Eun Young Lee**	South Korea	Xiaoli Wang**	China	Kyongmi Chon**	South Korea
		4	Yun Jeung Choi	China	Marta Bushe*	Russia	Laura González*	Argentina	LUO Feiya	China
		5	Dairo Portillo Estrada**	Colombia	Emre Durmus***	Turkey	Lee Jia Juan***	Singapore	Zoltán Szaller*	Hungary
	Team 2 (Subgroup B)	1	Kvetoslava Forisekova*	Slovakia	Jeremias Cardens**	Colombia	Krisztina Németh**	Hungary	Jenny Henke**	Germany
		2	Marie-Anne Botrel**	France	Nur Amani Shaari*	Malaysia	Marita Hoeppner*	Germany	Mirka Laavola**	Finland
		3	Shinta Katsuyama*	Japan	Claudia Cordel***	South Africa	Roguet Thibault**	France	Prachathipat Pongpinyo*	Thailand
		4	Tatiana Murzich**	Russia	Soojung Kim**	South Korea	Kwang Jin Kim*	South Korea	Xiaohuai Wu*	China
		5	Bogaert Waldo**	Belgium	Archawin Rojanawiwat**	Thailand	Dace Purina***	Latvia	Hatice Bilici***	Turkey
	Team 3 (Subgroup C)	1	Busarawan Sriwanthan*	Thailand	Wolfgang Baernthaler**	Austria	Wen-Tsin Poh*	Malaysia	Pauline Sylvest Salanti**	Denmark
		2	Marlies Sandbaumhüter**	Germany	Takano Yumi*	Japan	Chia-Chi Chen***	Chinese Taipei	Leiming CAI*	China
		3	Ahryum Kim**	South Korea	Thure Vigga Ulrich**	Denmark	Maria Mija**	Romania	Tshifularo Ramuedzisi***	South Africa
		4	DU Yikun	China	Yi-Wen Lan***	Chinese Taipei	Minkyoung Paik*	South Korea	Yuk Fung Louisa Wong*	Australia
		5	Furtado Andreia*	Portugal	ZHANG Fenglan	China	LIN Qingbin	China	Mijung Son	South Korea
									Habib Muhammed	Singapore
Total			15		15		15		16	

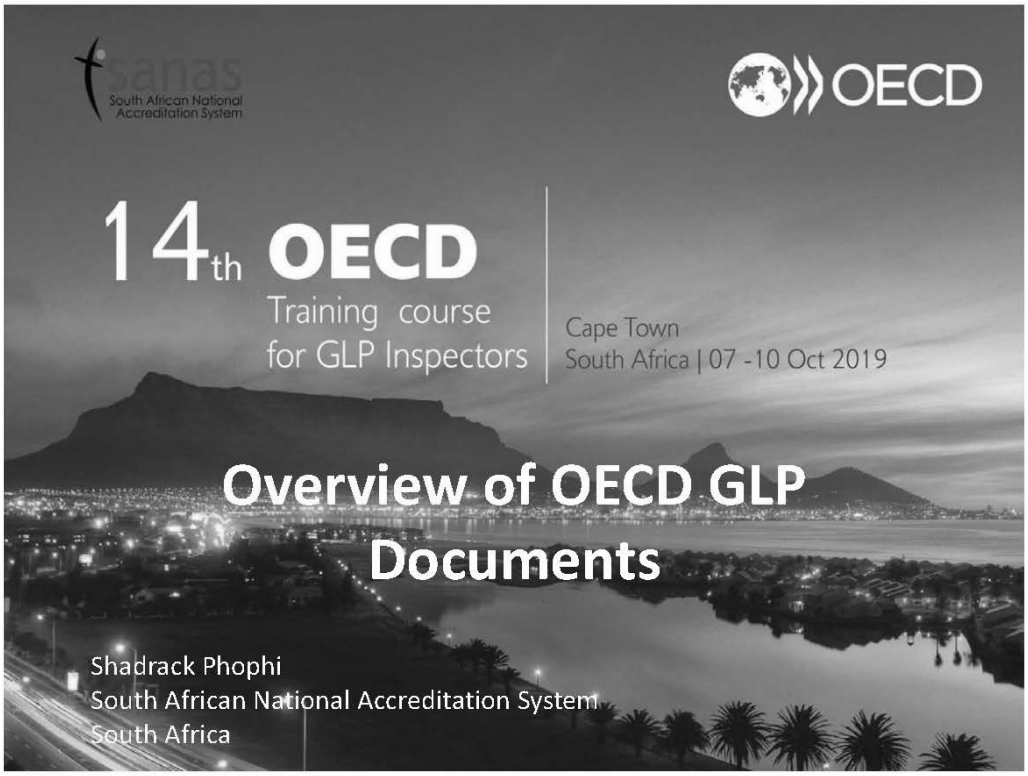
1. *They have little or no experience of an inspection - *******
2. *They have experience of less than 3 years as an inspector - ******
3. *They have experience of more than 3 years as an inspector - *****

附件三：OECDGLP 符合性監控系列之共通文件與內容

一、OECDGLP 符合性監控系列之共通文件

- 第 1 號：經濟合作暨發展組織優良實驗室操作規範(1997 年修訂版)
- 第 2 號：優良實驗室操作符合性監控指引修訂版(1995 年)
- 第 3 號：實驗室查核與研究稽核施行指引修訂版(1995 年)
- 第 4 號：品質保證與優良實驗室操作(1999 年修訂版)
- 第 5 號：實驗室供應商符合優良實驗室操作規範(1999 年修訂版)
- 第 6 號：優良實驗室操作規範於田間試驗研究之應用(1999 年修訂版)
- 第 7 號：優良實驗室操作規範於短期研究之應用(1999 年修訂版)
- 第 8 號：研究主持人於優良實驗室操作研究之角色與責任(1999 年修訂版)
- 第 9 號：優良實驗室操作查核報告製備指引(1995 年)
- 第 10 號：優良實驗室操作規範於電腦化系統之應用(1995 年)
- 第 11 號：試驗委託者在優良實驗室操作規範應用之角色與責任(1998 年)
- 第 12 號：要求在他國執行查核與試驗稽核(2000 年)
- 第 13 號：經濟合作暨發展組織優良實驗室操作規範於多重試驗地點研究組織與管理之應用(2002 年)
- 第 14 號：優良實驗室操作規範於體外研究之應用(2004 年)
- 第 15 號：符合優良實驗室操作規範之歸檔建立與控管(2007 年)
- 第 16 號：優良實驗室操作規範之組織病理學同儕審查要求指引(2014 年)
- 第 17 號：優良實驗室操作規範於電腦化系統之應用(2016 年)
- 第 18 號：經濟合作暨發展組織關於優良實驗室操作規範與 ISO/IEC 17025 之關係的立場聲明 (2016 年)
- 第 19 號：試驗物管理、特性描述與使用 (2018)

