Data Integrity and Compliance With Drug CGMP

Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

December 2018
Pharmaceutical Quality/Manufacturing Standards (CGMP)

数据完整性与药品 CGMP 合规

问答行业指南

美国卫生与公众服务部
食品药品监督管理局
药品评价与研究中心(CDER)生物制品评价与研究中心(CBER)
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Data Integrity and Compliance With Drug CGMP

Questions and Answers

Guidance for Industry

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数据完整性与合规性

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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required in 21 CFR parts 210, 211, and 212. Unless otherwise noted, the term *CGMP* in this guidance refers to CGMPs for drugs (including biologics). FDA's authority for CGMP comes from section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Part 210 covers Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; part 211 covers Current Good Manufacturing Practice for Finished Pharmaceuticals; and part 212 covers Current Good Manufacturing Practice for Positron Emission Tomography (PET) Drugs. All citations to parts 211 and 212 in this document pertain to finished pharmaceuticals and PET drugs, but these requirements are also consistent with Agency guidance on CGMP for active pharmaceutical ingredients with respect to data integrity.[2] This guidance provides the Agency's current thinking on the creation and handling of data in accordance with CGMP requirements.

FDA expects that all data be reliable and accurate (see the "Background" section). CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based on their process understanding and knowledge management of technologies and business models.[3]

Meaningful and effective strategies should consider the design, operation, and monitoring of systems and controls based on risk to patient, process, and product. Management's involvement

[1] This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] See the International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] See ICH guidance for industry *Q9 Quality Risk Management*.

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数据完整性与药品 CGMP 合规 行业指南问答 1

本指南代表美国食品药品监督管理局(FDA或本局)对该主题的当前思考。它不为任何人确立任何权利，也不对FDA或公众具有约束力。如果替代方法满足适用法规和规章的要求，您可以使用替代方法。如需讨论替代方法，请联系本指南标题页所列负责本指南的FDA办公室。

一、引言

本指南的目的是阐明数据完整性在药品现行药品生产质量管理规范(CGMP)中的作用，依据 21 CFR 第 210、211 和 212 部分的要求。除非另有说明，本指南中的术语"CGMP"指药品(包括生物制品)的 CGMP。FDA 对 CGMP 的授权来自《联邦食品、药品和化妆品法案》(FD&C Act)第 501(a)(2)(B)节。第 210 部分涵盖药品生产、加工、包装或贮存中的现行药品生产质量管理规范；总则；第 211 部分涵盖成品药品的现行药品生产质量管理规范；第 212 部分涵盖正电子发射断层扫描(PET)药品的现行药品生产质量管理规范。本文件中所有对第 211 和 212 部分的引用均涉及成品药品和 PET 药品，但这些要求也与本机构关于原料药 CGMP 的指南在数据完整性方面一致。2 本指南提供了本机构关于依照 CGMP 要求创建和处理数据的当前思考。

FDA期望所有数据可靠且准确(见"背景"部分)。CGMP法规和指南允许采用灵活且基于风险的策略来预防和发现数据完整性问题。企业应基于其对工艺的理解以及对技术和业务模式的知识管理，实施有意义且有效的策略来管理其数据完整性风险。[3]

有意义且有效的策略应考虑基于对患者、工艺和产品风险的系统与控制的设计、运行和监控。管理层的参与

[1]本指南由药品评价与研究中心的药品质量办公室和合规办公室与生物制品评价与研究中心、兽药中心以及美国食品药品监督管理局监管事务办公室合作编写。

[2]见国际人用药品注册技术协调会(ICH)行业指南*Q7*原料药药品生产质量管理规范指南。我们会定期更新指南。为确保您拥有指南的最新版本，请查阅FDA药品指南网页https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3]见ICH行业指南*Q9*质量风险管理。

in and influence on these strategies is essential in preventing and correcting conditions that can lead to data integrity problems. It is the role of management with executive responsibility to create a quality culture where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health. These data integrity-related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts, and consent decrees. The underlying premise in §§ 210.1 and 212.2 is that CGMP sets forth minimum requirements to assure that drugs meet the standards of the FD&C Act regarding safety, identity, strength, quality, and purity.[4] Requirements with respect to data integrity in parts 211 and 212 include, among other things:

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

[4] According to section 501(a)(2)(B) of the FD&C Act, a drug shall be deemed adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

