Current expectations and guidance, including data integrity and compliance with CGMP

数据完整性和cGMP合规性目前的期待及指南

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National Harbor, MD

Office of Policy for Pharmaceutical Quality
药品质量政策办公室(OPPQ)

- OPPQ = centralized, strategic policy development and evaluation
  - Dedicated office; dedicated staff
  - Quality governance through CDER Council for Pharmaceutical Quality (CPQ) – input on quality strategy and to speed OPQ-level clearance

OPPQ =集中、策略政策制定和评审
- 专门的办公室；敬业的员工
- 通过CDER药品质量委员会（CPQ）进行质量监管 – 制定质量策略、提升OPQ水平

OPPQ Work Products

- Regulations
- Guidance
- MAPPs
- Compliance Programs
- Citizen Petition consults/responses
- Controlled correspondence
- External inquiries (NDA/BLA/CGMP/503B compounding)
- USP inquiries/PF review
- Media inquiries
- Legislative inquiries (TA, Congressional inquiries, GAO, OIG)
- Individual policy questions/issues

OPPQ工作职责

- 法规
- 指南
- MAPPs
- 合规计划
- 公民请愿咨询/回复
- 沟通函
- 外部问询(NDA/BLA/CGMP/503B compounding)
- USP问询/PF审核
- 媒体问询
- 立法问询[TA, 国会调查、美国政府问责局（GAO），总监察长办公室（OIG)]
- 个别政策疑问/问题

SUNNY

Office of Manufacturing Quality
生产质量办公室

- We evaluate compliance with **C**urrent **G**ood **M**anufacturing **P**ractice (**CGMP**) for drugs based on inspection reports and evidence gathered by FDA investigators.
基于检查报告和FDA检察官收集的证据评估药品CGMP的合规性。

- We develop and implement compliance and enforcement actions to block adulterated drugs from the U.S. market.
制定和执行合规和实施措施，阻止假药进入美国市场。

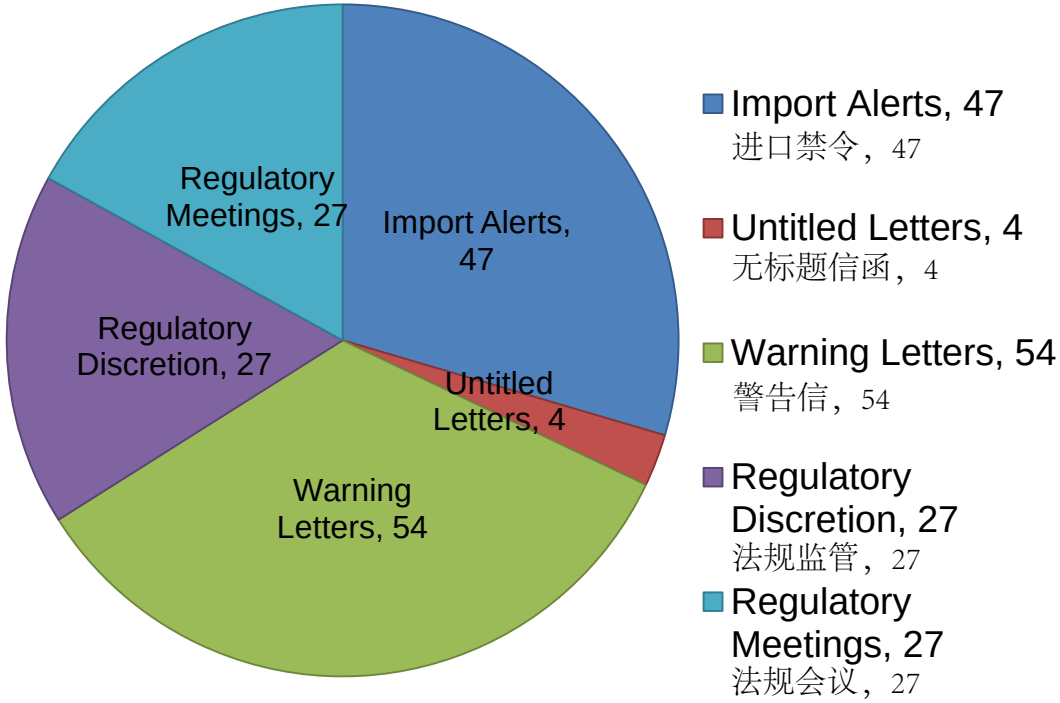
Source: FDA

Enforcement tools 实施工具

- Regulatory Meetings 法规会议
- Injunctions 禁令
- Consent Decrees 同意令
- Import Alerts 进口禁令
- Seizures 没收
- Warning Letters 警告信
- Untitled Letters 无标题信函
- And More 还有更多