二、OECDGLP 符合性監控系列內容 (主辦單位提供的訓練講義)



Presentation Outline

- Mutual Acceptance of Data
- Overview of the OECD GLP documents
- Guidance for Compliance Monitoring Authorities
- Consensus documents
- Advisory documents
- Position papers

Mutual Acceptance of Data (MAD)

- Consistency, basis for work sharing
- Avoid duplication; avoid non-tariff trade Barriers
- Shorten time to market
- Animal welfare concerns

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OECD COUNCIL ACTS ON GOOD LABORATORY PRACTICE

- 1981 Council Decision on Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30/Final]
- 1989 Council Decision/Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87/Final]
- 1997 Council Decision on Adherence of Non-Member Countries to the Council Acts related to the Mutual Acceptance of Data [C(97)114/Final]

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OECD COUNCIL ACTS ON GOOD LABORATORY PRACTICE

Integral part of 1981 Council Decision on MAD

PART I

"Decides that data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment"

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OECD COUNCIL ACTS ON GOOD LABORATORY PRACTICE

Integral part of 1981 Council Decision on MAD

PART II

"Recommends that Member Countries, in the testing of chemicals, apply the OECD Test Guidelines and the OECD Principles of GLP, set forth respectively in Annexes 1 and 2…"

Annex II, OECD Principles of Good Laboratory Practice

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1989 COUNCIL DECISION –RECOMMENDATION ON COMPLIANCE WITH PRINCIPLES OF GOOD LABOTAROTY PRACTICE C(89)87(Final)

1. Compliance Monitoring:

Decides that national Compliance monitoring Procedures be implemented (1983 Recommendation)

- based on laboratory inspections and study audits
- national compliance monitoring authority
- certification of GLP compliance by test facility

Recommends application of guidance in Annexes

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GLP – Publications from OECD

- OECD Principles of GLP: OECD Series on Principles of GLP and Compliance Monitoring
- Guidance Documents for GLP Compliance Monitoring Authorities
- Advisory Documents for GLP Compliance Monitoring Authorities
- Consensus Documents on the Application of the Principles of GLP

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Sr. No	Document	Adopted	Revised
No. 1	OECD Principles	1981	1997
No. 2	Guidelines for Compliance Monitoring Authorities	1992	1995
No. 3	Guidelines for conduct of inspections and study Audit	1992	1999
No. 4	Quality Assurance and GLP	1992	1999
No. 5	Compliance of Laboratory Suppliers with GLP Principles	1992	1999
No. 6	The Application of the GLP Principles to Field Studies	1992	1999
No. 7	The Application of the GLP Principles to Short Term Studies	1993	1999
No. 8	The Role and Responsibilities of the Study Director in GLP Studies	1993	1999
No. 9	Guidance for Preparation of Inspection Reports	1995	-

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Sr. No	Document	Adopted	Revised
No. 10	The Application of the Principles of GLP to Computerised Systems	1995	Obsolete (2016)
No. 11	The Role and Responsibility of the Sponsor in the Application of the Principles of GLP	1998	-
No. 12	Requesting and Carrying Out Inspections and Study Audits in Another Country	2000	-
No. 13	The Application of the OECD Principles of GLP to the Organization and Management of Multi-site studies	2002	-
No. 14	The Application of Principles of GLP in vitro studies	2004	-
No. 15	Establishment and Control of Archives that Operate in Compliance with the Principles of GLP	2007	-
No. 16	Guidance on the GLP requirements for Peer Review of Histopathology	2014	-
No. 17	Application of GLP Principles to Computerised Systems	2016	Replaced No. 10

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Sr. No	Document	Adopted	Revised
No. 19	Management, Characterisation and Use of Test Items	2018	-

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No. 1: OECD Principles on GLP

Section I: Scope – Regulatory Tool

- Unless specifically exempted by national legislation
  - ✓ "Principles of GLP apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products , and for the registration of industrial chemicals"

- Definitions of Terms
  - ✓ Good Laboratory Practice
  - ✓ Terms Concerning the Organisation of a Test Facility
  - ✓ Terms Concerning the Non-Clinical health and environmental studies
  - ✓ Terms Concerning the Test Item

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No. 1: OECD Principles on GLP

Section II: Principles governing the following are provided:

1. Test Facility Organisation and Personnel
2. Quality Assurance Programme
3. Facilities
4. Apparatus, Material, Reagents and Specimens
5. Test Systems
6. Test and reference items
7. Standard Operating Procedures
8. Performance of the Study
9. Reporting of study Results
10. Storage and Retention of Records and Materials

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Guidance Documents for Compliance Monitoring Authorities

No 2: Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No 3: Revised Guidance for the conduct of Test Facility Inspections and Study Audits (1995)

No 9: Guidance for the Preparation of GLP Inspection Reports (1995)

Consensus & Advisory Documents

Consensus and Advisory Documents

- To assist governments and test facilities to interpret and apply the OECD Principles on GLP

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Differences between Consensus documents and advisory documents

- **Consensus Documents**
  - ✓ Developed by consensus workshops comprising representatives of member countries and other stakeholders
- **Advisory Documents**
  - ✓ Developed by the Working Group, with assistance of experts

Endorsed by the Working Group on GLP and the OECD Joint Meeting of the Chemicals and Working Party on Chemicals, Pesticides and Biotechnology

Consensus Documents	Advisory Documents
Quality Assurance and GLP (No. 4)	Role/Responsibilities of Sponsor (No. 11)
Compliance of laboratory suppliers (No. 5)	Requesting and Carrying Out Inspections and Study Audits in Another Country (No. 12)
Application of GLP to field studies (No. 6)	The Application of Principles of GLP in vitro studies (No. 14)
Application of GLP to short-term studies (No. 7)	Establishment and Control of Archives that Operate in Compliance with the Principles of GLP (No. 15)
Roles/Responsibilities of Study Director (No. 8)	Guidance on the GLP requirements for Peer Review of Histopathology (No. 16)
Requesting and Carrying Out Inspections and Study Audits in Another Country (No. 12)	Application of GLP Principles to Computerised Systems (No. 17)
The Application of the OECD Principles of GLP to the Organization and Management of Multi-site studies (No. 13)	Management, Characterisation and Use of Test Items (No. 19)