对这些策略的参与和影响对于预防和纠正可能导致数据完整性问题的状况至关重要。具有行政责任的管理层的职责是创建一种质量文化，使员工理解数据完整性是组织的核心价值，并鼓励员工识别并及时报告数据完整性问题。如果管理层不支持质量文化，质量体系可能会崩溃并导致 CGMP 不合规。

一般而言，FDA的指南文件不确立具有法律强制执行力的责任。相反，指南描述本局对某一主题的当前思考，应仅视为建议，除非引用了具体的法规或法定要求。本局指南中使用*should*一词表示某事为建议或推荐，但并非要求。

II. 背景

近年来，FDA 在 CGMP 检查中日益发现涉及数据完整性的 CGMP 违规行为。这令人担忧，因为确保数据完整性是行业确保药品安全性、有效性和质量的责任的重要组成部分，也是 FDA 保护公众健康能力的重要组成部分。这些与数据完整性相关的 CGMP 违规行为已导致众多监管行动，包括警告信、进口警示和同意令。210.1 and 212.2 is that CGMP sets forth minimum requirements to assure that drugs meet the standards of the FD&C Act regarding safety, identity, strength, quality, and purity.[4]第 211 部分和第 212 部分中有关数据完整性的要求包括但不限于：

- •211.68(要求"备份数据准确且完整"以及"防止更改、意外擦除或丢失"并且"计算机输出..... 应检查准确性")。
- •212.110(b)(要求数据"储存以防止变质或丢失")。
- • 211.100和211.160(要求某些活动"在执行时记录"并且实验室控制"科学合理")。
- •211.180(要求记录作为"原始记录"、"真实副本"或其他"原始记录的准确复制件"保存)。
- • 211.188、211.194和212.60(g)(要求"完整信息"、"源自所有测试的完整数据"、"所有数据的完整记录"以及"所有已执行测试的完整记录")。

[4]根据FD&C法案第501(a)(2)(B)条，如果"用于其生产、加工、包装或保存的方法，或所使用的设施或控制措施不符合或不按照现行药品生产质量管理规范操作或管理，以确保该药品符合法案关于安全性的要求，并具有其声称或表示拥有的鉴别力和效价，且符合其声称或表示拥有的质量和纯度特征"，则该药品应被视为掺假。

- §§ 211.22, 211.192, and 211.194(a) (requiring that production and control records be "reviewed" and that laboratory records be "reviewed for accuracy, completeness, and compliance with established standards").

- §§ 211.182, 211.186(a), 211.188(b)(11), and 211.194(a)(8) (requiring that records be "checked," "verified," or "reviewed").

When considering how to meet many of these regulatory requirements, it may be useful to ask the following questions:

- Are controls in place to ensure that data is complete?

- Are activities documented at the time of performance?

- Are activities attributable to a specific individual?

- Can only authorized individuals make changes to records?

- Is there a record of changes to data?

- Are records reviewed for accuracy, completeness, and compliance with established standards?

- Are data maintained securely from data creation through disposition after the record's retention period?

This guidance helps answer these questions and enables an understanding of key concepts behind the regulatory requirements.

While not in the scope of this guidance, data integrity-related CGMP violations can also impact or be directly linked to application filing, review, and regulatory actions.

Electronic signature and record-keeping requirements are laid out in 21 CFR part 11 and apply to certain records subject to records requirements set forth in Agency regulations, including parts 210, 211, and 212. For more information, see guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application*, which outlines FDA's current thinking regarding the scope and application of part 11 pending FDA's reexamination of part 11 as it applies to all FDA-regulated products.

- 211.22、211.192和211.194(a)(要求生产和控制记录经过"审核"，并且实验室记录"审核准确性、完整性及对既定标准的符合性")。

- 211.182、211.186(a)、211.188(b)(11)和211.194(a)(8)(要求记录经过"检查"、"核实"或"审核")。

在考虑如何满足许多此类法规要求时，提出以下问题可能有所帮助：

- 是否有控制措施确保数据完整?

- 活动是否在执行时予以记录?

- 活动是否可以归因于特定个人?

- 是否只有经授权的人员才能更改记录?

- 是否有数据变更记录?

- 记录是否经过审核以确保准确性、完整性及对既定标准的符合性?

- 从数据创建到记录保存期后的处置，数据是否得到安全维护?