2016 Enforcement Actions
2016实施措施

Excludes compounding-related action
不包括化合物相关的法案



What is data integrity?
什么是数据完整性？

Data integrity – requirements that data are **complete**, **consistent,** and **accurate.**

数据完整性 – 要求数据完整、一致和和准确

ALCOA

- **Attributable**
  可追溯
- **Legible**
  清晰
- **Contemporaneous**
  同步
- **Original / true copy**
  原始/原件
- **Accurate**
  准确

Data integrity 数据完整性

- CGMP = minimum requirements CGMP = 最低要求
- Data integrity underpins CGMP 数据完整性加固CGMP
- Lapses obscure other problems 减少其他问题出现

Tip of the iceberg

冰山一角

Data integrity: Not a new concept

Principles from the paper-and-ink era still apply:

- 211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss.
- 212.110(b) requires that data be stored to prevent deterioration or loss.
- 211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound.
- 211.180 requires true copies or other accurate reproductions of the original records; and
- 211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

数据完整性：并非一个新的概念

纸墨书写原则依然适用

- 211.68要求备份数据准确完整，避免更改、无意删除或丢失。
- 212.110(b) 要求数据存储要防止老化或丢失。
- 211.100, 211.160 要求特定活动在执行时要有记录，实验室控制要有科学合理。
- 211.180要求原始记录要有原件或其他复印件；
- 211.188, 211.194, 212.60(g)要求所有检验要有完整的信息和数据，所有数据要有完整记录，所有检验要有完整记录。

API - ICH Q7

Computerized systems (5.4):

- Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.
- If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

API - ICH Q7

计算机系统（5.4）：

- 计算机化系统应当有足够的控制，以防止未经许可存取或改动数据。应当有防止数据丢失（如系统关闭而数据未捕获）的控制。任何数据的变更、上一次输入、谁作的更改和什么时候更改都应当有记录。

- 如果计算机的故障或失效会导致记录的永久丢失，则应当提供备份系统。所有计算机化的系统都应当有数据保护措施。

Q7 药物活性成分优良生产规范指南

API - ICH Q7 (cont.)

Computerized systems (5.4):

- GMP-related computerized systems should be validated.
- Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- Incidents related to computerized systems that could affect the quality of intermediates or API or the reliability of records or test results should be recorded and investigated.

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

API - ICH Q7（续）

计算机系统（5.4）：

- 与GMP相关的计算机化系统应当验证。
- 适当的安装确认和操作确认应当能证明计算机硬件和软件适合执行指定的任务。
- 应当加以记录可能影响中间体或原料药质量、或者记录或测试结果可靠性的与计算机化系统有关的偶发事件，并作调查。

Q7 药物活性成分优良生产规范指南

Paper requirements = electronic requirements

纸质要求 = 电子要求

Requirements for record retention and review do not differ by data format. 要求记录保留和审核与数据格式无关。

Paper-based and electronic data record-keeping systems are subject to the same requirements.

纸质和电子数据记录的保存系统要求要一样。

Draft guidance

Data Integrity and Compliance With CGMP, draft guidance for industry (April 2016)

- Why? FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections.

- Ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect public health.

Available at www.fda.gov/downloads/drugs/guidancecompliancere gulatoryinformation/guidances/ucm495891.pdf

起草指南

*数据完整性及**CGMP**合规性*, 草案（2016年4月）

- 为什么？FDA在CGMP检查期间越来越多地发现涉及数据完整性的CGMP违规行为。

- 确保数据完整性是行业职责以确保药物的安全性，有效性和质量以及FDA保护公众健康能力的重要组成部分。

草案链接
www.fda.gov/downloads/drug
gulatoryinformation/guidance

Data Integrity Concepts
数据完整性概念

- Metadata 元数据
- Audit Trail 审计追踪
- Static vs. Dynamic Records 静态和动态记录
- Backup Data 数据备份
- System Validation 系统验证

What is ‘metadata’?