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GLP Consensus Documents

❖ No. 4: Quality Assurance and GLP

- ✓ Reference to QA in the OECD principles of GLP
- ✓ The QA management link
- ✓ Qualifications of QA personnel
- ✓ QA involvement in the development of SOPs and study plans
- ✓ QA inspections
- ✓ QA planning and justification of QA activities and methods
- ✓ QA inspection reports
- ✓ Audit of data and final reports
- ✓ The QA statement
- ✓ QA and non-regulatory studies
- ✓ QA at small test facilities

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GLP Consensus Documents

- No.5: Compliance of Laboratory Suppliers with GLP Principles
  - ✓ Standards and accreditation schemes
  - ✓ Test systems, animal feed, bedding and water
  - ✓ Radio-labelled chemicals
  - ✓ Computer systems, applications software
  - ✓ Reference items, apparatus, sterilized materials, general reagents, detergents and disinfectants
  - ✓ Products required for microbiological testing

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GLP Consensus Documents

- No.6: The Application of the GLP Principles to Field Studies
  - ✓ Definition of the terms
  - ✓ Test facility organisation and personnel
  - ✓ QA programme
  - ✓ Facilities
  - ✓ Apparatus, materials, reagents, test systems
  - ✓ Test and reference items
  - ✓ Standard Operating Procedures (SOPs)
  - ✓ Performance of the study, reporting of study results
  - ✓ Storage and retention of records and materials

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GLP Consensus Documents

- **No.7: The Application of the GLP Principles to short-term studies**
  - ✓ Test facility organisation and personnel
  - ✓ QA programme
  - ✓ Facilities, Apparatus, materials, and reagents
  - ✓ Test systems
  - ✓ Test and reference items
  - ✓ Standard Operating Procedures (SOPs)
  - ✓ Performance of the study
  - ✓ Reporting of study results

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GLP Consensus Documents

- **No.8: The Role and Responsibilities of the Study Director in GLP Studies**
  - ✓ The role of the study director, management responsibilities
  - ✓ Responsibilities of the study director, study plan amendments and deviations
  - ✓ Qualifications of the study director, interface with the study
  - ✓ Replacement of the study director

GLP Consensus Documents

- **No.13: The Application of the OECD Principles of GLP to the Organization and Management of Multi-site studies**
  - ✓ Management and control of multi-site studies
  - ✓ Quality Assurance
  - ✓ Master schedules
  - ✓ Study plan
  - ✓ Performance of the study
  - ✓ Reporting of study results
  - ✓ Standard Operating procedures (SOPs)
  - ✓ Storage and retention of records and materials

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GLP Advisory Documents

- **No.11: The role and responsibilities of the sponsor in the Application of the principles of GLP**
  - ✓ Responsibilities of the sponsor
  - ✓ Other issues
- **No.14: The application of the Principles of GLP to I vitro studies**
  - ✓ Responsibilities, QA, facilities, apparatus, material and reagents
  - ✓ Test system, test and reference items, SOPs
  - ✓ Performance of the study and reporting of study results
  - ✓ Storage and retention of records and materials, glossary of terms

GLP Advisory Documents

- **No.15: Establishment and Control of Archives that operate in Compliance with the Principles of GLP**
  - ✓ Roles and Responsibilities, archive facilities and security
  - ✓ Archiving procedures, archiving electronic records, QA
  - ✓ Contract archive services, closure of an archive
  - ✓ Other issues
- **No.16: Guidance on the GLP Requirements for Peer Review of Histopathology**
  - ✓ GLP Requirements of Peer Review
  - ✓ GLP Compliance of Peer Review
  - ✓ Summary of Expectations

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GLP Advisory Documents

- **No.17: Application of GLP Principles to Computerised Systems (No. 17)**
  - ✓ Scope and definition of terms
  - ✓ Project phase
  - ✓ Operational phase
  - ✓ Retirement phase
  - ✓ Other issues

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GLP Advisory Documents

- **No.19: Management, Characterisation and Use of Test Items**
  - ✓ Definitions of terms
  - ✓ Responsibilities of Test Facility Management, Study Director, QA and Sponsor
  - ✓ Test item transportation and receipt
  - ✓ Identification, labelling and sampling
  - ✓ Handling and storage
  - ✓ Characterisation of the test item
  - ✓ Prepared test item
  - ✓ Archiving
  - ✓ Disposal

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Position Documents

- No. 18 : OECD Position Paper Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025 (2016)
- The use of laboratory accreditation with reference to GLP Compliance Monitoring (1994)
- Outsourcing of inspections functions by GLP Compliance Monitoring Authorities (2006)

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附件四、GLP 研究的稽核重點內容 (主辦單位提供的訓練講義)

The presenter

Worked in industry for 8 years

Joined MHRA June 2015

Conducted around 130 inspections to date (120 GLP)

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Lets begin in 1981…..

MUSIC TELEVISION®

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But also….

OECD mutual acceptance of data agreement contains a particular requirement:

"facilitate international-harmonised approaches to assuring compliance"

Which led to…..

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GLP Inspection Process - Agenda

- Before, during and after
- Inspector behaviours including communication
- Assessment and decision making

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Before the inspection

Understand the company you are going to visit:

- Previous inspection reports
- Internal summary reports
- Google, web searches, company website etc
- Master Schedule
- SOPs

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Inspection notification

OECD guidance states:
Test facility may be informed

Announced vs
Unannounced inspections

Medicines & Healthcare products Regulatory Agency

MHRA

OFFICIAL – SENSITIVE [COMMERCIAL]
Ms Stephen Vinter
Vinter Bioanalytical Industries
The Sidings
Didcot
Berkshire
RE12 5TF

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

www.gov.uk/mhra

18 July 2019

Inspection Reference: Insp GLP 001

Dear Mr Vinter,

GOOD LABORATORY PRACTICE LABORATORY INSPECTION
COMPLIANCE MONITORING INSPECTION

I am writing to inform you that, as part of our programme of inspection I intend to begin an inspection of your facilities on 02 August 2019.

I will be travelling by car and hope to arrive by 09:00. There is no need for any special arrangements to be made, but it would be appreciated if a car parking spaces and office facilities could be made available.

Good Laboratory Practice inspections will be performed in accordance with The Good Laboratory Practice Regulations, Statutory Instruments 1999 No. 3106 as amended.

In order that we can prepare for this inspection, we would be grateful if you could provide us with the following information in electronic format.