本指南有助于回答这些问题，并帮助理解法规要求背后的关键概念。

虽然不在本指南范围内，但与数据完整性相关的CGMP违规也可能影响或直接关联到申报文件的提交、审评和监管措施。

电子签名和记录保存要求规定于21 CFR part 11，适用于受机构法规(包括parts 210、211和212)中规定的记录要求约束的某些记录。更多信息，见行业指南*Part 11, Electronic Records; Electronic Signatures-Scope and Application*，该指南概述了FDA在FDA重新审查part 11对其适用于所有FDA监管产品的情况下，关于part 11范围和应用的当前思考。

III. QUESTIONS AND ANSWERS

1. Please clarify the following terms as they relate to CGMP records:

a. What is "data integrity"?

For the purposes of this guidance, *data integrity* refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).[5]

Data integrity is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record's retention period ends.[6] System design and controls should enable easy detection of errors, omissions, and aberrant results throughout the data's life cycle.

b. What is "metadata"?

Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. For example, the number "23" is meaningless without metadata, such as an indication of the unit "mg." Among other things, metadata for a particular piece of data could include a date/time stamp documenting when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, material status data, the material identification number, and audit trails.

Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194). The relationships between data and their metadata should be preserved in a secure and traceable manner.

c. What is an "audit trail"?

For purposes of this guidance, *audit trail* means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. For example, the audit trail for a high performance liquid chromatography (HPLC) run should include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any. Documentation should include change justification for the reprocessing.

[5] These characteristics are important to ensuring data integrity and are addressed throughout the CGMP regulations for drugs. For *attributable*, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see §§ 211.180(e) and 212.110(b); for *contemporaneously recorded* (at the time of performance), see §§ 211.100(b) and 211.160(a); for *original or a true copy*, see §§ 211.180 and 211.194(a); and for *accurate*, see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

[6] For examples of record retention periods, see §§ 211.180 and 212.110(c).

III. 问题与回答

1. 请澄清以下与 CGMP 记录相关的术语：

a. 什么是"数据完整性"?

就本指南而言，数据完整性是指数据的完整性、一致性和准确性。完整、一致和准确的数据应当可归属、清晰可读、同步记录、原始或真实副本，并且准确(ALCOA)。[5]

数据完整性在整个 CGMP 数据生命周期中都至关重要，包括在记录保存期限结束后对数据的创建、修改、处理、维护、归档、检索、传输和处置。[6]系统设计和控制应当能够在数据的整个生命周期中易于发现错误、遗漏和异常结果。

b. 什么是"元数据"?

元数据是理解数据所需的上下文信息。数据值本身如果没有关于该数据的附加信息，是没有意义的。元数据通常被描述为关于数据的数据。元数据是描述、解释或以其他方式使数据更易于检索、使用或管理的结构化信息。例如，数字"23"如果没有元数据(例如单位"mg"的指示)，是没有意义的。除其他内容外，特定数据的元数据可包括记录数据采集时间的日期/时间戳、执行生成该数据的测试或分析的人员的用户ID、用于采集数据的仪器ID、物料状态数据、物料识别编号以及审计追踪。

数据应在记录的整个保存期内予以维护，并附有重建CGMP活动所需的所有相关元数据(例如211.188和211.194)。数据与其元数据之间的关系应以安全和可追溯的方式予以保留。

c. 什么是"审计追踪"?

就本指南而言，审计追踪是指安全的、由计算机生成的、带有时间戳的电子记录，允许重建与电子记录的创建、修改或删除相关的事件过程。例如，高效液相色谱(HPLC)运行的审计追踪应包括用户名、运行日期/时间、所使用的积分参数以及重新处理的详细信息(如有)。文档应包括重新处理的变更理由。

[5]这些特征对于确保数据完整性很重要，并且在药品 CGMP 法规中通篇都有涉及。关于可归属，见 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see 211.180(e) 和 212.110(b)；关于同步记录(在执行时)，见 211.100(b) and 211.160(a); for *original or a true copy*, see 211.180 和 211.194(a)；关于准确，见 211.22(a)、211.68、211.188 以及 212.60(g)。

[6]关于记录保存期限的示例，见 211.180 和 212.110(c)。

Audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).

CGMP-compliant record-keeping practices prevent data from being lost or obscured and ensure that activities are documented at the time of performance (see §§ 211.68, 211.100, 211.160(a), 211.188, and 211.194). Electronic record-keeping systems, which include audit trails, can support these CGMP requirements.

d. How does FDA use the terms "static" and "dynamic" as they relate to record formats?