- Contextual information required to understand data
- Structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data
- For example: date/time stamp, user ID, instrument ID, audit trails, etc.
- Relationships between data and their metadata should be preserved in a secure and traceable manner

什么是‘元数据’?

- 了解数据所需的上下文信息
- 描述、解释或以其他方式使得检索、使用或数据管理更容易的结构化信息
- 例如：日期/时间印记、用户ID、仪器ID、审计追踪等等。
- 应以安全可追溯的方式保存数据与其元数据之间的关系

What is an ‘audit trail’?

- Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- Chronology: who, what, when, and sometimes why of a record
- CGMP-compliant record-keeping practices prevent data from being lost or obscured

什么是‘审计追踪’?

- 安全的、计算机生成的、时间戳的电子记录，允许与创建、修改或删除电子记录有关的事件重建
- 信息年表：谁、什么、什么时候、有的时候为什么记录
- 符合CGMP的记录保存措施可以防止数据丢失或隐藏

Audit trails capture…
审计追踪捕捉...

- Overwriting 重写数据
- Aborting runs 运行异常终止
- Testing into compliance 检验合规性
- Deleting 删除
- Backdating 倒填日期
- Altering data 更改数据
- *(not an all-inclusive list)* 还未全部列出

Use of “static” and “dynamic” in relation to record format

- Static: fixed data document such as a paper record or an electronic image
- Dynamic: record format allows interaction between the user and the record content such as a chromatogram where the integration parameters can be modified

记录格式采用 “静态”和“动态”

- 静态：固定的数据文件，如纸质记录或电子图片
- 动态：记录格式允许使用者和记录内容之间的互动，如一张图谱中的积分参数可以被修改。

How does FDA use the term 'backup' in 211.68(b)?

- True copy of the original data that is maintained securely throughout the records retention period.
- Should include associated metadata.
- Not backup copies that may be created during normal computer use and temporarily maintained for disaster recovery.

211.68(b)中'备份'的定义FDA如何使用？

- 原始数据的原件在整个记录保留期内都能被安全地保存。
- 应包含相关的元数据。
- 不是计算机正常使用期间可能创建的和暂时维护用于数据恢复的备份副本。

What are 'systems' in 'computer or related systems' in 211.68?

211.68中‘计算机或相关系统’中‘系统’指的是什么？

- Computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

  计算机硬件、软件、外部设备、网络、云架构、操作员及相关文件（例如：使用手册和SOP）。

How often should audit trails be reviewed?

- For audit trails that capture changes to *critical data,* FDA recommends review of each record before final approval of the record.
- Audit trails subject to regular review should include changes to:
  - history of finished product test results
  - sample run sequences
  - sample identification
  - critical process parameters

审计追踪应多久审核一次？

- 对于捕捉*关键数据*变化的审计跟踪，FDA建议在最终记录批准之前对每个记录进行审核。

- 审计追踪接受定期审核，应对以下变更审核：

  - 制剂产品历史检验结果
  - 样品运行序列
  - 样品鉴别
  - 关键工艺参数

How often should audit trails be reviewed? (cont.)

审计追踪应多久审核一次？（续）

- FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.
  FDA建议根据系统的复杂性及其预期用途定期审核例行的审计追踪。

Case study: Audit trails off

- Raw data was being deleted or altered on IR spectrometer
- No access controls
- No **active** audit trails on IR
- File names altered to make it appear tests supported additional lots of API

Warning letter: *Lack of audit trails for lab instruments and turning off audit trails. (April 2015)*

案例分析：审计追踪关闭

- 红外光谱仪原始数据被删除或更改
- 没有访问权限控制
- IR没有**有效的**审计追踪
- 为使检验支持更多批次的API而修改文件名

警告信：实验室仪器缺少和关闭审计追踪（2015年4月）

Case study: Audit trail review

- Observed repeat GC injections in the audit trail in June 12, 2013.
- Audit trail showed the computer date/time settings were set back in July 2013 to June 12, 2013 (audit trails go in chronological order, but the dates didn't and showed multiple June 12ths).
- Results were reprocessed and printed to show that they had achieved passing results on June 12, 2013.
- Firm relied on this data to release the batch.
- Similar situation was observed for HPLC testing.

Warning letter: *Because your qua*
original electronic raw data, you we
*deleted, or overwritten files. (*Janua

案例分析：审计追踪审核

- 2013年6月12日在审计追踪中发现重复的GC进样。
- 审计追踪显示计算机日期/时间设置被改回2013年6月12日至2013年7月(审计追踪按年代顺序，但这些日期不是，且显示有多个6月12日)。
- 2013年6月12日的结果被重新处理和打印以显示获得合格的检验结果。
- 公司基于这些数据来进行批放行。
- HPLC检验也发现类似情况

警告信：因你们的质量部门未审核原始电子记录，你们未能发现重新编写、删除或覆盖的文件(2015年1月)。

Who should review audit trails?

- Audit trails are considered part of the associated records.
- Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data…as they review the rest of the record.

谁来审核审计追踪？

- 审计追踪是相应记录的一部分。
- 负责CGMP项下的记录审核人员应审核审计追踪，捕捉关键数据的变更…因为他们审核记录的剩余部分。

When is it permissible to exclude CGMP data from decision making?

- Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes
- Electronic CGMP data should include relevant metadata
- To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion

什么时候可以将CGMP数据排除在决策之外？

- 作为CGMP记录一部分所创建的数据必须由质量部门评估，作为放行标准的一部分，并按CGMP要求维护。
- 电子版的CGMP数据应包含相关的元数据。
- 从放行标准决策中排除数据，必须有一个有效的、记录的、科学的理由依据来支持。

Case study: Tablet press

- Errors and discrepancies observed in tablet press log.
- Firm had justification and explanation in appropriate batch records.
- SOP was followed.
- Batch release decision included all pertinent data.

案例分析：片剂压片

- 片剂压片台账中发现错误和差异。
- 公司在合适的批记录中有论证和解释。
- 有遵循SOP。
- 批放行包含所有有关数据。

Does each workflow on our computer system need to be validated?

- Yes, a workflow, such as creation of an electronic MPCR, is an intended use of a computer system to be checked through validation
- If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly

我们计算机系统中的每个工作流程是否都需要验证？

- 是的，一个工作流，如电子MPCR的创建是为了使计算机系统在验证过程中可以被检查。

- 如果验证了计算机系统，但是验证其预期用途，就不知道工作流程运行是否正确。

Federal Register January 1995

"…manufacturing process. Less dramatic events, such as faulty data entry or programming, can also trigger a chain of events that result in a serious production error and the possible distribution of an adulterated product. Thus, while increasingly sophisticated system safeguards and computerized monitoring of essential equipment and programs help protect data, no automated system exists that can completely substitute for human oversight and supervision."

1995年1月的联邦公报

“...生产工艺。不太引人注目的事件，如错误数据录入或处理，也可能触发一连串的事件，导致严重的生产错误和销售可能的造假产品。因此，虽然越来越复杂的系统保障和对关键设备和程序的计算机监控有助于保护数据，但没有自动化的系统可以完全取代人的监督和监管。”

How should access to CGMP computer systems be restricted?

- Appropriate controls to assure only authorized personnel change computerized:
  - MPCRs
  - Input of laboratory data into records
  - Other records
- Recommend restricting the ability to alter:
  - Specifications
  - Process parameters
  - Manufacturing or testing methods

如何限制进入CGMP计算机系统？

- 适当的控制以确保只有授权的人员可以更改计算机系统的：
  - MPCRs
  - 录入记录的实验室数据
  - 其他记录
- 建议限制的修改包括：
  - 质量标准
  - 工艺参数
  - 生产或检验方法

How should access to CGMP computer systems be restricted? (continued)

- Recommend system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content.
- Recommend maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.
- May not be practical for small operations with few employees.

如何限制进入CGMP计算机系统？（续）

- 建议使用系统管理员，包括修改文件和设置的权限，分配给不负责记录内容的人。
- 建议每个在使用的CGMP计算机系统有一个授权人员清单及他们的访问权限。
- 对于员工数量少的小型公司来说可能不实用。

Case study: Administrator privileges

Warning letter: *We observed systemic data manipulation across your facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.*

Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events. (May 2016)

案例分析：管理员权限

警告信：我们发现你们厂区有系统数据篡改的现象，其中有多个分析员在多个检验设备上进行篡改。

具体来说，你们的质量控制（QC）分析员使用管理员权限和密码来操作高效液相色谱系统（HPLC）的时间，以更改实验室检验事件的记录年表。 （2016年5月）

Why is FDA concerned with the use of shared login accounts for computer systems?

A firm must:

- exercise appropriate controls to assure that only authorized personnel make changes to computerized records,
- ensure actions are attributable to a specific individual.

为什么FDA关注计算机系统的共享登录帐户？

一个公司必须：

- 进行适当的控制以确保只有授权的人员可以更改计算机的记录，
- 确保操作可以追踪到具体的每个人。

Case study: Shared logins

- No passwords were required to login
- Anyone who accessed the system had full software administrator privileges.
- An analyst stated that **someone else had used their login** to delete and modify data.

Warning letter: *Provide specific details of the steps you have taken to prevent unauthorized access to your electronic data systems and to ensure that data systems retain complete, accurate, reliable, and traceable results of analyses performed. (November 2015)*

案例分析：共享账号

- 登录无需密码
- 进入系统的每个人有全部的软件管理员权限。
- 有一个分析员说**有人曾使用他们的账户**删除和修改数据。

警告信：提供为防止未经授权访问电子数据系统，及为确保数据系统保持完整、准确、可靠和可追溯的分析结果而采取的详细步骤。（2015年11月）

How should blank forms be controlled?

- Blank forms (e.g., worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method.
- Numbered sets of blank forms may be issued and should be reconciled upon completion of the activity.
- Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement.

空白表格如何控制？

- 空白表格（如工作表、实验室记录和MPCRs）应由质量部门或另外一种文件控制方法进行控制。
- 可以发放有编号的空白表单，并在发放结束时确保收发平衡。
- 应将不完整或错误的表格作为永久保存记录的一部分，并附有书面理由予以更换。

Case study: Blank forms

- Uncontrolled blank and partially completed CGMP forms
- Supervisor photocopied a blank OOS form and transcribed the information because of “mistakes” in the original
- Did not follow own SOPs
- Firm stated that they “do not consider this OOS form to be an official document until it is initiated into the QA system”
- **Warning letter:** *Your quality unit is responsible for reviewing and approving these critical production records to ensure that, if an error occurred, a comprehensive investigation is conducted. Uncontrolled destruction of CGMP records also raises concerns, because retention of CGMP records must follow established procedures approved by your quality unit. (*January 2017)

案例分析：空白表格

- 未受控的空白和部分完整的CGMP表格
- 因原件有"错误"，负责人复印了一份空白OOS表格进行誊抄
- 未遵循自己的SOPs
- 公司表示，他们“不认为OOS表格在进入QA系统前是正式文件”

- **警告信：**你们的质量部门负责审核和批准这些关键生产记录，以确保如果发生错误，将进行全面的调查。 CGMP记录不受控的销毁也引起关注，因为保存CGMP记录必须遵循你们公司质量部门批准的既定程序。 （2017年1月）

Can electronic copies be used as accurate reproductions of paper or electronic records?

- Yes
- Provided copies preserve the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records.

电子副本可以作为纸质或电子记录的复印件吗？

- 可以
- 提供的副本可以保存原始数据的内容，其中包含关联的元数据及原始记录的静态或动态特性。

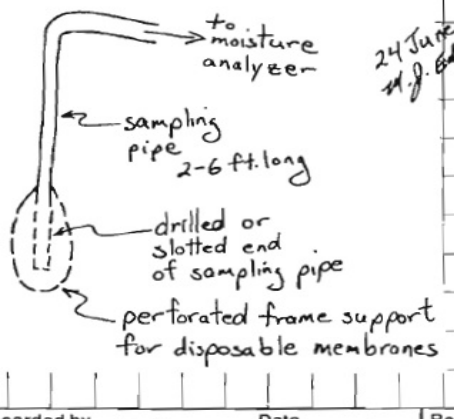
Electronic copy of a paper document
纸质文件的电子复印件

SUBJECT Novel Moisture Probe — Notebook No. MJE-6 Page No. 27 — Project New Ideas!

Continued from page no. 26 — Date 24 June 1985

As mentioned on the previous page, we need a probe that can be inserted into fine ceramic powders (mean diameters less than ~10μm) to sample the air for relative humidity.

At lunch today (when most good ideas come up!) Laura Gonzales and I spoke about the problem. She mentioned the "news note" about Gelman's microporous membrane technology in 17 June C&E News. Then, she and I realized the possibility of using inexpensive, disposable microporous filters to surround a sampler inlet. I made the following sketch on a napkin:



24 June 1985 M.J. Edwards "NOTHING UNDERNEATH" L. Salvador

The "teardrop" shape of the tip gives easy penetration of powders & is easily cleaned. The large membrane surface area will permit rapid sampling + fast equilibration.

Continued on page no. 28

Recorded by M.J. Edwards Date 24 June 1985 — Read and Understood by L. Salvador Date 24 June 1985

Related work on pages: Working models described pp 34-36; 50-52

Source: H. Kanare, ACS, *Writing the lab notebook*
书写实验室记录

Can you retain paper printouts/static records instead of original electronic records from computerized laboratory instruments?

- If it is a complete copy of the original record.
- For example, pH meters and balances may create a paper printout or static image during data acquisition as the original record.
- Electronic records from certain types of laboratory instruments are dynamic records, and a printout or a static record does not preserve the dynamic format which is part of the complete original record.

可以保存纸质打印/静态记录，而不保存实验室仪器的原始电子记录吗？

- 要是原始记录的完整复印件。
- 例如，pH计和天平的数据获取可能有纸质打印或静态图片作为原始记录。
- 实验室某些仪器的电子记录是动态记录，保存打印或静态记录不能作为完整原始记录动态格式的一部分。

Stand-alone electronic instrument
单机版电子仪器

Source: Omega.com

Can electronic signatures be used instead of handwritten signatures for master production/ control records?

- Yes.
- Part of the intent of the full signature requirement is to be able to clearly identify the individual signing the record.
- Appropriate controls to securely link the signature and associated record.

主生产/控制记录是否可以用电子签名替代手写签名？

- 可以
- 完整签名要求目的之一就是能够清楚地识别签名记录的个人。
- 适当的控制以安全地链接到签名和相关记录。

When does electronic data become a CGMP record?

- When it is generated to satisfy a CGMP requirement.
- You must document, or save, the data at the time of performance.
- Not acceptable to store data in temporary memory; this allows for manipulation, before creating a permanent record.

什么时候电子数据变成CGMP记录？

- 当它生成以满足CGMP要求的时候。
- 必须记录或保存操作时的数据。
- 不可以用临时存储器存储数据；它可以在永久记录生成前篡改数据。

When does electronic data become a CGMP record? (cont.)

- You may employ a combination of technical and procedural controls to meet CGMP documentation practices.
- Computer systems, such as LIMS or EBR systems, can be designed to save after separate entries.

什么时候电子数据变成CGMP记录？(续)

- 可以采用技术和程序控制来满足CGMP文件要求。
- 计算机系统，如LIMS或EBR系统，可以设计为在单独输入后保存。

Case study: Mock sheets

- Operators used “mock” sheets to capture critical manufacturing data.
- Batch production records were completed and backdated days after operations ended.
- Discrepancies between the “mock” sheets and the complete batch production record
- No evidence that batch production records were accurate

Warning letter: *Failure to record activities at the time they are performed, and destruction of raw data. (May 2016)*

案例分析：模拟表单

- 操作人员使用“模拟”表单来捕捉关键生产数据。
- 批生产记录是在生产操作结束后完成和倒填日期的。
- “模拟”表单和完整的批生产记录之间的差异。
- 无证据显示批生产记录是准确的。

警告信： 未在操作时记录，且销毁原始数据。（2016年5月）

Case study: Retesting

- Batch samples were routinely re-tested following failing or atypical results until acceptable results were obtained.
- Failing or atypical results were not investigated or included in the official laboratory control records.

Warning letter: *Substitution of results following failing lab results; failure to record critical values at time activities were performed in cases involving highly potent drugs. (November 2015)*

案例分析：复检

- 批样品常规复检失败或结果不合格复检直至获得合格的结果。

- 失败或不合格的结果没有调查或未在正式的实验室控制记录中体现。

警告信：替代失败的检验结果；高活性药物操作时未记录关键数据。（2015年11月）

What is wrong with using samples during 'system suitability' or test, prep, or equilibration runs?

- FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result.
- For example: using test, prep, or equilibration runs as a means of disguising testing into compliance.

'系统适用性'、检验、配制或平衡运行时使用样品有哪些错误?

- FDA禁止为了实现具体的结果或覆盖不合格的结果而进行的取样和检测。

- 例如：使用检验、配制或平衡运行来隐瞒不合格的检验结果。

What is wrong with using samples during 'system suitability' or test, prep, or equilibration runs? (cont.)

- If a sample is used for system suitability:
  - It should be a properly characterized secondary standard.
  - Written procedures should be established and followed.
  - Sample should be from a different batch than the sample(s) being tested.
- All data should be included in records retained and subject to review unless there is documented scientific justification for its exclusion.

'系统适用性'、检验、配制或平衡运行时使用样品有哪些错误？(续)

- 如果样品用于系统适用性：
  - 二级标准品应做结构确认
  - 应建立和遵循书面程序
  - 样品应取自待检样品的不同批次
- 所有数据应包含在保存的记录中，并经过审核，除非有书面的科学依据证明无需包含。

Case study: Stability samples

- Trial injections of “stability samples” saved in the “test” folder.
- Official samples analyzed after trial injection.
- **Warning letter:** *Your response indicates that the “Test” folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments… (March 2015)*

案例分析：稳定性样品

- "稳定性样品"实验进样保存在"检验"文件夹中。
- 正式样品在试验进样后检验。
- **警告信：**你们回复称“检验”文件夹用于色谱柱平衡，及确定系统何时可以进行检验。你们有责任遵循验证过的方法，包括具体的程序来评估仪器的适用性...（2015年3月）

Is it acceptable to only save the final results from reprocessed laboratory chromatography?

- No.
- Analytical methods should be capable and stable.
- If reprocessed, written procedures must be established and followed.
- FDA requires laboratory records include complete data derived from all tests.

返工的实验室图谱只保存最终结果是否可以接受？

- 不可以
- 分析方法应有效且稳定。
- 如果返工，必须建立和遵循书面程序。
- FDA要求实验室记录包含所有检验的所有完整数据。

Can internal quality tips, e.g., suspected data falsification, be handled outside the quality system?

- No.
- Fully investigate under the quality system to:
  - Determine the effect of the event on patient safety and product quality and on data reliability
  - Determine root cause.
  - Ensure the necessary corrective actions are taken.

Report suspected data integrity problems: DrugInfo@fda.hhs.gov with “CGMP data integrity” in the subject line.

内部质量问题，如数据疑似造假，是否可以在质量体系之外处理？

- 不可以
- 在质量系统下进行全面调查：
  - 确定事件对病人健康和产品质量及数据可靠性的影响
  - 确定根本原因
  - 确保采取必要的整改措施

报告可能的数据完整性问题给：
DrugInfo@fda.hhs.gov 主题写 “CGMP数据完整性”

Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?

- Yes, detecting data integrity issues is consistent with the CGMP requirements for personnel qualifications.
- Personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

是否将数据完整性问题作为常规CGMP培训计划的一部分进行培训？

- 是的，发现数据完整性问题要与CGMP要求的人员资质一致。
- 人员必须有教育、培训和经验，或任意结合，以履行其分配的职责。

Is the FDA investigator allowed to look at my electronic records?

- Yes.
- All records required under CGMP are subject to FDA inspection.

See FDA guidance, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* (October 2014)

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

FDA检察官是否可以查看我的电子记录？

- 可以
- 所有CGMP下的记录都要接受FDA检查。

见FDA指南：*延误、抵制、限制或拒绝药品检查的情况*(2014年10月)

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

Case study: U

- Investigator observed analyst using a U drive and asked to see the contents of the drive.
- The analyst ran.

Warning letter: *During the inspection, an analyst removed a U thumb drive from a computer controlling an HPLC. When asked to provide the drive, the analyst instead exited the room with the thumb drive. After approximately 15 minutes, management provided our investigator with what they asserted was the U thumb drive in question. It is impossible to know whether management provided the same U thumb drive that the analyst had removed. (December 2015)*

案例分析：U盘

- 检察官发现分析员使用U盘，并要求查看U盘中的内容。
- 分析员跑了。

警告信：检查期间，分析员从控制HPLC的计算机中拔出U盘。当被要求提供U盘时，分析员带着U盘离开了房间。 大约15分钟后，管理层向我们的检察官提供了U盘。是否提供的是分析员移除的同一U盘不得而知。（2015年12月）

How does FDA recommend data integrity problems identified during inspections be addressed?

- Demonstrate effective remediation by:
  - Hiring third party auditor
  - Determining scope of the problem
  - Implementing corrective action plan (globally)
  - Removing individuals responsible for problems from CGMP positions
- FDA may re-inspect

检查期间发现的数据完整性问题FDA如何建议解决?

- 通过有效的补救措施证明:
  - 聘请三方审计人员
  - 确定问题范围
  - 执行整改措施计划（全局的）
  - 从CGMP职位解雇出问题的负责人
- FDA可能再次检查

Responding to Data Integrity Failures

Data Integrity section in recent FDA Warning Letters with data integrity citations, requests firms respond with 3 key pieces:

- Comprehensive Evaluation (Scope)
- Risk Assessment (Scope)
- Remediation and Management Strategy (including corrective action plan)

对数据完整性失败的回复

数据完整性内容在最近FDA的警告信中被引用，要求公司从以下3个关键点回复：

- 全面评估（适用范围）
- 风险评估（适用范围）
- 补救和管理策略（包括整改措施计划）

Comprehensive investigation

A comprehensive investigation should include:

- **Detailed investigation protocol and methodology**; summary of all laboratories, manufacturing operations, and systems to be covered; justification for anything to be excluded.
- **Interviews of current and former employees** to identify the nature, scope, and root cause of data inaccuracies. Should be conducted by a third party.
- **Assessment of the extent of data integrity deficiencies**. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion. Describe all operations with data integrity lapses.
- **Comprehensive retrospective evaluation** of the nature of the data integrity deficiencies. Qualified third party with expertise specific to firm's breaches should evaluate the lapses.

全面调查

全面调查应包括：

- **详细的调查方案和方法**； 汇总所有涵盖的实验室、生产操作和系统；未包含的要提供个理由依据。

- **跟现在和之前的员工谈话**以确定误差发生的性质、范围和根本原因。应由第三方进行会谈。

- **评估数据完整性缺陷的程度。**识别遗漏、修改、删除、记录破坏和不同时期完成的记录。描述数据完整性失败的所有操作。

- **全面回顾评估**数据完整性缺陷的性质。应该由了解公司缺陷的有资质的第三方来评估缺陷。

Risk assessment & management strategy

A current **risk assessment** of the potential effects of data integrity failures on the quality of your drugs.

Should include analyses of risks to patients due to release of drugs produced with data integrity lapses as well as risks posed by ongoing operations.

风险评估 & 管理策略

数据完整性失败对药物质量的潜在影响的现行的**风险评估**。

应包括因数据完整性失误产生的药物放行以及正在进行的操作带来的风险，对患者的风险进行分析。

Management strategy

A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A **detailed corrective action plan** that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the **root causes** of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. **Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.**
- **Interim measures** describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- **Long-term measures** describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

管理策略

公司的管理策略包括详细的全面整改和预防措施计划。应包含：

- **详细的整改措施计划**描述如何确保所有生成数据的可靠性和完整性，包括分析数据、生产记录和所有提交给FDA的数据。
- 全面描述数据完整性失败的**根本原因**，包括证据证明当前行动计划的范围和深度与调查结果和风险评估相符。 **指出负责数据完整性失败的人是否会影响公司CGMP相关的或药物的应用数据。**
- **临时措施**是描述采取或将采取的保护患者的行为并确保药物的质量，例如通知客户、召回产品、进行额外检验、增加计划的稳定性批次以确保稳定性、药物应用措施和加强投诉监控。
- **长期措施**是描述为确保公司的数据完整性对程序、工艺、方法、控制、系统、管理监督和人力资源（例如培训，员工改进）所做的补救和改进。
- 上述任何正在进行或已完成的措施要有状态报告。

THANK YOU!

QUESTIONS?