- A copy of the GLP organisation chart
- A list of facilities for which compliance with the Principles of Good Laboratory Practice is claimed with a site plan as appropriate
- Details of any restrictions on movement between areas
- A copy of the Master schedule for on-going studies, and studies completed since the last inspection
- A copy of the SOP index and SOPs relating to QA inspections, archives and document control
- A list of computer systems used within the GLP test facility to include a brief description of the system purpose and date of the last validation activity undertaken.
- Details of significant changes since the last inspection

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Study selection and the use of pivot tables

Row Labels	Count of Department
Aquatic Ecotox & Biodeg ERC	**1**
Growth Inhibition	1
Environmental Analysis ERC	**78**
Adsorption/Desorption	7
Independent Laboratory Validation	1
Method Validation	31
RAC Analysis	8
Rate of Degradation	10
Residue Analysis	18
Residues	2
Storage Stability	1
Field Trials	**7**
Dissipation	4
Operator Exposure	1
Processed Commodity	1
Residues	1
Histotech ERC	**20**
Pathology Contract Histology L/T Rodent	1

PivotTables
Tables
Illustrations

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Opening meeting

Sets the scene

- Tells the company why we are there
- Provide an outline of the inspection, areas we want to visit, studies and documents selected for review
- Clarify changes at the facility since the last inspection
- Tell them when we will hold a close out meeting
- Clarify deficiency grading definitions

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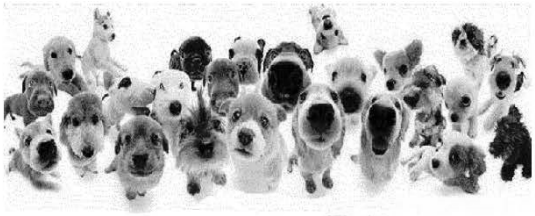
Quality System Assessments

- Company structure
- QA
- SOPs
- Test systems
- Facilities
- Equipment (including computerised systems)
- Test items
- Study conduct
- Storage



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Onsite

Key Inspector Behaviours:

- Professional and polite
- Good communicator (including active listening)
- Well organised
- Builds rapport quick and easily
- Shows appropriate empathy

The Importance of LISTENING

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Questioning style

Types of questions:

- Open vs. Closed
- Probing vs. Reflective
- Paraphrasing
- Leading
- Hypothetical

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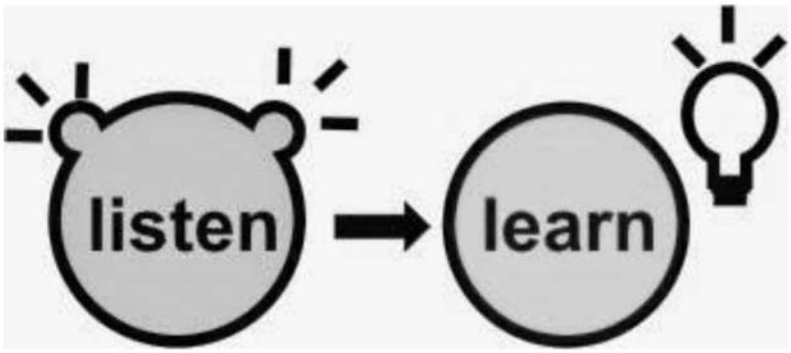
Listening Styles



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So what now?

You have asked the questions

You have heard the answers

You've gathered your evidence

Now it's……

Decision time…

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Deficiencies – The So What Questions

What GLP Principles have been breached and how?

What is the extent of the deficiency? (isolated, widespread, systemic)?

What is the impact of the breach? Does it impact upon the compliance of a study or a facility?

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Decisions are based on

Information collected

Data reviewed

GLP knowledge

Wisdom

Experience

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Closing meeting

Summary of inspection

- Areas covered, systems assessed, studies looked at

Findings will be presented

- Final opportunity to address anything on site

Next steps covered

- Timescale for report

After the inspection

Inspection will be written up

- Report peer reviewed?

CAPA assessed

- Additional information requests

Risk assessment performed

Out of compliance notification?

Post inspection - CAPA

- Have they addressed the issue?
- Assessed the extent of the finding – one off or systematic?
- Appropriate preventative actions
- Achievable timescales

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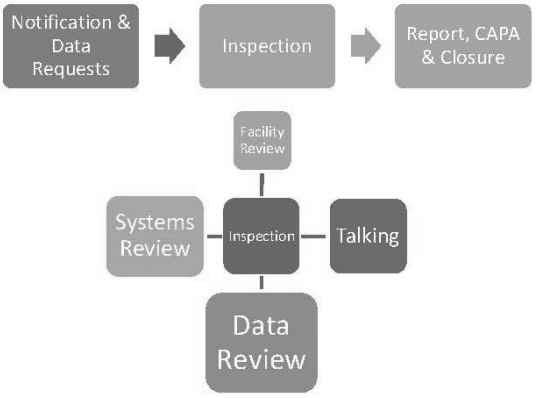
Certificate issued!

Test Facility Management

Inspections in a nutshell



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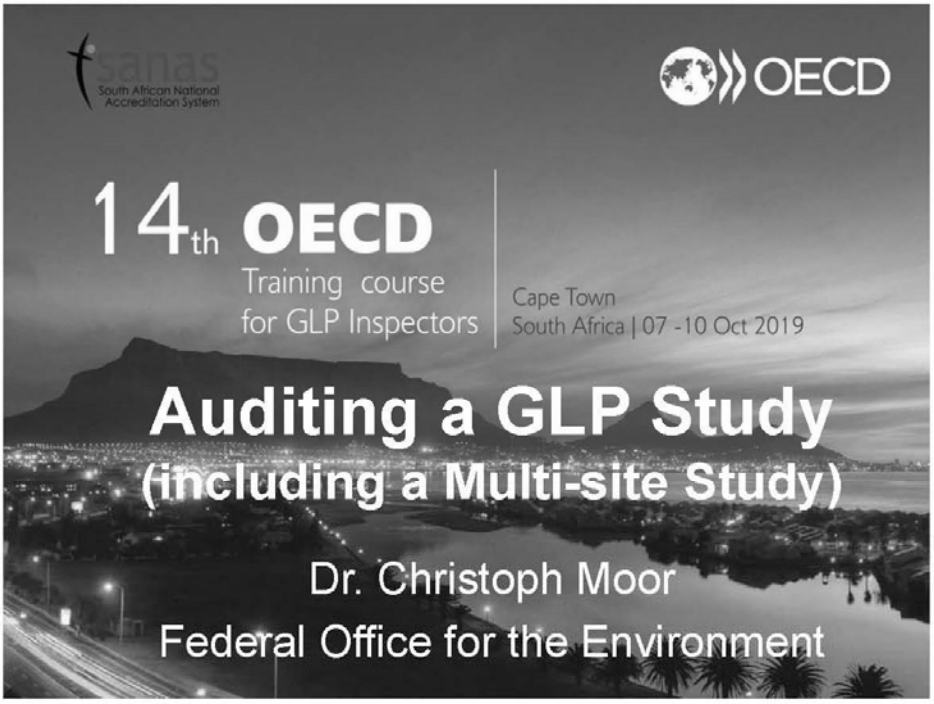

Outline

1. Study Audit
   - Introduction
   - How to perform a study audit

2. Multi-site Study
   - Introduction
   - How to inspect a multi-site study

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Why is a Study Audit needed?

- Key Factors: Data Quality and Data Integrity
- For example…
  - Test item exactly administered/exposed?
  - Test system with high quality (ex., disease-free)?
  - Raw data correctly reflects the facts?

If not

We can NOT trust the outcomes/conclusion of the study

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Not Responsible:

- ~~Judge the scientific design of the study~~
- ~~Concern with the interpretation of the findings of studies~~

These are the responsibility of the regulator

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Goal of a study audit

- To reconstruct the study by comparing the final report with the study plan, relevant SOPs, raw data and other archived material

(OECD series on Principles of GLP and Compliance Monitoring, Number 3, rev.)

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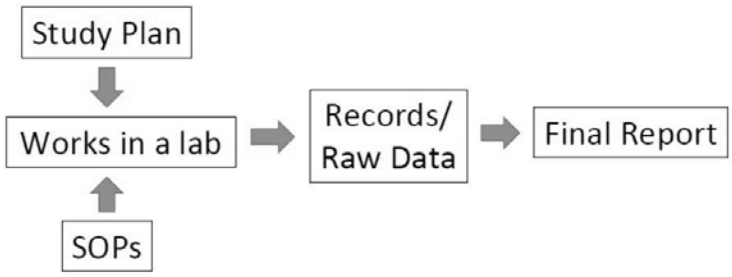
Normal flow at Test Facility



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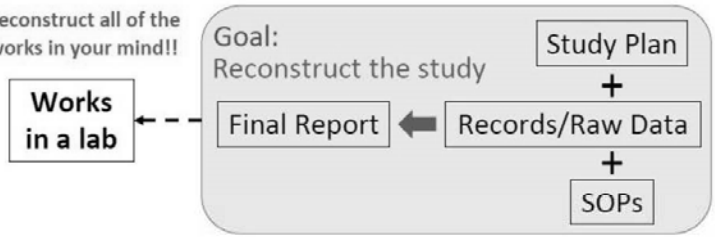
Normal flow for Study Audit

Ultimate Goal:

Reconstruct all of the works in your mind!!



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Two Instruments for GLP Compliance

TYPE	Description	Purpose
Routine inspections	Normally called as full inspections, including facility inspections + study audits	To audit a set of studies, representative of the GLP work at the test facility
Study audits	Normally conducted on request of domestic or overseas receiving authorities	To provide receiving authorities with confidence that the specific study reports are true, accurate and complete

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Outline

1. Study Audit
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   - Introduction
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What documents are needed for a Study Audit?

- Study Plan and its amendments
- SOPs in use at the time the study was done
- Raw Data
  - log books, lab notes, worksheets, etc
  - print-outs from apparatus and computer system
  - environmental monitoring
  - communication among personnel, with sponsor, etc
- Final Report and its amendments

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Study Audit - Study Plan

- Exist prior to the initiation of the study?
- Be approved by dated signature of the SD?
- Be verified for GLP compliance by QA personnel?
- Be approved by the TFM (and Sponsor if required)?
- Contain the following information?:
  - Identification of the Study and Test Item (Title, Purpose, ID of Test Item/Ref. Item, etc)
  - Information of the sponsor and test facility (Names and Addresses of SP, TF, SD, etc)
  - Dates (SD and TFM approval, experimental starting and completion, etc)
  - Test methods
  - Issues (selection and characterization of test system, method of administration, etc)
  - Records (a list of records to be retained)
- If amended, be justified and approved by dated signature of the SD?

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Study Audit - Test Item

- Identification (name, code number, etc) consistent?
- Characterization (lot number, purity, etc) defined?
- Stability known?
- Receipt, storage, use, dispose/return recorded and consistent?
- Preparation for dosing formulation traceable?
- Concentration, stability, and homogeneity in vehicle determined?
- If not a short-term study, a sample from each batch retained?

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Study Audit - Test System (biological)

- Following items in accordance with study plan and SOPs?
  - Number, species, race, sex, weight, and source
  - Quarantine and Identification
  - Monitoring health status
  - Feed, water and bedding
  - Environmental control and monitoring
  - Grouping and Dosing
  - Collection of specimen and Autopsy
- Data tracking: follow individual animals from arrival to autopsy
  - Body weight, food/water intake
  - Dosing
  - Clinical observations
  - Clinical chemistry
  - Autopsy and pathology

Study Audit - Raw Data

- Measurements, observations, examinations in accordance with the study plan and SOPs?
- Measurements etc. recorded directly, promptly, accurate, and legibly, signed and dated?
- Changes in raw data
  - not obscure original entries?
  - reason for change given?
  - responsible person signed/dated?
- Computer-generated/stored data adequately protected?
- Unforeseen events properly evaluated?

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Study Audit - Final Report

- Exist for each study?
- Approved by dated signature of the SD?
- Extent of compliance with GLP indicated?
- QA statement included?
- All information and data required by Study Plan described?
- Raw data accurately reflected?
- Deviations correctly described?
- Contain the following information?:
  - Identification of the Study and Test Item, Information of the sponsor and test facility, and Dates
  - Description of materials and test methods
  - Results (summary, presentation of results, and evaluation/discussion)
  - Storage (location for all documents/raw data/specimens/samples to be retained)
- If amended, be justified and approved by dated signature of the SD?

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Study Audit - Methods

- Read all documents and try to answer the questions
- Interview involved people (study director, lab personnel, QA)
- Drill down if necessary (test item, SOP, instruments, test system, personnel)
- Inspect a study of the same type in the laboratory if possible

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What is a Multi-site Study (MSS)?

Definition:

Any study that has phases* conducted at more than one site**

*phase: a defined activity (or a set of activities) in a study, e.g., analysis, field work, histopathological exam, etc

**sites: places, geographically remote, and/or organisationally distinct

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Why are additional rules required for MSS?

Use of multiple test sites increases the complexity of study design and management tasks, resulting in additional risks to study integrity

- Field studies were first recognised as "problematic" studies
  - ➢ OECD Consensus Document (No. 6) published in 1992, where the concept of Principal Investigator (PI) was first introduced
- Realisation of studies at more than one site extended to toxicological and other GLP studies
  - ➢ OECD Consensus Document (No. 13) published in 2001, where the general expectations of Multi-site Studies were compiled

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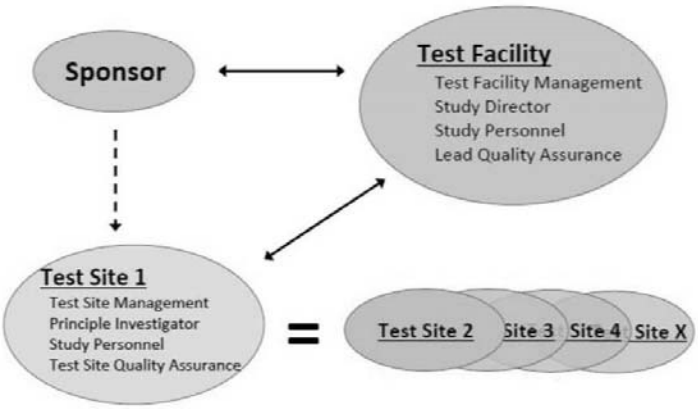
Typical Structure of MSS



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Typical Examples of MSS

Toxicological study	Residue study (field study)
<Test Facility> Laboratory with animal facility <Test Sites> Analytical laboratory (test substance) Analytical laboratory (blood analysis) Histopathology	<Test Facility> Analytical laboratory <Test Sites> Agricultural fields

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Important Concept of MSS

A Multi-site Study will consist of work being conducted at more than one site, but it is still a single study and thus:

- ONE single study plan
- ONE single Study Director
- ONE single final report

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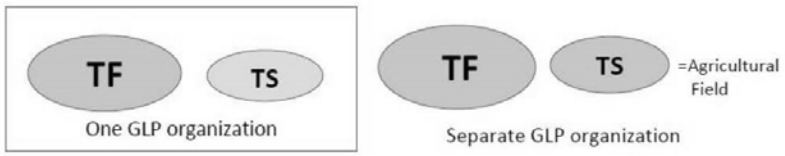
Types of Inspections to MSS

1) normally conducted within the framework of a test facility inspection



2) could be an independent inspection from a test facility's one

=Analytical Lab, Histopath Lab, etc

Could be separately certified!!

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Inspection Planning for MSS

- Gathering information of test sites
  - How many test sites concerned, and where they are
  - Whether they are part of the test facility
  - Whether inspected by another authority (domestic/international)
  - When activities are going on
- Inspecting test facility
  - Check whether finalised multi-site studies are available
  - Check raw data for phase activities is available (may not !!)
- Inspecting test site
  - Make sure PI is available (in case temporary test site)
  - Ask foreign CMA to inspect the site if located overseas

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Auditing a MSS (Study Plan)

- Who chose the test site (test facility, or sponsor)?
  - If sponsor: give more attention to communication between SD and PI
- Are all the test sites and PIs defined in the study plan?
- How is the study phase described in the study plan?
  - Could introduce the information later per amendment (PI's contribution)
- How is the agreement of the PI documented?
- How is the form of PI contribution defined?
  - Raw data or phase report
- How is the planning of samples to be transferred between sites defined?
- Who did QA audit for PI's contribution of the study plan?
  - Lead QA or Test Site

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Auditing a MSS (Performance and Recording)

- Conditions for temporary storage of materials
- Documented communication between SD and PI
- Pre-announcement of material transfer between TF and TS, and Feedback on quality and quantity received
- Intended changes
  - PI can suggest intended changes, but SD is responsible to issue the amendment
- Deviations
  - Deviations occurred at TS should be acknowledged by PI and then by SD
- Documentation on QA activities
  - Test site QA should report inspection results to SD, lead QA, and TFM (and PI and TSM)

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Auditing a MSS (Reporting) I

- Principal investigator (to study director)
  - Phase report (with signature and date), or raw data
  - GLP compliance statement
  - QA statement (mentions activities of test site QA)
- Study director
  - Include PI contribution into the final report (e.g., phase report in appendix)
  - GLP statement for all activities

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Auditing a MSS (Reporting) II

- Quality Assurance Statement
  - QA activities at the TF and TSs should be reported in the QA Statement
  - Test site QA activities may be reported in the form of QA Statement attached to the phase report
- Final report
  - Identify the test sites, PIs and study phases
  - Identify the storage location(s) of raw data and specimen

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Auditing a MSS (Archiving)

- Raw data produced at the test site can be archived at the test site or be sent to the test facility.
- If TSs located in different countries, the archiving period should be aligned to the conditions at the test facility.

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SUMMARY

- A Study Audit is needed in order to confirm Data Quality and Data Integrity of the study.
- The goal of Study Audit is to reconstruct the study by comparing the final report with the study plan, SOPs, raw data and other archived material.
- A Multi-site Study consists of work being conducted at more than one site, but it is still a single study.

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Thank you for your attention!!

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附件五、電腦化系統在 GLP 試驗體系的查核重點內容 (主辦單位提供的訓練講義)

INSPECTING THE COMPUTERIZED SYSTEM

Martijn Baeten
Sciensano

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Outline

- General considerations
- IT in GLP environment
- Tips/Tricks/Examples

General considerations

- Why inspecting computerized systems.
- Computerized system are of high importance in the production of preclinical data.
- A test facility should give the authorities confidence into the quality of their data and the integrity of their data

IT in GLP

- Why and how did I start inspecting computerized systems?
- Computerized systems and e-data of of growing importance in GLP.
- A lot of facilities have complex systems and substantial amount of e-data

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IT in GLP

- Training
  - OECD training courses
  - External training courses (GxP orientated)
  - Other experienced inspectors (joint inspections)
  - Know the principles
  - Reading

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IT in GLP

- Training
  - Self training by performing inspections on IT
  - Start with simple systems (COTS)
  - Familiarize yourself with terminology
  - Learn from the people who performed the validations. Let them explain in detail what was done

IT in GLP

- IT environment/computerised systems in a GLP set up is not rocket science
- Very similar to a regular GLP inspection → 3 main parts
  - How is IT organised in the facility ←→ organisation of the facility
  - Validation files ←→ Study audits
  - Facilities

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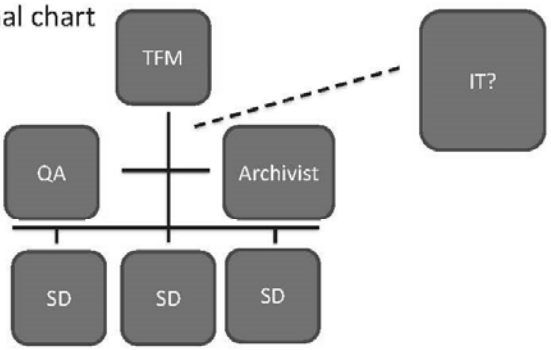
IT in GLP

Get the big picture (1):

- Organisational chart



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IT in GLP

Based on organisational chart:

- Identify responsibilities related to computerised systems
- Position of IT in relation to GLP Test Facility
- SLA (Service level agreement)?
- Job description & training file IT personnel
- Interview with key personnel from IT

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IT in GLP

Based on organisational chart:

- Identify responsibilities related to computerised systems
- Position of IT in relation to GLP Test Facility
- SLA (Service level agreement)?
- Job description & training file IT personnel, QA
- Interview with key personnel from IT

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IT in GLP

- List of SOP's and policies related to computerised systems (see OECD Adv doc 17, 47)
- List of computerised systems (including validated spread sheets) (validation status, make, model or version as relevant, and business process owner and IT system owner)
- System description of every system (physical and logical arrangements, data flows, interfaces with other systems or processes, any hardware and software prerequisites, security measures should be available)

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IT in GLP

- Floor plan:
  - IT room?
  - Server room?
- If available, general schema of computerised systems, interactions with data flow (network diagram)

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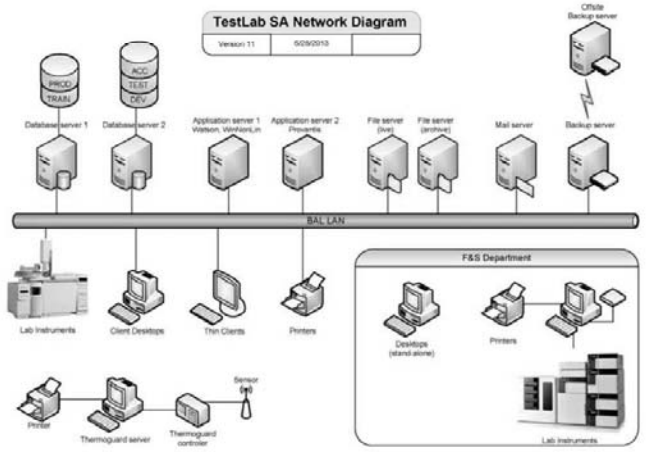
IT in GLP



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IT in GLP

- Inspection of a validation file:
  - Selection of computerised system → first things to consider:
    - Is the system programmable? Are there multiple parameters that can be changed, does it allow to manipulate data sets
    - Is the system a COTS (commercial of the shelf) or bespoke
    - Frequency of use of the system in the facility (look to the Master Schedule and the overview of computerised systems)

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IT in GLP

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IT in GLP

- Understand how the system you selected works, What is the system used for, what functionalities are used in the facility, data flow?
  - Interview with personnel
  - Demo during facility tour
  - SOP
  - Validation plan
  - From previous inspections (also in other facilities)
  - Study audits

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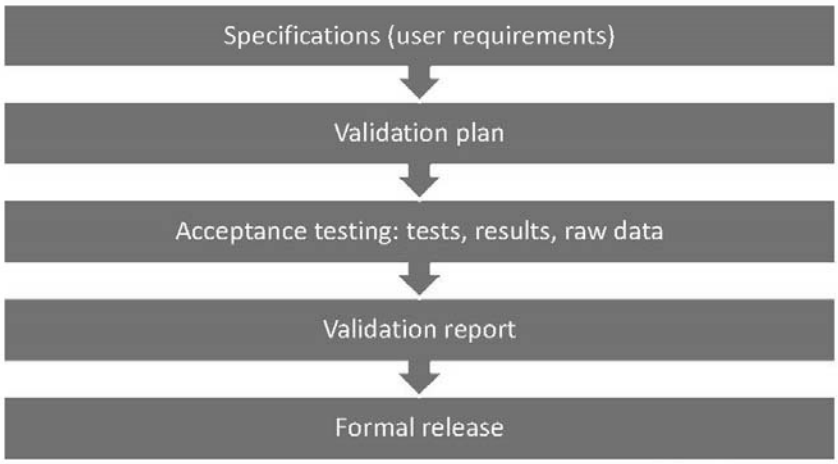
IT in GLP



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IT in GLP

Specifications (user requirements)

Validation plan

Acceptance testing: tests, results, raw data

Validation report

Formal release

IT in GLP

- How are functionalities validated?
  - All functionalities should be translated into acceptance criteria/specifications/user requirements (often called URS = user requirements specifications)
  - It should be documented what the facility wants the system to do

IT in GLP

- Example: Validation file to environmental monitoring system:
  - From corresponding SOP:

	T (°C)	% R.H.
Fridges/leachable fridges	5+/- 3 °C	N/A
Climatic chambers	Condition +/- 2 °C	Condition +/- 5%R.H.
Freezer/leachable freezers	-20 +/- 5 °C	N/A
Incubators/leachable incubators	Condition +/- 2 °C	N/A
CO_2-incubator	Condition +/- 1 °C	N/A

Table 6: ICH guideline limits.

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IT in GLP

- Example: Validation file to environmental monitoring system:
  - From corresponding SOP:

	T (°C)	% R.H.
Fridges/leachable fridges	5+/- 3 °C	N/A
Climatic chambers	Condition +/- 2 °C	Condition +/- 5%R.H.
Freezer/leachable freezers	-20 +/- 5 °C	N/A
Incubators/leachable incubators	Condition +/- 2 °C	N/A
CO_2-incubator	Condition +/- 1 °C	N/A

Table 6: ICH guideline limits.

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IT in GLP

- Example: how are the specifications translated in the validation file?→ URS are included in the validation file

System Requirements					
UR LCD 1	Qualified registration system	The temperature of the leachable fridge must be registered with a qualified registration system.	C	Covered during OQ phase	OQ
UR LCD 2	Sensor location	The registration sensor of the registration system for temperature must be located in/on a representative location inside the controlled storage system.	C	Covered during OQ phase	OQ
UR LCD 3	Range	The system has to operate according to ICH guidelines in a range of 2 - 8°C with 5°C as target value.	C	Covered during OQ phase	OQ
UR LCD 4	Power failure	The system must restart with the original settings after a power failure.	C	Covered during OQ phase	OQ
UR LCD 5	Accuracy	Temperature Accuracy must be within the following Acceptance criteria: ΔT_1 (Registration sensor - Datalogger) < 0.5°C ΔT_2 (Target – Datalogger) < 0.2°C	C	Covered during OQ phase	OQ
UR LCD 6	Temperature distribution	The temperature mapping at 9 points must be performed for an empty en fully loaded leachable fridge. Acceptance criteria: ΔT_3 (Max - Min of Dataloggers) < 1.0°C	C	Covered during PQ phase	PQ
UR LCD 7	Alarm generation	An alarm must be generated (out of specification) by opening the leachable fridge. An email must be sent to the 'lg_alert_group'.	C	Covered during PQ phase	PQ

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IT in GLP

- Validation plan should describe how al specifications will be tested:
  - acceptance testing: tests, results, raw data
  - The specifications are translated into test(s) and/or test script(s) providing raw data and results

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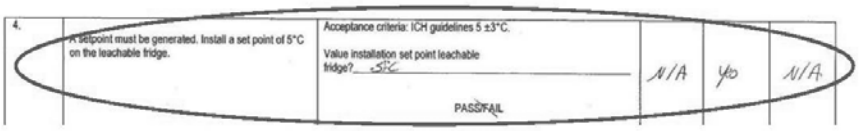
IT in GLP

- Example: URS translated into test scripts



4. A setpoint must be generated. Install a set point of 5°C on the leachable fridge.	Acceptance criteria: ICH guidelines 5 ±3°C. Value installation set point leachable fridge? 5°C PASS/FAIL	N/A	Yo	N/A

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IT in GLP

- For more complex systems, a lot more documentation will be available.
  - Compliance plan, URS protocol, FT protocol, IQ report, URS and FT reports, traceabilty matrix …

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IT in GLP

- Validation report:
  - With the validation plan, specifications, formal acceptance testing (including results, raw data), as inspector, we should be able to reconstruct the report (similar to study audit)
- Formal release of the system:
  - Adequate documentation and communication

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IT in GLP

review

- Definition of raw data
- Training: operation, maintenance, inspection
- SOP's:
  - Operation
  - Maintenance
  - Back-up and recovery

verify

- Access rights
- Audit trail
- Communication links
- Change control
- Archiving

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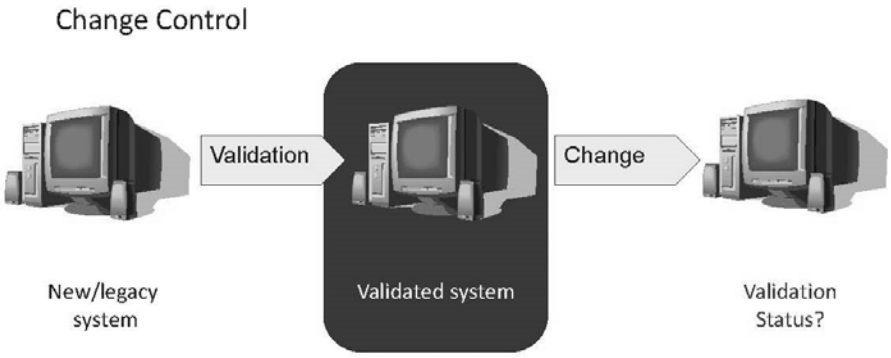

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IT in GLP

- Change control: maintain the validated state of a system through the life cycle of the system
  - Policy/procedure which covers responsibilities for evaluation of the change, approval, documentation and re-validation following software updates (execution and testing)
  - Risk assessment:
    - Validated state of the system
    - Data integrity

→ Full, partial or no re-validation

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IT in GLP

- Inspectors expectations:
  - Facility should know what software version is running
  - Is this the same version as the one used during the initial validation of the system?
  - Are the changes and intermediate versions been formally assessed and documented?
    - SOP
    - Planned & documented validation
    - Reported
    - Communication

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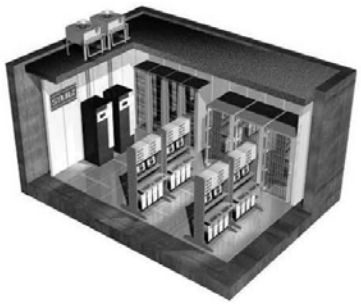
IT in GLP

Facilities

- Restricted access
- Environmental conditions
- Electrical supply
- Adequate facilities for secure retention of electronic storage media
- Physical location: extremes of temperature, humidity, dust, electromagnetic interference
- ...



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Tips & Trics

- Ask "stupid" questions
- Use knowledge as GLP inspector
- In doubt, try to consult with a colleague or an expert (and go back to the principles)
- Consider use of checklist, but stay flexible

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Tips & Trics

- Start simple and build up experience (COTS, simple validated spreadsheets to complex systems)
- Learn and "steal" knowledge from facilities
- Be open minded
- Be 110% certain before judging an observations as deviation (investigate further for evidence)

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Example

- Example 1: Validation of communication between Analyst and Watson Lims:
  - Data from Analyst are transferred to Watson Lims for further analysis.
  - It is claimed that there is an "digital interface" that connects Analyst and Watson Lims and data is transferred directly

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Example

- Example 1: Analyst & Watson
  - From validation file: data generated in Analyst is 100% transferred to Watson
  - From Validation file: very poorly described how this actually works.
  - From the SOP's: Analyst: click export / Watson: click import
  - Is this really automated and integrated transfer????

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Example

- Example 1: Analyst & Watson
  - Asked for demo in the lab
  - After a lot of investigation …..
  - Original (well secured data) from Analyst are exported as *.txt files to an insecure location (dump folder) before being pulled or pushed into the LIMS

Example

- Example 2: Provantis
  - Provantis is a system for in live data collection
  - During study audits, raw data has to be audited in Provantis (all e-data)
  - One of the first things a request is to open the audit trail

Example

- Example 2: Provantis
  - Audit trail for body temperature was verified
  - One value for one animal was changed, this was fully traceable (original entry and corrected entry, signed and dated)
  - Based on the provided reason (click wrong animal), and entries for other animals (including reviewing of metadata), also another animal should have had a corrected entry
    → No audit trail available on other animals

Example

- Example 2: Provantis
  - After investigation, there was no problem with the validation of Provantis
  - Problem was related to insufficient training and understanding of personnel to use Provantis.
  - Additional functionalities were included in Provantis and well validated.

圖一、與資深 GLP 查核員訓練講師拍照留影。與資深講師拍照留影與交流，如 Shardrack Phophi, Lene Bjerring Bork。