For the purposes of this guidance, *static* is used to indicate a fixed-data record such as a paper record or an electronic image, and *dynamic* means that the record format allows interaction between the user and the record content. For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger. It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as calculated yield.

e. How does FDA use the term "backup" in § 211.68(b)?

FDA uses the term *backup* in § 211.68(b) to refer to a true copy of the original record that is maintained securely throughout the record retention period (e.g., § 211.180). Backup data must be exact, complete, and secure from alteration, inadvertent erasures, or loss (§ 211.68(b)). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format.

FDA's use of the term *backup* is consistent with the term *archive* as used in guidance for industry and FDA staff *General Principles of Software Validation.*

Temporary backup copies (e.g., in case of a computer crash or other interruption) would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

f. What are the "systems" in "computer or related systems" in § 211.68?

The American National Standards Institute (ANSI) defines systems as people, machines, and methods organized to accomplish a set of specific functions.[7] *Computer or related systems* can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, personnel, and associated documents (e.g., user manuals and standard operating procedures).[8]

[7] American National Standard for Information Systems, *Dictionary for Information Systems*, American National Standards Institute, 1991.

[8] See guidance for industry and FDA staff *General Principles of Software Validation.*

审计追踪包括追踪数据创建、修改或删除(如处理参数和结果)的审计追踪，以及追踪记录或系统层面操作(如试图访问系统或重命名或删除文件)的审计追踪。

符合CGMP的记录保存实践可防止数据丢失或被掩盖，并确保活动在执行时予以记录(见 211.68、211.100、211.160(a)、211.188和211.194)。包含审计追踪的电子记录保存系统可以支持这些CGMP要求。

d. *FDA*如何使用"静态"和"动态"这两个术语来描述记录格式*?*

就本指南而言，静态用于表示固定数据记录，如纸质记录或电子图像，而动态意味着记录格式允许用户与记录内容之间进行交互。例如，动态色谱记录可允许用户更改基线和重新处理色谱数据，使所得峰可能显得更小或更大。它还可允许用户修改用于计算测试结果或其他信息(如计算收率)的电子表格中的公式或条目。

e. *FDA* 在*211.68(b)* 中如何使用"备份"一词*?*

FDA 在 211.180)。备份数据必须准确、完整，并防止被篡改、意外擦除或丢失(211.68(b))。备份文件应当包含数据(包括相关元数据)，并且应当采用原始格式或与原始格式兼容的格式。

FDA 对术语备份的使用与行业指南和 FDA 工作人员指南《软件验证的一般原则》中使用的术语归档一致。

临时备份副本(例如在计算机崩溃或其他中断情况下)不能满足211.68(b)中维护数据备份文件的要求。

f. *211.68* 中的"计算机或相关系统"指的是哪些"系统"*?*

美国国家标准学会(ANSI)将系统定义为为完成一组特定功能而组织起来的人员、机器和方法。[7]计算机或相关系统可以指计算机硬件、软件、外围设备、网络、云基础设施、人员及相关文件(例如用户手册和标准操作规程)。[8]

[7]美国国家标准信息系统，《信息系统词典》，美国国家标准学会，1991。

[8]见行业指南和 FDA 工作人员指南《软件验证的一般原则》。

2. When is it permissible to invalidate a CGMP result and exclude it from the determination of batch conformance?

Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180).[9] Electronic data generated to fulfill CGMP requirements include relevant metadata required to reconstruct the CGMP activity captured in the record. Invalidating test results to exclude them from quality unit decisions about conformance to a specification requires a valid, documented, scientifically sound justification. See, for example, §§ 211.160(b), 211.188, 211.192, and 212.71(b) and the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. Even if test results are legitimately invalidated on the basis of a scientifically sound investigation, the full CGMP batch record provided to the quality unit would include the original (invalidated) data, along with the investigation report that justifies invalidating the result. The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.

2. 何时允许使CGMP结果无效并将其排除在批次符合性判定之外?

作为CGMP记录一部分创建的数据必须由质量部门作为放行标准的一部分进行评估(见 211.22和212.70)，并为CGMP目的予以保存(例如211.160(b), 211.188, 211.192, and 212.71(b) and the guidance for industry *Investigating Out-of-specification (OOS) Test Results for Pharmaceutical Production*。即使测试结果基于科学合理的调查被合法地判定无效，提供给质量部门的完整CGMP批记录仍将包括原始(无效)数据，以及证明该结果无效合理的调查报告。记录保存和审核的要求不因数据格式而有所不同；纸质和电子数据记录保存系统受相同要求的约束。

3. Does each CGMP workflow on a computer system need to be validated?

Yes, a CGMP workflow, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation (see §§ 211.63, 211.68(b), and 211.110(a)). The extent of validation studies should be commensurate with the risk posed by the automated system. When the same system is used to perform both CGMP and non-CGMP functions, the potential for non-CGMP functions to affect CGMP operations should be assessed and mitigated appropriately.[10]

If you validate the computer system but you do not validate it for its intended use, you cannot know if your workflow runs correctly.[11] For example, qualifying the Manufacturing Execution System (MES) platform, a computer system, ensures that it meets its relevant requirements and specifications; however, it does not demonstrate that a given MPCR generated by the MES contains the correct calculations. In this example, validating the workflow ensures that the intended steps, requirements, and calculations in the MPCR are accurate and perform properly. This is similar to reviewing a paper MPCR and ensuring all supporting procedures are in place before the MPCR is implemented in production (see §§ 211.100, 211.186, and 212.50(b) and the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP)*).

3. 计算机系统上的每个 CGMP 工作流程都需要验证吗?

是的，CGMP 工作流程，例如创建电子主生产和控制记录(MPCR)，是计算机系统的一种预期用途，需要通过验证进行检查(见 211.63, 211.68(b), and 211.110(a)).The extent of validation studies should be commensurate with the risk posed by the automated system.When the same system is used to perform both CGMP and non-CGMP functions, the potential for non-CGMP functions to affect CGMP operations should be assessed and mitigated appropriately.[10]

如果您对计算机系统进行了验证但未针对其预期用途进行验证，您就无法知道您的工作流程是否正确运行。[11]例如，对制造执行系统(MES)平台(一种计算机系统)进行确认可确保其满足相关要求和规格；然而，这并不能证明MES生成的给定MPCR包含正确的计算。在此示例中，验证工作流程可确保MPCR中的预期步骤、要求和计算准确且正确执行。这类似于审核纸质MPCR并确保在MPCR投入生产之前所有支持性程序均已到位(见 211.100, 211.186, and 212.50(b) and the guidance for industry *PET Drugs-Current Good Manufacturing Practice (CGMP)*) .

[9] For purposes of this guidance, the term *quality unit* is synonymous with the term *quality control unit*. For the definition of *quality control unit*, see § 210.3(b)(15).

[10] See note 8.

[11] In computer science, *validation* refers to ensuring that software meets its requirements. However, this may not meet the definition of *process validation* as found in guidance for industry *Process Validation: General Principles and Practices: "*The collection and evaluation of data … which establishes scientific evidence that a process is capable of consistently delivering quality products." See also ICH guidance for industry *Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients,* which defines *validation* as providing assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. For purposes of this guidance, *validation* is being used in a manner consistent with the above guidance documents.

[9]就本指南而言，术语质量部门与术语质量控制部门同义。关于质量控制部门的定义，见210.3(b)(15)。

[10]见注释8。

[11]在计算机科学中，验证是指确保软件满足其要求。然而，这可能不符合行业指南《工艺验证：一般原则与规范》中对工艺验证的定义："数据的收集和评估.....用以建立科学证据，证明某一工艺能够持续稳定地生产出质量合格的产品。"另见ICH行业指南*Q7*《原料药药品生产质量管理规范指南》，其中将验证定义为提供保证，证明某一特定工艺、方法或系统将持续产生符合预定可接受标准的结果。就本指南而言，验证的使用方式与上述指南文件一致。

FDA recommends you implement appropriate controls to manage risks associated with each element of the system. Controls that are appropriately designed to validate a system for its intended use address software, hardware, personnel, and documentation.

4. How should access to CGMP computer systems be restricted?

You must exercise appropriate controls to assure that changes to computerized MPCRs or other CGMP records or input of laboratory data into computerized records can be made only by authorized personnel (§ 211.68(b)). Other examples of records for which control should be restricted to authorized personnel include automated visual inspection records, electronic materials management system records, and automated dispensing system weighing records. FDA recommends that you restrict the ability to alter specifications, process parameters, data, or manufacturing or testing methods by technical means where possible (e.g., by limiting permissions to change settings or data).

The system administrator role, including any rights to alter files and settings, should be assigned to personnel independent from those responsible for the record content. To assist in controlling access, it is important that manufacturers establish and implement a method for documenting authorized personnel's access privileges for each CGMP computer system in use (e.g., by maintaining a list of authorized individuals) (see § 211.68(b)).

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

When login credentials are shared, a unique individual cannot be identified through the login and the system would not conform to the CGMP requirements in parts 211 and 212. FDA requires that system controls, including documentation controls, be designed in accordance with CGMP to assure product quality (e.g., §§ 211.100 and 212.50). For example, you must implement documentation controls that ensure that the actions as described in question 4 are attributable to a specific individual (see §§ 211.68(b), 211.188(b)(11), 211.194(a)(7) and (8), and 212.50(c)(10)).

Shared, read-only user accounts that do not allow the user to modify data or settings are acceptable for viewing data, but they do not conform with the part 211 and 212 requirements for actions, such as second person review, to be attributable to a specific individual.

6. How should blank forms be controlled?

There must be document controls in place to assure product quality (see §§ 211.100, 211.160(a), 211.186, 212.20(d), and 212.60(g)). For example, bound paginated notebooks, stamped for official use by a document control group, provide good document control because they allow easy detection of unofficial notebooks as well as any gaps in notebook pages. If used, blank forms (e.g., electronic worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method. As appropriate, numbered sets of blank forms may be issued and should be reconciled upon completion of all issued forms. Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement (see, e.g., §§ 211.192, 211.194, 212.50(a), and

FDA建议您实施适当的控制措施来管理系统各要素相关的风险。为验证系统预期用途而适当设计的控制措施涉及软件、硬件、人员和文档。

4. **应如何限制对 CGMP 计算机系统的访问?**

您必须实施适当的控制措施，以确保对计算机化MPCR或其他CGMP记录的更改，或将实验室数据输入计算机化记录的操作，只能由经授权的人员进行(211.68(b))。其他应限制为仅经授权人员方可控制的记录示例包括：自动化目视检查记录、电子物料管理系统记录以及自动化配料系统称量记录。FDA建议您在可能的情况下通过技术手段限制更改规格、工艺参数、数据或生产或检验方法的能力(例如，通过限制更改设置或数据的权限)。

系统管理员角色，包括任何修改文件和设置的权限，应分配给独立于负责记录内容的人员。为协助控制访问权限，制造商必须建立并实施一种方法，记录每个在用的CGMP计算机系统的授权人员访问权限(例如通过维护授权人员名单)(见211.68(b))。

5. **FDA为何关注计算机系统使用共享登录账户的问题?**

当登录凭证被共享时，无法通过登录识别出唯一的个人，系统将不符合 211 和 212 部分中的 CGMP 要求。FDA 要求系统控制(包括文件控制)按照 CGMP 设计，以确保产品质量(例如 211.100 and 212.50).For example, you must implement documentation controls that ensure that the actions as described in question 4 are attributable to a specific individual(see 211.68(b)、211.188(b)(11)、211.194(a)(7) 和 (8) 以及 212.50(c)(10))。

不允许用户修改数据或设置的共享只读用户账户可用于查看数据，但不符合211和212部分中关于操作(如第二人审核)应可归属于特定个人的要求。

6. **空白表格应如何控制?**

必须建立文件控制措施以确保产品质量（见 211.100, 211.160(a), 211.186, 212.20(d), and 212.60(g)). For example, bound paginated notebooks, stamped for official use by a document control group, provide good document control because they allow easy detection of unofficial notebooks as well as any gaps in notebook pages. If used, blank forms (e.g., electronic worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method. As appropriate, numbered sets of blank forms may be issued and should be reconciled upon completion of all issued forms. Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement (see, e.g., 211.192、211.194、212.50(a) 以及

212.70(f)(1)(vi)). All data required to recreate a CGMP activity should be maintained as part of the complete record.

7. Who should review audit trails?

Audit trail review is similar to assessing cross-outs on paper when reviewing data. Personnel responsible for record review under CGMP should review the audit trails that capture changes to data associated with the record as they review the rest of the record (e.g., §§ 211.22(a), 211.101(c) and (d), 211.103, 211.182, 211.186(a), 211.192, 211.194(a)(8), and 212.20(d)). For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit (§ 211.192). The regulations provide flexibility to have some activities reviewed by a person directly supervising or checking information (e.g., § 211.188). FDA recommends a quality system approach to implementing oversight and review of CGMP records.[12]

8. How often should audit trails be reviewed?

If the review frequency for the data is specified in CGMP regulations, adhere to that frequency for the audit trail review. For example, § 211.188(b) requires review after each significant step in manufacture, processing, packing, or holding, and § 211.22 requires data review before batch release. In these cases, you would apply the same review frequency for the audit trail.

If the review frequency for the data is not specified in CGMP regulations, you should determine the review frequency for the audit trail using knowledge of your processes and risk assessment tools. The risk assessment should include evaluation of data criticality, control mechanisms, and impact on product quality.[13]

Your approach to audit trail review and the frequency with which you conduct it should ensure that CGMP requirements are met, appropriate controls are implemented, and the reliability of the review is proven.

See the audit trail definition in 1.c. above for further information on audit trails.

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

Yes. Electronic copies can be used as true copies of paper or electronic records, provided the copies preserve the content and meaning of the original record, which includes all metadata

[12] See guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations.* See also guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* for information about auditing as it relates to contract facilities.

[13] Risks to data include, but are not limited to, the potential to be deleted, amended, or excluded without authorization or without detection. Examples of audit trails that may be appropriate to review on a risk-based frequency include audit trails that capture instrument operational status, instrument communication logs, and alert records.

212.70(f)(1)(vi))。重建CGMP活动所需的所有数据应作为完整记录的一部分予以维护。

7. **谁应审查审计追踪?**

审计追踪审查类似于在审查数据时评估纸质记录上的划改。根据CGMP负责记录审查的人员在审查记录的其余部分时，应审查捕获与该记录相关数据更改的审计追踪(例如， 211.22(a)、211.101(c)和(d)、211.103、211.182、211.186(a)、211.192、211.194(a)(8)和212.20(d))。例如，所有生产和控制记录(包括审计追踪)必须由质量部门审查和批准(211.188)。FDA建议采用质量体系方法来实施对CGMP记录的监督和审查。[12]

8. **审计追踪应多久审查一次?**

如果CGMP法规中规定了数据的审核频率，则审计追踪审核应遵循该频率。例如， 211.22要求批放行前进行数据审核。在这些情况下，您应对审计追踪适用相同的审核频率。

如果 CGMP 法规未规定数据的审核频率，您应当利用对工艺的了解 and 风险评估工具来确定审计追踪的审核频率。风险评估应当包括对数据关键性、控制机制以及对产品质量影响的评估。[13]

您的审计追踪审核方法及实施频率应确保满足CGMP要求、实施适当的控制措施，并证明审核的可靠性。

关于审计追踪的更多信息，见上文1.c.中的审计追踪定义。

9. **电子副本能否用作纸质或电子记录的准确复制件?**

是的。电子副本可作为纸质或电子记录的真实副本使用，前提是副本保留了原始记录的内容和含义，包括所有元数据

[12]参见行业指南*Quality Systems Approach to Pharmaceutical CGMP Regulations*。关于与合同设施相关的审计信息，另参见行业指南*Contract Manufacturing Arrangements for Drugs: Quality Agreements*。

数据风险包括但不限于：数据可能在未经授权或未被发现的情况下被删除、修改或排除。可能适合基于风险频率进行审核的审计追踪示例包括：记录仪器运行状态的审计追踪、仪器通信日志以及警报记录。

required to reconstruct the CGMP activity and the static or dynamic nature of the original records.

True copies of dynamic electronic records may be made and maintained in the format of the original records or in a format that allows for the content and meaning of the original records to be preserved if a suitable reader and copying equipment (e.g., software and hardware, including media readers) are readily available (§§ 211.180(d) and 212.110).

10. Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

A paper printout or static record may satisfy retention requirements if it is the original record or a true copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). During data acquisition, for example, pH meters and balances may create a paper printout or static record as the original record. In this case, the paper printout or static record, or a true copy, must be retained (§ 211.180).

However, electronic records from certain types of laboratory instruments—whether stand-alone or networked—are dynamic, and a printout or a static record does not preserve the dynamic record format that is part of the complete original record. For example, the spectral file created by FT-IR (Fourier transform infrared spectroscopy) is dynamic and can be reprocessed. However, a static record or printout is fixed and would not satisfy CGMP requirements to retain original records or true copies (§ 211.180(d)). Also, if the full spectrum is not displayed in the printout, contaminants may be excluded.

You must ensure that original laboratory records, including paper and electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain that all test results and associated information are appropriately reported. Similarly, in microbiology, a contemporaneous written record is maintained of the colony counts of a petri dish, and the record is then subject to second-person review.

Document control requirements in § 211.180 pertain only to CGMP records.

For more information on static and dynamic records, see 1.d. in this guidance. For PET drugs, see the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP)* for discussion of equipment and laboratory controls, including regulatory requirements for records.

11. Can electronic signatures be used instead of handwritten signatures for master production and control records?

Yes, electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record. Although § 211.186(a) specifies a "full signature, handwritten," an electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement (21 CFR 11.2(a)). See part 11, which establishes criteria for when electronic signatures are considered the legally binding

重建CGMP活动以及原始记录的静态或动态性质所需。

动态电子记录的真实副本可以以原始记录的格式制作和保存，也可以以能够保留原始记录内容和含义的格式制作和保存，前提是合适的读取器和复制设备(例如，软件和硬件，包括介质读取器)随时可用(211.180(d) 和 212.110)。

10. 是否可以保留纸质打印件或静态记录，而不保留来自独立计算机化实验室仪器(如FT-IR仪器)的原始电子记录？

如果纸质打印件或静态记录是原始记录或原始记录的真实副本，则可以满足保存要求(见 211.68(b)、211.188、211.194 和 212.60)。例如，在数据采集过程中，pH计和天平可能生成纸质打印件或静态记录作为原始记录。在这种情况下，必须保留纸质打印件或静态记录，或其真实副本(211.180)。

然而，某些类型实验室仪器(无论是独立式还是联网式)产生的电子记录是动态的，打印件或静态记录不能保留作为完整原始记录一部分的动态记录格式。例如，FT-IR(傅里叶变换红外光谱)创建的光谱文件是动态的，可以重新处理。然而，静态记录或打印件是固定的，不能满足CGMP关于保留原始记录或真实副本的要求(211.180(d))。此外，如果打印件中未显示完整光谱，污染物可能被排除在外。

您必须确保原始实验室记录(包括纸质和电子记录)经过第二人审核(211.194(a)(8))，以确保所有检验结果及相关信息得到适当报告。同样，在微生物学中，应保存培养皿菌落计数的同步书面记录，然后该记录须经第二人审核。

211.180 中的文件控制要求仅适用于 CGMP 记录。

关于静态记录和动态记录的更多信息，见本指南第1.d节。关于PET药品，见行业指南*PET*药品--现行药品生产质量管理规范*(CGMP)*中关于设备和实验室控制的讨论，包括记录的监管要求。

11. 电子签名能否代替手写签名用于主生产和控制记录？

是的，在具备适当控制措施的情况下，电子签名可用于替代任何CGMP所需记录中的手写签名或姓名缩写。尽管211.186(a) 规定"完整签名，手写"，但具备适当控制措施以安全地将签名与相关记录关联的电子签名可满足该要求(21 CFR 11.2(a))。见第11部分，该部分规定了电子签名何时被视为具有法律约束力的

equivalent of handwritten signatures. Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.

手写签名等效物的标准。使用电子签名的公司应记录所使用的控制措施，以确保能够识别对记录进行电子签名的具体人员。

There is no requirement for a handwritten signature for the MPCR in the PET CGMP regulations (21 CFR part 212).

PET CGMP法规(21 CFR第212部分)不要求MPCR具有手写签名。

12. When does electronic data become a CGMP record?

12. 电子数据何时成为 CGMP 记录？

When generated to satisfy a CGMP requirement, all data become a CGMP record.[14] You must document, or save, the data at the time of performance to create a record in compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and 211.160(a).

当为满足CGMP要求而生成时，所有数据均成为CGMP记录。[14]您必须在执行时记录或保存数据，以创建符合CGMP要求的记录，包括但不限于 211.100(b) 和 211.160(a)。

FDA expects processes to be designed so that data required to be created and maintained cannot be modified without a record of the modification. For example, chromatographic data should be saved to durable media upon completion of each step or injection (e.g., peak integration or processing steps; finished, incomplete, or aborted injections) instead of at the end of an injection set, and changes to the chromatographic data or injection sequence should be documented in an audit trail. