從Warning Letter 談製造與品質的要求- Data Integrity

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09/26,30 2016

Data Integrity

產品放行檢測，先用一台品質體系外的儀器做預檢測。預檢測合格再上品質體系內的儀器做放行檢測。若是預檢測不合格，就繼續取樣做預檢測，直到合格再做放行檢測。預檢測的資料不予以保留。

問題一：這種做法有問題，為什麼？問題出在哪？

問題二：這種做法雖並不滿足GMP要求，但並不影響產品品質和安全，這個說法對嗎？說明理由？

Table of Content

數據完整性“不是”新的查核(監管)要求

- 電子化系統的使用越來越多,對於電子數據的完整性缺乏相對應的理解與執行基於風險的控制
- DI不僅是QC實驗室問題而是貫穿研發、註冊、生產、質量到變更等整個產品週期。
- 對QC實驗室的檢驗檢查只是對DI關注的開始且未來會由實驗室轉移至其他文件

什麼是“資料完整性”

資料收集完整、一致、準確無誤的程度。

- FDA法規更新與聚焦
- 關鍵品質管制體系
- 模式轉變——紙質向電子化
- GxPs與21 CFR Part11及歐盟GMP附錄11
- “電子資料的良好檔規範”

MHRA*對data integrity的定義可簡述為：資料完整性（complete）、一致性(consistent)和準確無誤（accurate）的程度。將Accurate譯為準確無誤是基於其英文原意：用心保持原狀或真相（Accurate implies fidelity to fact or truth attained by exercise of care），及其通常翻譯：準確、精確、正確無誤。據上段所述，這個定義中的最後一個屬性，即準確無誤性，實際上是data本身的屬性，

MHRA* =Medicines and Healthcare products regulatory agency
英國藥品與醫療產品管理處

資料完整性的問題

- 未能及時記錄 Not record contemporaneously
- 回填 Backdating
- 編造 Fabricating data
- 反復檢驗 Re-test/Re running Samples/trial
- 銷毀資料 Discarding Data

保證資料完整性的前提

- 遵循檔案品質管制規範
- 資料內容可信、可靠

保證資料完整性

* GMP要求說啥（規程/工藝，SOP）做啥，做啥記啥（記錄，record）。“做”既包括生產工序、實驗室檢測，也包括資料處理等。如果藥廠全面嚴格執行GMP，資料（規程/工藝和記錄都是資料）就會是一致、無誤的。例如:若是藥廠都能做到，數據完整性，就會避免犯最嚴重的data integrity問題。

良好的檔案品質管制規範

- 良好檔案規範引入**ALCOA**

  A=Attributable可追蹤至產生資料的人

  L=Legible清晰

  C=Contemporaneous同步

  O=Original原始

  A=Accurate準確

Attributable=歸屬

A代表對產生資料的人的歸屬性

- **紙質記錄**
  手寫簽名
- **電子記錄**
  登錄用戶名ID
  電子簽名

Legible=清晰

L代表清晰可辨及耐久性

- 紙質記錄
  - 不用鉛筆
  - 不褪色墨水
  - 不用修正液
  - 使用單劃線簽名日期理由
  - 記錄歸檔
- 電子記錄
  - 強制保存
  - 不能覆蓋
  - 不能刪除
  - ‘隱藏輸入框’和‘失效’記錄必須可見
  - 資料注釋工具不能模糊
  - 修改被審計追蹤採集
  - 備份和歸檔

什麼是完整的數據/資訊?

什麼是“數據”+“中繼資料”？

What is “data”+ ”metadata”？

Data 數據

- 原始記錄指任何實驗室記錄，紙質的或是電子的，或保存了原始記錄內容與含義的準確影本。也包括電子記錄與電子簽名，以及相關中繼資料。

- 在GxPs記錄保存的時限內，相對應電子備分應有可用的讀取設備，以便展示原始資料。

Metadata 中繼資料

- Metadata-中繼資料

定義為：描述數字資料的資料，對資料及資訊資源的描述性資訊。

舉例：*sodium chloride batch 1234,* ***3.5mg.*** *J Smith 01/07/14*

中繼資料是初始記錄密不可分的一部分，如果沒有中繼資料，則該資料是無意義的。

Contemporaneous=同步

C代表活動必須在其發生時記錄

- 紙質記錄
  - 不倒填
  - 不事先完成記錄
  - 記錄日期和時間
- 電子記錄
  - 記錄必須在資料登錄後立即保存
  - 鎖定系統的時間、日期戳的存取權限
  - 所有時間、日期戳同步到認證的時間源

Original=原始性

- 原始=資料首次採集（不是轉錄資料）
- 必須審核原始資料
- 必須保留原始資料或原始資料記錄的“認證副本”

不能聲稱電腦列印輸出的是原始的電子記錄的真實拷貝

Original=原始性

- **紙質記錄**

-原始記錄本必須審核

-認證副本

-照片

-pdf文件

-對比原始記錄本，如果該拷貝完整，包含全部“中繼資料”簽字作為真實拷貝。

- **電子記錄**

-原始電子FT-IR光譜檔必須審核

-認證副本

-FI-IR光譜原始檔的電子備份

-對比原始電子資料設置，確定全部中繼資料包含在電子拷貝設置中

Accurate=準確性

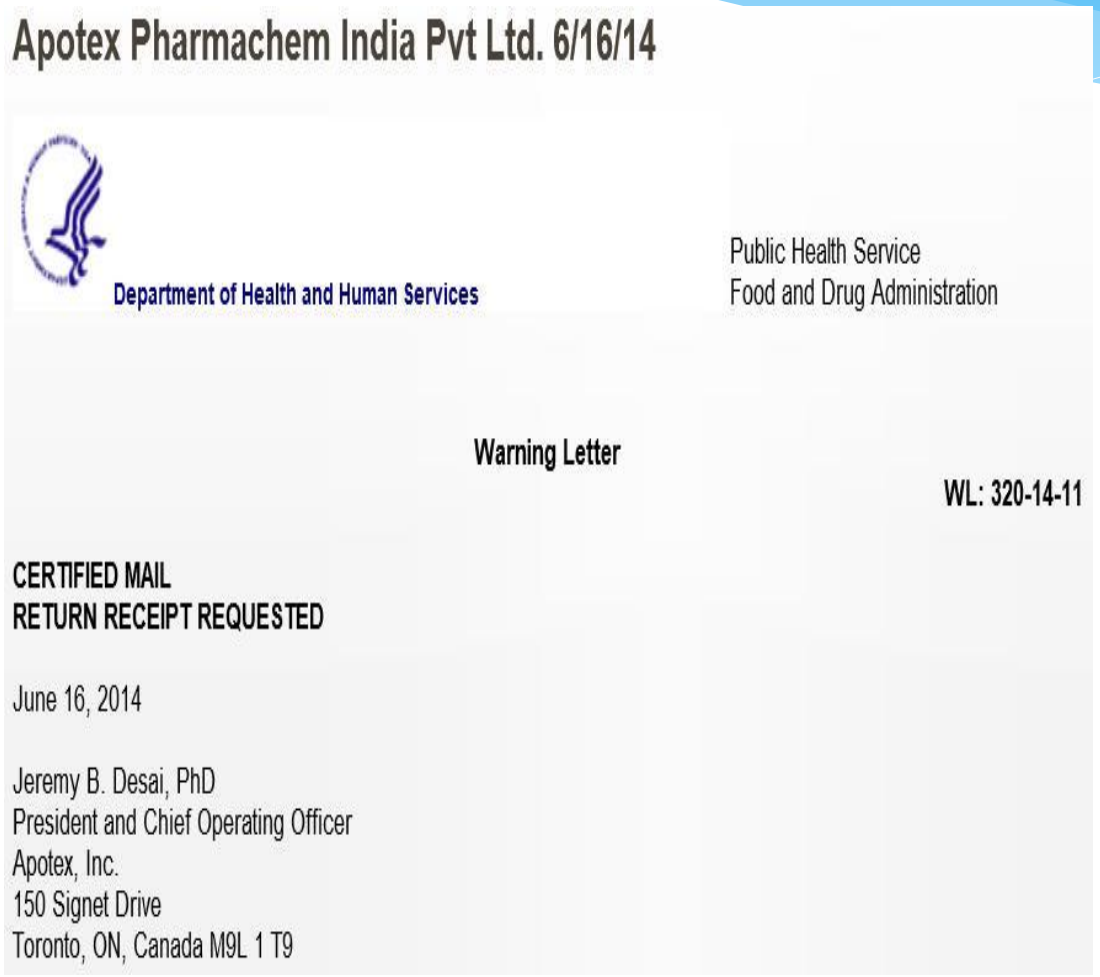
- 記錄必須準確
- 通過品質管制體系實現，例如：
  - 設備確認、校準、維護
  - 電腦驗證
  - 品質審計和檢查
  - 資料審核實踐
  - 偏差和CAPA計畫
  - 其他

Warning letter – 1

Apotex Pharmachem India Pvt. Ltd.

6/16/14

FDA Warning letter



Apotex Pharmachem India Pvt Ltd. 6/16/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Warning Letter

WL: 320-14-11

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

June 16, 2014

Jeremy B. Desai, PhD
President and Chief Operating Officer
Apotex, Inc.
150 Signet Drive
Toronto, ON, Canada M9L 1 T9

1. *Audit date*: ***January 27, 2014 through January 31, 2014***
2. Plant: ***Apotex Pharmachem India Pvt. Ltd.***
3. active pharmaceutical ingredients (***APIs***).

Data integrity problem - **Violate**

1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards
2. Failure to investigate and document out-of-specification results.
3. Failure to include adequate documentation during complaint investigation.
4. Failure to record activities at the time they are performed

Finding(1)

1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards
   - GC data 7/13 有OOS，沒有報告，最終結果用7/14和7/15
   - HPLC data 7/3有OOT，沒有報告，最終結果用7/4和7/5。分析員解釋是因為看到有some small extra peaks identified in the chromatogram fingerprint and an unexpected high assay result.
   - KF data 11/21 有OOS，沒有報告，一小時後，取另一個sample重作。

該公司的一般做法是:
the common practice was to complete the analysis and to record the sample preparation data only if the results were acceptable. If the results obtained were atypical, a fresh sample was to be prepared and analyzed. The original sample testing was not recorded.

Auditor concern:
We are concerned that your laboratory allowed the practice of retesting for GC, HPLC, and Karl Fischer methods without appropriate documentation, justification, and investigation

Finding(2)

2. Failure to investigate and document out-of-specification results.

- unknown peaks found during the HPLC testing, 沒有調查，銷毀原始數據
- 調查的scope太短只有一個月的區間，也只限定一型的HPLC。經理說他那個月太忙…
- 在調查的過程中發現一支unknown peak，但因為這是未知的peak，也沒有所謂的failure，所以沒有調查。

Auditor concern:
Your management failed to prevent the practices of product sample retesting without investigation, and rewriting and/or omission of original CGMP records persisted without implementation of controls to prevent data manipulation

Finding(3,4)

3. Failure to include adequate documentation during complaint investigation.

- 客訴說是2/26收到，但auditor發現有一筆1/8 retention sample assay化驗不合格，進一步回復改說客訴是1/8收到。而且這個failure沒有在調查報告中。
- Repeat finding

4. Failure to record activities at the time they are performed

Specifically, your staff used “finished product reports review data” worksheets to document critical laboratory information days after the actual testing was performed. The worksheets reported observations from your firm’s secondary reviewer, and next to each of these listed observations the analyst marked them as corrected. A review of these worksheets revealed that your analysts did not always record data in the laboratory records in a contemporaneous manner

Warning letter -2

Trifarma S.p.A. 7/7/14

Warning Letter

Trifarma S.p.A. 7/7/14

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Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-10

July 7, 2014

Mr. Giulio Volante
President
Trifarma S.p.A.
Via G. Guarini Matteucci 1
20162 Milano
Italy

- Audit date: ***January 27 – 29, 2014 USFDA inspection***
- Plant: ***Trifarma S.p.A Italy***
- **API** manufacturer in Italy

Violations

1. Failure to maintain complete data derived from all testing and to ensure compliance with established specifications and standards pertaining to data retention and management.

   未能保持由測試所得出完整的數據，以確保符合規格和標準有關數據保留和管理

2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

   未能防止未經授權的登陸或改變的數據，並進行適當的控制以防止數據的遺漏

3. Failure to ensure that employees receive appropriate and documented training on the particular operations that the employee performs.

   未能確保員工得到適當和記錄培訓

Failure to maintain complete data (1)

* Your firm did not **retain complete raw data** from testing performed to ensure the quality of your APIs.
* Your firm **deleted all electronic raw data** supporting your high performance liquid chromatography (HPLC) testing of all API products released to the U.S. market.
* Your firm failed to retain basic chromatographic information such as **injection sequence**, **instrument method** or **integration method** for the tests.
* Your firm's lack of data control causes us to question the reliability of your data.

Failure to maintain complete data (1)

* Your laboratory management was unaware of, and therefore **did not follow, the written procedure** detailing the review of analytical data.
* Your management confirmed that the review of analytical data did not include evaluating the system suitability parameters to ensure proper column performance.

Response (1)

DI issues:

* Your response states that your firm has been researching backup systems since July 2013 and will have a backup system online by the third quarter of 2014.
* Your response also states you have begun provisionally storing backup data on each computer, including the integration method as part of that data. However, you do not address the backup of the **injection sequence**, the **instrument method** or **audit trails**.
* In addition, your response does not address how your firm will ensure that **electronic files are not deleted prematurely from local computers**.

Failure to prevent unauthorized access or changes to data (2)

* Your firm did not have proper controls in place to prevent the **unauthorized manipulation** of your laboratory's raw electronic data.
* Specifically, your laboratory systems did not have **access controls** to **prevent deletion** or **alteration of raw data**.
* The inspection noted that all laboratory employees were granted **full privileges** to the computer systems.

Failure to prevent unauthorized access or changes to data (2)

* HPLC and gas chromatograph (GC) computer software **lacked active audit trail** functions to **record changes to data**, including information on **original results**, the identity of the **person making the change**, and the **date of the change**.

Response (2)

DI issues:

* Your response states your Agilent GC system and HPLC systems now have audit trails, with **(b)(4)** more GC systems to be upgraded by the second quarter of 2014.

* However, your response did not describe the audit trails for the processing of the data on your Agilent systems. Your response also states your firm has begun to **retain electronic raw data on the local hard drive**, but without proper safeguards to ensure they **cannot be deleted prematurely**.

* Such safeguards will not be implemented until the third quarter of 2014.

Failure to ensure that employees receive appropriate and documented training (3)

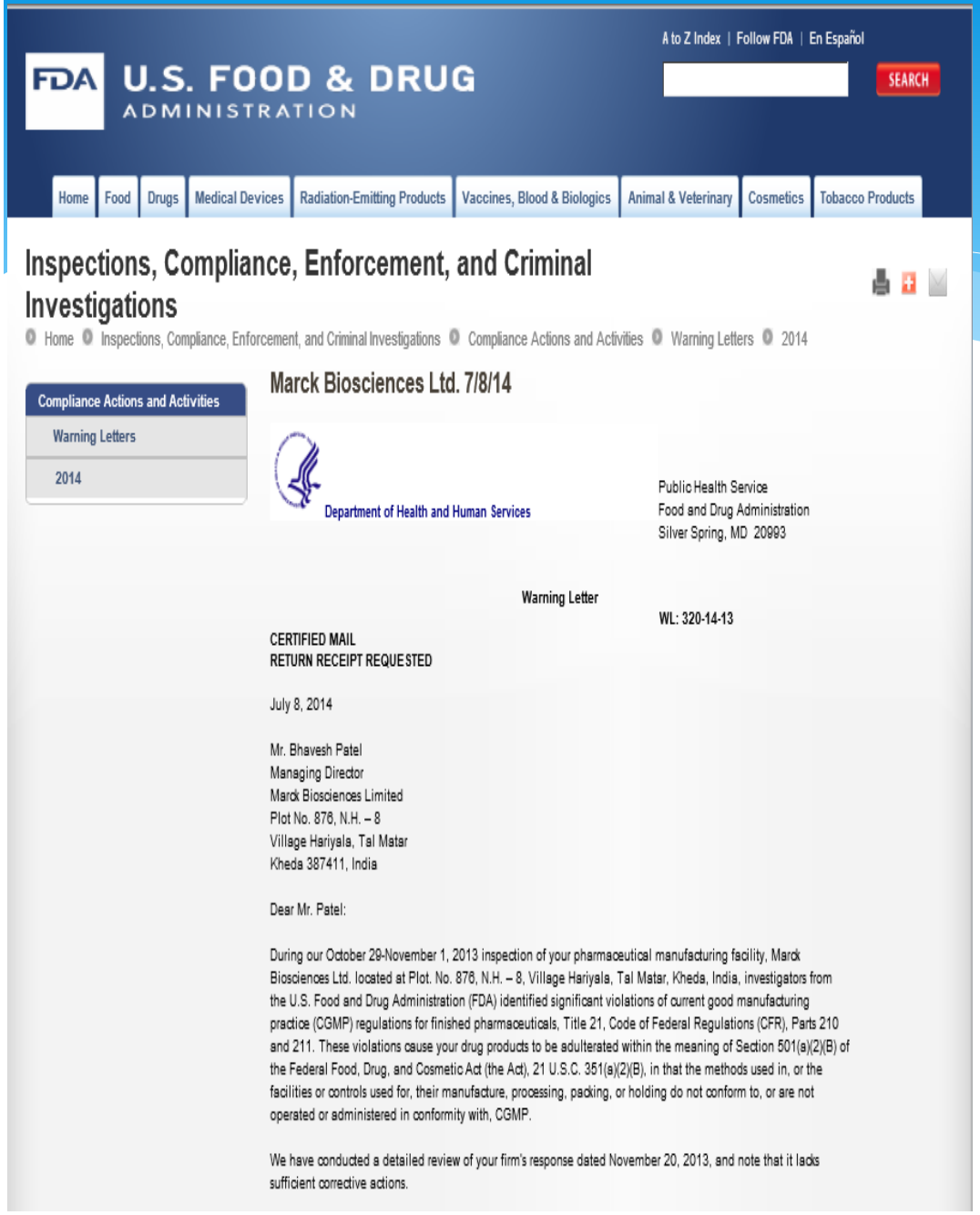
* Your firm did not **document any training of production employees** on the production operations they perform.
* Specifically, operators in Synthesis Plant **(b)(4)** did not have any documented on-the-job training associated with the production operations they perform.
* In addition, your management was unaware that they should **follow the SOP for the issuance of CoAs**, which provides for a review of relevant analytical data.
* Without documented training, there is a lack of assurance that your employees can reliably execute their API manufacturing responsibilities.

Response (3)

* Your response states your firm had updated your training SOP in July 2013 to include on-the-job training along with CGMP training requirements.
* However, the current inspection revealed that your firm is not following this procedure.

FDA Warning Letter -3

Marck Biosciences Ltd.



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Compliance Actions and Activities

Warning Letters

2014

Marck Biosciences Ltd. 7/8/14

Department of Health and Human Services

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

Warning Letter

WL: 320-14-13

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

July 8, 2014

Mr. Bhavesh Patel
Managing Director
Marck Biosciences Limited
Plot No. 876, N.H. – 8
Village Hariyala, Tal Matar
Kheda 387411, India

Dear Mr. Patel:

During our October 29-November 1, 2013 inspection of your pharmaceutical manufacturing facility, Marck Biosciences Ltd. located at Plot. No. 876, N.H. – 8, Village Hariyala, Tal Matar, Kheda, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated November 20, 2013, and note that it lacks sufficient corrective actions.

- Marck Biosciences Ltd. India pharmaceutical manufacturing facility
- October 29-November 1, 2013 inspection
- Drug product

Violate

- Manufacture, processing, packing, or holding do not conform CGMP practice

  製造、加工、包装或保存不符合CGMP規範

- Firm's response lacks sufficient corrective actions

  公司回覆缺乏矯正措施

1. Your firm **failed to prepare batch production and control records for each batch of drug product** that include documentation of each significant step in the manufacture, processing, packaging, or holding of the batch.
沒有準備每一批產品的製造、加工、包裝或保存關鍵步驟

a) Our inspection revealed "unofficial" visual inspection records, signed by production personnel, with data that is different from the official batch records reviewed by your firm's quality unit. In many of the cases reviewed, the unofficial records showed significantly more quality defects than the official batch records.
稽核發現生產人員的非正式記錄與品質部門審核的正式記錄不同。許多案例顯示，非正式記錄不合格明顯比正式批次記錄多。

- **Response**: your production personnel add extra units into the **(b)(4)** unit and lower the number of rejected units on the official paperwork to account for these extra units.

  貴司回應陳述是因為生產人員加了額外的數量來降低正式文件中被拒用的數量

  - ✓ This explanation is unacceptable for several reasons, including that this practice does not accurately represent the number of units with quality defects present in each batch in the official batch records, it obscures the number of rejected units in any given batch, and it misrepresents the number of units sterilized during each batch. Given that your unofficial and official records are discrepant, there is no assurance that your firm rejected all units that did not meet your acceptance criteria.

    有幾個理由這個解釋無法被接受：

    - 這種操作不是正確表達品質批次記錄品質有缺陷的數量
    - 隱藏任何批次被拒用的數量造成誤判每批滅菌數量
    - 由於非正式記錄與正式記錄不符，貴司無法保證所有不合格數量都被拒用

- **Response:** you have audited a random selection of 848 batch records and found a difference between unofficial and official records in 2.5% of instances
  貴司回應陳述內稽隨機抽選848批次記錄發現非正式與正是記錄差異2.5%
  - However, during the inspection, our investigators found discrepancies between official and unofficial records in 76 of 156 (48.7%) batches reviewed. Your response does not include an explanation as to the differences between your internal audit results and our inspectional findings.
    然而稽核當時發現，審核156批有76批(48. 7%)正式與非正式記錄有差異。貴司的回覆為解釋你們內稽與我們稽核之間的差異性。

In response to this letter, 請回覆

- **provide** an updated assessment of the extent of the differences between unofficial and official records used at your facility.
  重新評估非正式與正式記錄的差異性
- **Provide** documentation showing whether you exceeded the maximum validated number of units in the (b)(4), and explain the significance of that unvalidated condition.
  提供文件顯示貴司是否超過確效數量最大值，並解釋不能確效狀況
- **Describe** controls in place to prevent data manipulation (操作) by your operators and supervisors.
  陳述已有管制方式避免被操作員與主管數據造假

b) The inspection revealed your firm's use of scratch paper containing critical manufacturing data. The data on these scratch paper records did not always match the data on the corresponding official batch records, as in the case for the amount of raw materials

稽核發現貴司使用便條紙記錄關鍵製造數據，而且便條紙記錄與正式批次記錄總是不相符，例如很多原料案例

- **Response:** 貴司回覆
  - ✓ does not explain why your production personnel used scratch paper for documenting CGMP-relevant data

    沒有解釋為何貴司生產人員使用便條紙記錄CGMP相關數據
  - ✓ the discrepancy between your destruction records and your quarantine records provide further evidence that your documentation is not accurate and reliable

    貴司銷毀紀錄與隔離記錄的差異性證明貴司文件不正確與不可靠
  - ✓ The use of unofficial and scratch paper records is not acceptable CGMP.

    使用非正式與便條紙是不可被接受的CGMP

- In response to this letter, 請回覆
  - ✓ **provide** assurance that the use of unofficial and scratch paper records has been discontinued and **describe** how your firm will prevent this practice in the future. 確保不再使用非正式與便條紙，並防止未來有這種行為
  - ✓ **describe** your procedure to assure that all CGMP-related operations are documented at the time of occurrence.

    陳述SOP確保所有CGMP相關操作都是當下記錄

c) Employees interviewed during the inspection admitted that your firm recorded activities in batch records that were not performed. Specifically, your head of production reported to our investigator that he completes "in process quality assurance check" fields in the batch record but does not actually perform the listed operations.

稽核時貴司員工承認貴司批次所記錄活動並沒有實際執行。尤其生產部門主管向我們稽核員訴說他完成在批次記錄的"in process quality assurance check" 空格，其實是沒有實際執行該項操作。

- In response to this letter, 請回覆
  - ✓ describe your investigation into this situation, outlining your efforts to determine the scope of data falsification (偽造) within batch records and your corrective and preventive actions.

    陳述貴司調查這事件的結果，條列批次記錄數據偽造的範圍以及貴司矯正與預防措施

2. Your firm failed to maintain adequate written records of major equipment maintenance
貴司沒有保持充分的主要設備保養文件記錄

a) FDA investigators identified two maintenance logbooks that included multiple entries describing significant equipment malfunctions, but for which no investigation into the potential effect on product quality was performed. In addition, your records do not always include information on repairs following these malfunctions. For instance, no maintenance actions or product impact investigations were recorded for out-of-limit findings during equipment calibration.

FDA稽核員確認兩份保養紀錄本，包括重要的生產設備的幾筆記載，沒有調查對產品品質的潛在影響。再者，貴司記錄總是沒有這些設備損壞的修理資訊。例如，沒有記錄設備校正超規時的維護動作或對產品衝擊的調查。

b) In addition, we note that ten serialized entries had been torn out (被撕去) of the logbooks. Your staff could not locate these records during the inspection and reported to our investigator that the entries had likely been destroyed.

再者，我們發現記錄本有十筆連續編號的記錄被撕去。你的員工稽核當時無法找到這些記錄，應該像是被銷毀

- Your response does not address this issue in a comprehensive manner, does not discuss your investigations into the potential impact on product quality, does not discuss any investigation into the missing records or address the root cause or extent of these deficient practices

規司的回覆未針對這事件有合理的解釋，未討論調查對產品品質的衝擊，未討論調查這些不見記錄的根本原因或不適的行為程度

- In response to this letter, 請回覆
  - ✓ include your plan for systemic improvements to be made to address these deficiencies. 貴司的計畫與系統性的改進這些缺失

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions

貴司沒有確保每一位參與產品生產、加工、包裝、或儲存的員工有教育、訓練、及經驗有能力去執行其工作

a) your **(b)(4)** contract employees had not received any training on CGMP. These contract employees performed critical manufacturing operations, such as sterilizing operations.

貴司的派遣員工沒有CGMP訓練，但他們有操作關鍵生產操作，例如無菌操作

- **Response:** general CGMP training would be given to contract employees,.
  - ✓ but you do not address why contractors were not trained prior to our inspection or the effect of this deficiency on product quality.

貴司的回覆將會給這些派遣員工訓練，卻未解釋我們稽核時這些員工為何沒有訓練以及對產品品質的衝擊。

b) your firm falsified documents designed to demonstrate the effectiveness of CGMP training. Your production head admitted to pre-filling out the answers to post-training comprehension assessment questions and entering the names of employees on these documents.

貴司偽造文件試圖證明CGMP訓練的有效性。生產部門主管承認先填好應該要在訓練後的評估問題的答案，再填上員工姓名在這些文件

- **Response:**
  - ✓ your response to the FDA Form-483 is deficient in that it fails to address the root cause or the extent of the falsification of training documents.

    貴司回覆FDA483是不足夠的，未說明偽造訓練文件的根本原因與程度

- In response to this letter, 請回覆
  - ✓ indicate how your systems will be changed to address these fundamental issues. 說明如何改變系統去實行這些基本功能
  - ✓ Provide a summary of your investigation into the training status of all employees participating in CGMP activities at your facility.

    提供摘要你的調查所有餐與CGMP活動的員工訓練狀況

4. Your firm did not follow written procedures regarding storage and warehousing of drug products
貴司沒有遵守產品儲存與倉庫的核定的SOP

a) your firm was unable to locate approximately **(b)(4)** units of **(b)(4)** injection from Batch #**(b)(4)** that had been manufactured several weeks earlier. Both your staff members and our investigators carefully examined the entire warehouse in an attempt to locate the missing units, but the units were not found during the inspection. We have concerns that your firm may have released and distributed these units outside of the quality system.

貴司無法找到幾個禮拜前生產的針劑產品。你的員工與我們的稽核員很仔細尋找整個倉庫，在稽核地當時都無法找到這些失蹤的產品。我們關注貴司可能在品質系統以外放行與銷售這些產品。

- **Response:** you state that you found the missing units in **(b)(4)** boxes after the investigators left, in the same warehouse that they thoroughly checked during the inspection.

  貴司的回覆陳述當稽核員離開後，在被稽核的同一倉庫找到了失蹤的產品

  - ✓ However, you did not provide any photographic evidence of this discovery. 然而你未提供任何照片證明此發現

- In response to this letter, 請回覆
  - ✓ **provide** evidence that these units were released by your quality unit prior to being distributed. 提供證明這些產品是在品質系統內被放行
  - ✓ **describe** any new procedures intended to achieve full accountability and control over all products in your facility, and **describe** any controls in place to prevent unauthorized product shipments. 提供新SOP如何管控所有產品並陳述防止未被授權的銷售

5. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition and keep them free of infestation by rodents, birds, insects, and other vermin

貴司沒有維護用於生產、加工、包裝、儲存之建築物，關於清潔與衛生條件。防止老鼠、小鳥、蚊蟲等侵襲。

a) investigators noted significant mold growth in the washroom located at the entry to the sterile manufacturing area. The ceiling of this room had been allowed to deteriorate(惡化)to such an extent that it caved in. This room shares a common mezzanine(夾層)with the adjacent sterile processing rooms.

稽核員注意到位於無菌室入口處的洗手間嚴重的黴菌滋生。這房間天花板惡化有洞，與相鄰的無菌製程室共用相同夾層。

- **Response:**
  - ✓ does not identify any efforts to identify the mold growth or relate it to environmental monitoring data from the neighboring sterile suite, nor does it discuss the potential effect on the microbial quality of products made in your facility.

    貴司回覆沒有確認黴菌滋生結果或與相鄰無菌室的環境監視數據是否相關，也未討論對產品品質的衝擊

- ✓ does not discuss why this deterioration was permitted by your management until our inspection of the facility
  沒有討論為何管理階層允許這種損壞
- In response to this letter, 請回覆

- ✓ describe your investigation into the extent of mold within your facility, including within your HVAC system.
  陳述調查貴司廠房包括HVAC系統黴菌滋生程度
- ✓ Describe any additional findings of mold, corrective measures, and your investigation into the effect of any findings on product quality.
  陳述任何黴菌新發現，矯正，檢測，以及調查對產品的衝擊

b) The investigators noted numerous dead insects in the "Sample Pass Through" Room, located approximately **(b)(4)** from the Sterile Filling Line #**(b)(4)** of the small volume parenterals facility. In addition, dead and decaying frogs were found next to the product exit dock.

稽核員發現許多死昆蟲在"Sample Pass Through" Room，位於無菌充填室。再者，發現死掉腐敗的青蛙在產品碼頭附近。

- **Response:** these pest infestation issues would be corrected. It also includes a commitment to remove the manufacturing waste near the entrance to the facility and to fill in the swamp-like perimeter that appeared to be serving as a harborage for vermin.

  貴司回覆防蟲計畫將執行，並清理廢棄物

  - ✓ Your response does not address why the observed conditions were permitted to exist in and around the manufacturing facility.

    你的回覆未闡述為何這些事可以允許存在於廠房

- ✓ In response to this letter, 請回覆
  - ✓ discuss this issue and provide details of your pest prevention program.

    討論這些事件並提供詳細防蟲計畫

6. Your firm failed to exercise strict control over labeling issued for use in drug product labeling operations
貴司未嚴格管制產品標籤的使用

a) Our investigators found numerous loose and uncontrolled labels for multiple products in the open office area adjacent to the packaging lines. Unused labels were not stored in a manner to prevent mix-ups or mislabeling.

稽核員發現許多鬆散與未管制的多種產品的標籤再包裝室隔壁的開放辦公室裏，未使用的標籤沒有儲存於防止混淆或錯用的方式

- **Response:**
  - ✓ does not include any explanation as to why your firm allowed unused labels to remain in the production area, lacks adequate explanation of whether this deviation has affected any production lots and led to mislabeling deviations or complaints regarding in-date marketed products.

貴司回覆為何允許未使用的標籤遺留在生產區域，缺乏足夠的解釋是否這違規造成產品影響

Summary

- You are responsible for the accuracy and integrity of the data generated by your firm.

  貴司對數據的正確性與完整性要負責

- A firm must maintain all raw data generated during each manufacturing run. These records should be properly identified to demonstrate that each released batch was manufactured appropriately, tested, and found to meet release specifications.

  貴司必須保持每一次生產的所有的原始數據。這些記錄應該要正當的

  確認每批放行批次是適當的生產、檢測及合格的

- Appropriate record retention policies should also be in place. Our inspection discovered that your firm could not provide basic records for your products.

  應該有適當的記錄保存政策。我們稽核發現貴司沒有基本的產品記錄

Your data integrity expert should:

1. Identify all instances in which unofficial and scratch paper records have been used in your manufacturing and laboratory facilities and assess the possibility of misrepresentation of data on official records in each case. 確認所有已用於貴司生產與實驗室的非正式與便條紙記錄的實例，評估正式紀錄的數據被誤判的可能性
2. Interview current and former employees to identify activities, systems, procedures, and management behaviors that may have resulted in or contributed to inaccurate data reporting in CGMP records. 訪問現任與解任的員工去確認可能造成不正確數據的動作、程序與管理行為
3. Identify the specific managers in place who participated in, facilitated, encouraged, or failed to stop subordinates from falsifying data in CGMP records, and determine the extent of top and middle management's involvement in or awareness of data manipulation. 確認那些經理參與、煽動、鼓勵、或未阻止偽造CGMP記錄的數據，並確定上層與中層管理階級參與或知情數據偽造

Your data integrity expert should:

4. Determine whether any managers identified in item (3) above are still in a position to influence data integrity with respect to CGMP requirements or the submission of applications to FDA.

   確定任何第3點的經理是否仍在可以影響CGMP數據完整性的位置上

5. Audit past distribution practices and complete a detailed accounting of the distribution of all batches of product manufactured within the past two years to determine under what circumstances batches were distributed prior to release by the Quality Unit.

   稽核過去銷售行為，完成過去兩年生產的所有批次產品詳細帳目，確定何種情況是品質部門放行前就被銷售

Your data integrity expert should:

6. Perform a comprehensive data integrity audit of all data submitted to FDA supporting drug applications and describe any discrepancies between data or information submitted to FDA and any "unofficial" accounting of actual data or practices onsite. This audit should include both manufacturing data and laboratory data, including data used in process validation studies and analytical method validation studies.

執行一徹底的數據完整性稽核關於所有呈送FDA支持藥品申請的數據

陳述任何呈送FDA的數據與資訊與實際非正式數據得差異性

這稽核應包括生產與實驗室包括製程確效與分析方法確效的數據

Warning letter - 4

九洲藥業7/09/14

FDA Warning letter

浙江九州藥業

Zhejiang Jiuzhou Pharmaceutical Co., Ltd. 7/9/14

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Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-12

July 9, 2014

Ms. Hua Lirong
CEO
Zhejiang Jiuzhou Pharmaceutical Co., Ltd.

Audit Information

- Audit date: October 21, 2013 through October 24, 2013
- Plant: Zhejiang Jiuzhou Pharmaceutical Co., Ltd. (浙江九洲藥業)
- Active pharmaceutical ingredients (APIs).

Summary - Violate

1. Failure to implement an effective system of managing quality and failure to transfer all quality or regulatory information received from the API manufacturer to your customers. 未能實施有效的品管系統，未能將所有從原料藥生產商處收到的品質和法規資訊轉達給客戶。

2. Failure of the quality unit to review batch production records prior to distribution of an API batch. 品質部門在原料藥批次銷售前未審核批次記錄

3. Failure to document manufacturing operations at the time they are performed.在生產操作時未及時記錄

4. Failure to adequately maintain equipment in a state appropriate for its intended use in the manufacture of APIs.設備沒有適當的維護保養，使設備能維持於良好的狀態

1. Failure to implement an effective system of managing quality and failure to transfer all quality or regulatory information received from the API manufacturer to your customers. 未能實施有效的品管系統，未能將所有從原料藥生產商處收到的品質和法規資訊轉達給客戶

Your trading company, hereafter referred to as **Zonebanner**, **purchased APIs from an outside supplier and relabeled them without the oversight of a quality unit**. The information from the original certificate of analysis, generated by the actual manufacturer, was transferred to a new certificate of analysis on Zhejiang Jiuzhou Pharmaceutical Co. letterhead **with no information about the original manufacturer or analytical laboratory performing the analyses**. In addition, a new label identifying Zhejiang Jiuzhou Pharmaceutical Co. as the manufacturer was added to drums. In doing so, your firm essentially obscured the supply chain of these APIs.

Zonebanner had no quality system in place for the relabeling operations. In addition, we note that in at least one instance of a lot of gabapentin shipped to the U.S., the retest date from the original manufacturer's certificate of analysis (November 2013) was changed to an expiration date listed as eleven months later (October 2014) on the new certificate of analysis.

- 九洲藥業底下的貿易商Zonebanner，從外部供應商處採購了原料藥，未經品質部門審核即重新貼標，且沒有重新貼標的品質管控流程。
- 原始供應商提供的原始檢驗報告書中的資訊被謄寫到以浙江九洲藥業有限公司為抬頭的新檢驗報告書上，在新的報告書上沒有體現原始生產商和原始分析化驗室的資訊。
- 另外，包裝桶上被加貼了標示為浙江九洲藥業有限公司的新標籤。掩蓋了這些原料藥的原始供應鏈資訊。
- 竄改COA的有效期。新COA上的有效期比原複驗期推遲了11個月（2013年11月改成2014年10月）

FDA concern:

In your response, your firm states that Zonebanner exists as a separate legal entity under Chinese law. However, the FDA considers this entity to be under your control. During the inspection, your employees **stated that Zonebanner is a group within Zhejiang Jiuzhou Pharmaceutical Co. Ltd. and provided organizational charts showing that Zonebanner management reports to you as CEO.** Zonebanner is located at the same physical address as the inspected manufacturing facility, and the Zonebanner personnel work in the same office space. Moreover, API shipments from Zonebanner are accompanied by a letter stating that Zhejiang Zonebanner and Zhejiang Jiuzhou Pharmaceutical Co. Ltd. are in one group. Despite this close relationship, **however, your management has allowed the Zonebanner group to continue to operate outside of your firm's quality system**.

- FDA認為該貿易公司在九洲藥業控制之下，且被允許其進行不合品管系統的作業。

  在檢查期間，你們員工聲明Zonebanner是浙江九洲藥業有限公司的集團內，所提供的組織機構圖顯示Zonebanner管理層向九洲（CEO）彙報。Zonebanner人員的工作在同一個辦公區域內。還有，從Zonebanner發運的原料藥隨貨有一封信函，聲明浙江Zonebanner和浙江九洲藥業有限公司同屬一個集團。即使沒有這些緊密的關係，無論如何也是你們管理層允許了Zonebanner集團繼續在你公司的品質體系以外進行不合規運作。

FDA 要求在對本警告信的回覆中，

1. 提供你們建議在Zonebanner擬實施的品質體系詳細資訊，要描述運作流程，提交例子證明
   a.如何維護現有分銷原料藥的可追溯性，
   b.如何保證提交給客戶的資料中包括準確的生產商和分析化驗室資訊。

2. 提交你們對上述批次有效期的制定理由。如果你們的資料不能支援上述操作或其它類似的延期，要描述對有問題批次準備採取的措施。

2.Failure of the quality unit to review batch production records prior to distribution of an API batch. 品質部門在原料藥批次銷售前未審核批次記錄

Our investigator discovered that your firm **shipped finished lots without reviewing the batch records for these lots**. Although your firm has procedures requiring the review of batch records prior to their release and distribution, on several occasions your quality unit authorized the shipment of lots prior to their release. Several of your firm's employees were aware of this practice but took no measures to prevent it.

During the inspection, **your firm's personnel conducted an internal review and found three additional lots that were distributed prior to release by the quality unit.** However, we are concerned that your internal review would be unable to detect every instance for which your firm shipped materials whose batch records had not yet been reviewed based on your poor documentation practices described below under #3. We remind you that the quality unit's approval of batch records should not merely serve as a paperwork exercise but should include a thorough review of all deviations which occurred and any unexpected results which were obtained during the manufacture of the lot being reviewed.

- 將未完成的批次紀錄批直接出貨，品質部門在產品放行前即核准發貨。
- 內部審核間發現三批次有同樣狀況
- 公司的幾個員工很清楚這種情況，但都沒有採取措施去防止其發生。

FDA concern:

Quality unit review of batch records is a clear expectation of CGMP. Responsible management should ensure that the quality unit performs its assigned functions. In response to this letter, please provide a full accounting of this practice and describe all actions taken to prevent its recurrence. Describe any improvements to ensure that your internal auditing program will detect and correct similar instances in the future.

- 品質部門對批記錄的審核在CGMP裡是一個非常清楚的要求。已嚴重違反CGMP規定。

FDA 要求在對本警告信的回復中，

- 請提交一份完整的實施清單，描述所有防止這些情況重複發生的措施，描述在將來能保證你們內稽計畫可以發現和糾正類似事件改進情況。

3. Failure to document manufacturing operations at the time they are performed.在生產操作時未及時記錄

When reviewing the entries in your (b)(4) use, cleaning, and maintenance logbook for the days immediately prior to the inspection, our investigator found **missing entries**. Your operators stated that lines were left blank to later add information about cleaning events that may have occurred during a previous shift. During the inspection, our investigator found other similar instances of missing data or belated data entry in your manufacturing records. These practices are not consistent with CGMP. Operators acknowledged that there is no system in place to report these lapses in the documentation system; documentation errors of this type did not require deviation investigations or notification to the Quality Unit.

In addition, during the inspection, one of your quality unit employees presented the investigator with a batch record containing his signature, stating that he had performed the review of this batch record. The employee later admitted that he had falsified this CGMP record and stated that he in fact had not performed the review, despite having signed the batch record as the QA reviewer and having released the batch.

- 生產記錄中也有類似的資料缺失或資料填寫滯後的現象。且作假資料，這種操作不符合CGMP要求。
  操作人員被告知公司沒有體系用來報告這種記錄中的滯後情況，這種記錄失誤是不需要進行偏差調查的，也不需要通知品質部門。在檢查期間，你們品質部門的一名員工還給檢查官出示了一份批記錄，其中有他的簽名，他說他已經對該批記錄進行了審核。該員工後來承認，他偽造了該CGMP記錄，並說事實上他並沒有進行審核，完全不顧其實他已經在該批記錄上作為QA審核員簽字並已放行了該批產品。

FDA concern:

This data falsification and the record-keeping deficiencies described above raise doubt regarding the validity of your firm's records.

上述這種資料做假和記錄保存缺陷使得我們非常懷疑你們公司記錄的有效性。

3. Failure to document manufacturing operations at the time they are performed.在生產操作時未及時記錄

In response to this letter, provide a comprehensive investigation into your personnel' s data falsification practices. In addition, provide your procedures governing the timing of data entry with respect to actions being recorded and describe how you ensure that these procedures are followed. Also provide your procedures describing the filing of deviation notifications when your firm' s documentation practices are not followed. Provide your specific corrective actions to avoid instances of data falsification and/or alteration by your personnel.

FDA 要求在對本警告信的回復中

1. 要提交一份對人員的資料做假行為的全面調查。
2. 要提交你們公司如何記錄操作時管理資料所登錄的時間的流程，並說明你們如何保證這些流程會被遵守。
3. 特別要提交你們公司避免資料作假和/或人員做假的情況發生所要採取的矯正措施。

4.Failure to adequately maintain equipment in a state appropriate for its intended use in the manufacture of APIs.設備沒有適當的維護保養，使設備能維持於良好的狀態

Our investigator noted a leak in the purified water (PW) system during the current inspection; this is noteworthy given our previous inspection's similar findings of leaks in the same PW system. Your preventive measures described in your previous response were not sufficient to allow your staff to detect and repair leaks in the PW system; we therefore question whether the current measures will be effective.

- 純水系統有一個地方有洩漏，值得注意的是前一次檢查中也是這套純化水系統被發現有類似的問題。你們對上次檢查的回復中所描述的預防措施其實並未足以讓你們的員工發現和修補純化水系統的洩漏。

FDA concern:

- 質疑現有的措施是否有效。

In your response to this letter, describe why the previous measures failed, what new measures have been taken, and why these measures will be effective. The current inspection also found other pieces of manufacturing equipment in need of repair. The effectiveness of your revised preventive maintenance program will be reviewed in more detail during a future inspection.

FDA 要求在對本警告信的回復中

- 描述先前措施為何失效與新的監測措施且新措施為何可行.

錯誤標識違規

In addition to violating CGMP, your firm shipped a misbranded active pharmaceutical ingredient to the U.S. As described above, according to our inspection, your firm prepared a certificate of analysis (COA) for gabapentin on your firm's letterhead, indicating that the product was manufactured by your firm, Zhejiang Jiuzhou Pharmaceutical Co., Ltd, when in fact it was not. The gabapentin was manufactured by (b)(4). In addition, the expiration date on your firm's COA is not one supported by the COA from the original manufacturer, (b)(4).

你們公司除了違反CGMP外，還向美國發運了錯誤標識的原料藥。如上所述，根據我們的檢查情況，你公司製作了加巴噴丁的檢驗報告書（COA），用的是你們公司的抬頭，說該產品是你們公司（浙江九洲藥業有限公司）生產的，但實際上並不是這樣的。該加巴噴丁是由某公司生產的，該生產商出具的COA並不支持你們公司出具的COA上所給出的有效期。

Moreover, your firm relabeled gabapentin and included on the label an official stamp that identifies your firm, Zhejiang Jiuzhou Pharmaceutical Co., Ltd, as the manufacturer of the product, rather than the actual manufacturer, (b)(4). Based on our findings, the active pharmaceutical ingredient, gabapentin, is misbranded within the meaning of Section 502(a) of the Act [21 U.S.C. 352(a)] in that its labeling is false or misleading in any particular. See also 21 CFR 201.1(h)(2).

錯誤標識違規

更有甚者，你公司對加巴噴丁重新貼了標籤，標籤上還有你們浙江九洲藥業有限公司的正式蓋章，表示該產品是由你們公司生產，而不是某公司。根據發現的問題，我們認為該原料藥加巴噴丁符合聯邦法案[21 U.S.C. 352(a)]可第502(a)條對標籤錯誤的定義，這種情況下，標識行為屬於做假或故意誤導。也請參見21 CFR 201.1（h）(2)。

- 用自己公司標籤標示非本公司生產的原料並銷往美國
- 原生產單位COA上的有效日期與公司出具COA不符
- 標籤上有九洲藥業的正式蓋章偽造成生產單位

Data Integrity

1. 標籤資訊無法回溯,且可任意改標
2. CoA 可任意竄改
3. 品質部門未對批次紀錄進行把關
4. 人員偽造cGMP紀錄

FDA Concern： In your response to this letter, provide a comprehensive corrective action plan to address data integrity practices at your firm. We highly recommend that you hire a third party auditor with experience in detecting data integrity problems, who may assist you in evaluating your overall compliance with CGMP.

回覆信中提交一份綜合的整改行動計畫，說明公司保證資料完整性的方式。
我們強烈推薦你們聘請一位,對資料完整性問題具有較好經驗的協力廠商審計員，讓他幫助你們評估你們的整體GMP符合性。

During the inspection, your Quality Unit's personnel indicated that the unit's workload was too large for its current staffing levels. Our review of the significance of current findings indicates that your quality unit is not able to fully exercise its responsibilities. For instance, at the time of the inspection, your chief operating officer informed our investigator that your quality unit had not yet had time to review batch records for any products manufactured that month. It is your responsibility to ensure that adequate and appropriate resources are available to the quality unit to allow it to carry out its responsibilities.

在本次檢查中，你們品質部門的員工說該部門的**工作量對於現在的人員數量來說太大**了。我們發現的這些重大問題顯示你們品質部門**無法完全履行其職責**。例如，在檢查期間，你們的運營主管告訴我們檢查官說你們的品質部門還沒有時間對那個月生產的所有產品進行審核。你有責任保證給品質部門提供充分適當的資源，使他們能完成自己的工作。

FDA Warning letter - 5

Hospira Australia Pty Ltd.

FDA Warning letter

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-15

September 26, 2014

Mr. Andrew Holder
Vice President Operations
Hospira Australia Pty, Limited
1 Lexia Place, Mulgrave
Victoria 3170, Australia

1. Audit date: ***February 24 ~ March 1, 2014***
2. Plant: ***Hospira Australia Pty Ltd.***
3. Pharmaceutical manufacturing facility.

Violations

1. Your firm failed to thoroughly investigate unexplained discrepancies or failures of a batch or its components to meet its specifications, whether or not the batch has already been distributed.
   貴公司未能徹底調查批次失敗/符合規範的原因，不管是不是該批次已經放行。
2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess
   貴公司未能建立與製程工序相關的控制書來確保藥品聲稱或表明擁有製造的藥品的成份、劑量、質量和純度
3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas
   貴公司未能建立一個適當的系統，用於無菌加工區監測環境狀況

Findings (1)

- Your firm failed to thoroughly investigate unexplained discrepancies or failures of a batch or its components to meet its specifications, whether or not the batch has already been distributed .
  貴公司未能徹底調查批次失敗/符合規範的原因，不管是不是該批次已經放行。

  A. Several out-of-specification (OOS) results for the impurity XXXX from the stability studies of multiples batches of KKK Injection were inadequately investigated.
  KKK注射產品的數個批次，其安定性研究的結果。其雜質XXXX超出規格（OOS），但未充分研究調查。

  B. No effective corrective action and preventive action plan were implemented to address the recurrent findings of foreign matter (specifically, N particles) in OOXX injection drug product.
  沒有有效的糾正措施和預防措施計劃（CAPA）付諸實施，以解決在OOXX注射藥品異物（特別是，N個粒子）的經常性調查結果。

Findings (2)

- Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess貴公司未能建立與製程工序相關的控制書來確保藥品聲稱或表明擁有製造的藥品的成份、劑量、質量和純度

  ■The information related to the increase in levels of XXX (refer to #1a above) raises concern about the validation of your KKK manufacturing process. Your firm identified a correlation between the increase in the XXX impurity and D exceeding (E)%. However, this was not addressed in a subsequent study to demonstrate that the process remains in a state of control. Provide a comprehensive protocol for the revalidation of your process as it relates to (F) process (Filling Stage) in removing (G) in the (H).
  （參見上文＃1A）XXX增加的信息引起了人們對你的KKK的製造工藝的驗證問題。你的公司認為XXX的雜質的增加和D成份超過（E）％有相關性。然而，在隨後的研究中無法證明過程保持在可控制的狀態。

Findings(3)

- Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas
  貴公司未能建立一個適當的系統，用於無菌加工區監測環境狀況

  Your firm does not have a scientific justification for alternating the use of (AAA) and (BBB) for sampling by settle plates and swabs on different (CCC). We are concerned that you may have underestimated the number and type of bacterial species that are present on the (DDD) you use (EEE) because you have no data to support the equivalent sensitivity and efficiency of bacterial recovery on the (FFF) media as for (GGG). FDA expects that microbial culture media used for environmental monitoring be validated as capable of recovering fungi (i.e., yeast and molds), as well as bacteria. Appropriate trending of environmental monitoring data depends on consistent methods to provide an indication of the amount and type of microbiological organisms present
  你的公司不具備科學依據說明採樣沉降片和棉籤可以交替使用。我們擔心你可能低估了細菌的數量和種類，因為你沒有數據來支持（GGG）與（FFF）培養基的細菌恢復靈敏度和效率相當於。FDA的要求用於環境監測微生物的培養基需進行驗證為能夠回收真菌（即，酵母和黴菌）以及細菌。用一致的方法進行環境監測並研究趨勢數據，以提供微生物生物體的數量和類型。

FDA Warning letter - 6

Sharp Global Limited 10/15/14

FDA Warning letter

Department of Health and Human Services

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

Warning Letter

WL: 320-15-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

October 15, 2014

Mr. Sanjay Sinhal
Managing Director
Sharp Global Limited
Sharp House, Plot No. 9, 1st Floor, Part 1, Sagar Centre
Gujranwala Town, New Delhi, 110009
India

1. Audit date: ***March 6, 7, and 10, 2014***
2. Plant: ***Sharp Global Limited***
3. active pharmaceutical ingredients (**APIs**).

Findings (1)

- Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.
  - Not have proper controls in place to prevent manipulation of your laboratory's electronic raw data. Specifically, your NuCon 5700 gas chromatographs (GCs) did not have access controls that would prevent the deletion or altering of raw data files. In addition, the GC software lacked active audit trail functions to record any changes to the data, including the previous entries, who made the changes, and when the changes were made.

    實驗室的原始資料沒有登錄權限的控管，而且軟體無法tracking在系統上的任何變更。
  - Specifically, electronic raw data files, supporting your GC testing for release (assay) were deleted.

    GC 試驗的原始電子檔已被刪除

Findings(2)

- Failure to have appropriate controls for issuance of batch records.
  - batch records were uncontrolled in that operators had the ability to print batch records from their personal computers. In addition, various uncontrolled blank manufacturing batch records were found in a binder located in the production office.
    批次紀錄沒有管控，現場人員可以用個人的電腦列印批次紀錄。此外,在製造地點的辦公室發現空白批次紀綠。
  - the revisions made to SOP No. SGL-IMS-04 (section 2.3), "Control of Records,"：no evidence demonstrating that all operators have been trained on the revised procedure.
    改版的SOP並無任何的證據可證明操作人員已被訓練

Findings(3)

- Failure to have appropriate documentation and record controls.
  - Placed correction tape over multiple entries of raw material batch numbers in a logbook used to track crude (raw material). In addition, you used correction fluid on a recurring basis to make corrections in a logbook used to record various details of (b)(4) within the (b)(4) USP manufacturing process. Corrections to entries should be dated and signed, and the original entry must remain legible for review.

    使用修正液及修正帶來修改文件

  - In addition, your current SOP SGL-SOP-GEN-001 "Correct Way of Making Monitoring Records," prohibits the use of white ink for corrections of any written matter; however, operator training records did not show training on this procedure.

    SOP已明文禁止使用修正液但並無任何的訓練紀錄可證明操作人員已受訓

Findings(4)

- Failure to validate non-compendial analytical test methods.
  - Failed to validate the non-compendial analytical test method used to analyze for chromatographic purity.
    對於使用於CG 純度檢測的non-compendial分析方法沒有成功的確效
  - In addition, the system suitability for this test method was inadequate because it did not comply with the official United States Pharmacopoeia (USP) monograph .
    此檢驗方式因為沒有遵循USP 的Monograph而被判定為不合適。

Summary for data integrity

1. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

- no access controls
- software lacked active audit trail functions to record any changes to the data, including the previous entries, who made the changes, and when the changes were made.

2. Failure to have appropriate controls for issuance of batch records.

- batch records were uncontrolled in that operators had the ability to print batch records from their personal computers.
- various uncontrolled blank manufacturing batch records were found in a binder located in the production office.

FDA Warning letter - 7

Hikma Farmaceutica, (Portugal) S.A

10/21/2014

Hikma Farmaceutica, (Portugal) S.A. 10/21/14

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Department of Health and Human Services

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

Warning Letter

WL: 320-15-003

1. Audit date: March 20, 2014 through March 28, 2014
2. Plant: Hikma Farmaceutica, (Portugal) S.A
1. Finished Pharmaceuticals.

Violate

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192). For example,

您的公司沒有針對無法解釋的偏差、批次失效或是未能符合規範的結果進行全面性的調查，不論該批次是否已經流通於市面上。例如，

Your firm failed to conduct thorough investigations of your environmental monitoring (EM) excursions (i.e., exceeds action levels) found in your Class 100 areas. During the inspection, the review of the available data for the period of January 2012 to December 2013 revealed that your firm identified 23 EM samples that exceeded action levels in the Class 100 aseptic area on Line **(b)(4)** in your building identified as Hikma **(b)(4)**. Our review of the investigations collected during the inspection noted that all investigation reports identified "possible root causes" of the EM excursions as mishandling and/or poor aseptic technique during sampling. In all of these investigations you were unable to determine an actual root cause; yet, you disregarded the EM excursions without justification. In addition, your firm failed to evaluate the potential impact of these EM excursions on the quality of the product manufactured.

針對Class 100區域的環境監控偏離(超出行動值)沒有進行全面性的調查。在稽核時發現於January 2012 到December 2013 發現有23個結果超出行動值。調查報告中說明的"**可能根本原因**" 是樣品的處理不當或是差的無菌取樣技巧。針對環境的偏離沒有任何的根本原因的說明辯護且沒有評估對產品的品質是否有潛在性的影響。

Your firm also failed to implement corrections to address possible contributing factors for the isolates recovered during environmental monitoring (EM) in the class 100 areas. Your response states that you will improve the preparation of the EM plates as a corrective action. We disagree with your proposed corrective action since you have no evidence to support your claim that these results may be false positives. Your firm fails to address the possible microbial contamination you may have in your facility.

於Class 100區域的環境監測期間，針對分離菌的產生沒有說明可能的影響原因並實行矯正。您回覆的矯正措施是將提升EM plate的製備。我們不認同您的根本原因，因沒有證據支持假陽性的結果。且沒有說明於工廠內可能會造成微生物汙染源。

We note that your firm prepares the media plates used for EM sampling at your site. Prior to using these plates, your firm incubates them for **(b)(4)** and we are concerned that this practice may compromise the media's growth promotion potential. Provide evidence to demonstrate that pre-incubation of the media plates does not adversely impact the ability to promote microbial growth. Absent evidence to support this practice, you lack critical information demonstrating the suitability of the Class 100 production environment to assure product sterility.

We note that the lack of adequate investigations is a repeat violation from your September 2011, June 2007, and March 2004 inspections. In response to this letter provide a comprehensive plan to improve your investigations.

我們發現你們公司使用自行配製的培養皿進行環境監測取樣。在使用這些培養皿之前，你們公司培養這些培養皿，而我們關心的是這規範可能會危及培養基成長促進性。提供證據說明培養基的預先培養是不會影響微生物生長的能力。缺乏證據支持此項規範，則你們缺乏關鍵性的資訊說明Class 100製造區可確保產品無菌。

因缺乏適當的調查，所以重複性的違反行為可從歷年的稽核時被發現。應提供一個廣泛的計畫去提升你們的調查。

Finding (2)

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

你們公司針對生產和製程管控設計，沒有建立適當的紀錄程序去確保你們生產的產品具有可識別性、效力、品質與純度。且品質管控單位沒有覆核與核准這些程序，其中還包含任何的改變。

Finding (2)

Your firm failed to provide adequate challenge test set vials to qualify your operators and Quality Assurance (QA) staff to perform visual inspection of your drug product. Our investigators identified that 14 of **(b)(4)** vials used to qualify the operators for visual inspection were marked on top of the stopper with a number or a dot that was easily visible to the operator who was holding the vial during qualification. This practice allowed the operator to know in advance which vials were to be rejected.

你們公司沒有提供適當的挑戰試驗品，去驗證操作員與品質保證人員是否有能力進行產品的目視外觀檢測。我們的調查員發現有14瓶的驗證樣品其塞子上有標示號碼或點，此項作法讓被驗證人員可事先清楚的發現有問題的樣品。

Finding (2)

Your firm's response attributes the use of marked vials to the combining of an old challenge set with a new set without taking into consideration that the vials were previously numbered. Your response is inadequate in that it did not include a product impact assessment for all the batches inspected by operators that were not properly qualified.

你們公司的回應是，使用標示的瓶子與舊的挑戰組合併成新的一組並沒有考慮這些瓶子已經被編號了。你的回應是不適當的，因操作員已被不適當的驗證合格且並沒有考慮評估所有批次產品已被目視檢測所造成的影響。

Finding (2)

In response to this letter describe the actions you have implemented to ensure that the finished parenteral drugs you manufacture are essentially free of particulate matter. Also, provide an assessment of your quality system procedures to detect quality defects in your marketed products.

We note that your firm was previously cited during the September 2011, inspection for failing to detect and evaluate particulates.

你們必須確認你們製造的產品是沒有顆粒物的。也要提供你們品質系統程序的評估是如何確認市售產品的品質。

因我們發現你們公司於2011年9月被稽核發現是沒有通過偵測和評估顆粒物。

FDA Warning letter - 7

Apotex Research Private Limited

1/30/15

Warning letter

Apotex Research Private Limited 1/30/15

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Department of Health and Human Services

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

Warning Letter

WL: 320-15-06

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 30, 2015

Jeremy B. Desai, PhD
President and Chief Operating Officer
Apotex, Inc.
150 Signet Drive
Toronto, ON, Canada M9L 1 T9

1. Audit date: June 23, 2014 through July 1, 2014
2. Plant: Apotex Research Private Limited
3. Finished Pharmaceuticals.

Observation 1

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a))未確保實驗記錄包含所有必要檢驗項目之完整化驗數據以保證其符合建立的規格及標準

- **Trial Injection 試打:** official release data for unknown impurities was reported to be within specification. However, the chromatographic data showed that the "trial" injection data for this batch failed the unknown impurities specification. 不純物放行的數據呈現合格但未呈現的試打數據是不合格的
- 2,803 of 44,643 injection results were not processed or reported in the official data folder for dissolution analysis via HPLC for (b)(4) Tablets. Our inspection identified numerous examples of "trial" injections for various drug products (U.S. and non-U.S. markets), which suggests that this is a common practice.
  除上述例子外，亦發現某一錠劑之溶離化驗結果中，44643筆打樣紀錄內有2803筆未處理或報告於正式數據中。如此大量的案例發現於各個美國或非美國產品，認定為這是廠內的一般執行方式。

Observation 1

Company response 公司回覆:

- "the unknown were intermittent spikes resulting in aberrant chromatography caused by electronic disturbance or pressure fluctuation."

  該未知不純物訊號為來自電子信號的間歇性干擾或壓力波動
- "the unknown impurity peak… is not characteristic of the product and was not observed in the analysis of all commercial and exhibit batches."

  該未知不純物非為該產品的特徵，且未在其他市售與既有批次中發現
- "sample injections were not processed as the analyst failed to record the sample preparations in the analytical laboratory notebook and did not integrate the chromatograms for reporting."
  打樣數據未處理為分析者未紀錄樣品配置於實驗紀錄簿中，且無將圖譜積分並呈現於報告中

FDA response FDA 回覆:

- The fact that you did not observe the peak in commercial and exhibit batches does not justify disregarding the test run or failing to follow up with appropriate corrective actions and preventive actions.

  未於市售及現有批次發現該波峰，並無法支持可以不用考慮試打或是不以適當CAPA後續追蹤

Observation 1

- This explanation does not resolve the Agency's concerns, but instead raises further issues.
  這些解釋並無法消除官方的擔憂反倒引起更多議題

- Your response is inadequate because you did not extend the scope of the investigation to the other electronic systems used in each of your laboratories.
  你的回覆不適當，因為未擴展調查範圍至其他實驗室使用的電子系統

What observation 1 against 缺失一違反?

- **21 CFR 211.194 (a)**

	Attributable	Legible	Contemporaneous	Original	Accurate	Complete	Consistent	Enduring	Available
Against			V	V	V	V			

- **ALCOA+**

Observation 2

2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

未有適當的電腦或相關系統管控，以確保只有被授權人能執行製造與品管主紀錄變更

- QC personnel created unauthorized folders on laboratory computerized systems without appropriate oversight.

  品管人員在無適當監管下於實驗室電腦系統內建立未授權資料夾

- a data folder entitled "WASH." According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no standard operating procedure (SOP) detailing this process. Investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples

  無SOP規範流程下建立清洗管柱的資料夾，用於進樣前的管柱清洗。稽核者於該資料夾內發現3353筆打樣結果，其中部分包含了分析樣品

Observation 2

Company response 公司回覆:

- during an interview of the laboratory analyst conducted approximately six months after the incident, you determined that he may inadvertently have used an old sample vial from the LC tray for the single injection made for the purpose of a column wash

  在事件發生6個月後與分析者面談，該公司認為分析者在清洗管柱時誤用了舊的進樣瓶

- No malicious data integrity patterns and practices were found. No intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found

  無發現惡意的數據完整性狀況與作業，無有意的隱瞞、扭曲或是替換失敗的數據為合格數據，亦無證據顯示有資料的刪除或是竄改

Observation 2

FDA response FDA 回覆:

- We question your conclusion about the likely cause without having any supporting documentation or record, and based only on memory of what may have happened six months earlier

  我們質疑你們所下的結論，這個可能原因無任何支持文件或紀錄，僅仰賴於6個月前的記憶

- FDA's inspection did not include observations related to deletion of specific files, intentionally or otherwise. Rather, FDA's concern pertains to the practice of disregarding failing results, conducting trial injections and retesting products without any investigation. We are also concerned that you do not have documentation to support your decision to retest samples of lots that had initially failed to meet specifications, and you allowed manufacturing activities to occur without the oversight of your quality unit.

  FDA的稽核並未包含有意地刪除相關數據或是其他的缺失，FDA關注的是忽視失敗的結果、執行試打樣以及無調查的情況下重驗。FDA亦關注你們無任何文件支持重驗那些一開始化驗超標的樣品至符合規格的決定，以及你們允許製造相關作業在沒有品質單位監管下執行。

Observation 2

What observation 2 againsts 缺失一違反?

- **21 CFR 211.68 (b)**

  Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel…

- **ALCOA+**

	Attributable	Legible	Contemporaneous	Original	Accurate	Complete	Consistent	Enduring	Available
Against	V			V	V	V	V		

Observation 3

3. Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile (21 CFR 211.113(a))

   無建立及遵循適當的程序以防止非無菌產品的特定菌株汙染

   - Missing in-progress microbiological test plates for various finished drug products, in-process products, water, and media growth promotion samples. Even though records indicated that they were in the incubator

     遺失許多成品、半成品、水以及培養基生長試驗等正在執行的微生物培養皿，即便是紀錄培養皿正在培養箱的紀錄也遺失了

Observation 3

Company response 公司回覆:

- "The majority of the missing plates were found in the decontamination area for disposal" 大多數遺失的培養皿於滅菌拋棄區域發現
- "… two analysts momentarily panicked (upon (1) learning that FDA Investigators were approaching the microbiology Lab and (2) seeing used petri plates from the weekend scattered throughout the laboratory)[*sic*] and directed the lab technician to immediately remove the petri plates from the microbiology lab … in an utterly misguided and ill-conceived attempt to clean up the microbiology lab prior to the start of the FDA inspection." 於FDA稽核前，兩名分析員得知FDA稽核員會稽核微生物實驗室，且見周末的培養基被散佈在整個實驗室內，因驚慌立即請技術員移除實驗室內的培養基

FDA response FDA 回覆:

- Your response lacks a comprehensive risk assessment of your failure to follow procedures, your inadequate documentation system and your inadequate practices related to microbiological control. 你的回覆欠缺對你無法依循程序、不適當的文件系統以及不適當的微生物管控相關操作進行全面性的風險評估
- Your response failed to evaluate the effect of these violations on product quality, and did not include an assessment as to whether any other batches have been compromised. 你的回覆無對違反規範所造成的產品品質評估，也無含括是否有其他批次遭受影響的評估

Observation 3

What observation 3 againsts 缺失一違反?

- **21 CFR 211.113 (a)**

  Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

- **ALCOA+**

	Attributable	Legible	Contemporaneous	Original	Accurate	Complete	Consistent	Enduring	Available
Against								V	V

Observation 4

4. Your firm failed to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)) and your quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192)

   不遵循品質單位適用之程序，且你的品質單位失能於在產品放行或銷售前，覆核及核准所有藥品製造與品管紀錄以決定其是否符合以建立且核准之程序

思維模式轉變

- 如何理解“資料”，如何設計作業流程？
- 如何驗證 – 對患者安全、藥品品質、申請完整性等有直接影響的資料來源及系統？
- 如何在整個資料生命週期內管理風險？
- DI 僅限於/針對QC Lab嗎?
- DI v.s GMP

需要考慮的5個問題 - QC

- 是否存有全部的電子資料？
- 審核了全部的電子資料嗎？
- 電子資料的審核是否包括了有意義的中繼資料（例如審計追蹤）？Sop有規定嗎？培訓了嗎？
- 安全存取權限是否有適當的職責劃分？
- 系統是否按“預期用途”進行了驗證？

用什麼來保證資料完整性？

- 是否存有全部的電子資料？
  - 資料收集的設計：方案，流程和方法
  - 資料和中繼資料的資料生命週期的控制
- 資料是否被客觀的處理？
  - 對於“結果導向的檢驗”阻止和發現
- 是否審核了全部的資料？
  - 列印結果與電子記錄源比對
  - 審計追蹤的覆核
- 是否已經報告了所有資料？
  - 避免和阻止選擇性報告資料


Q&A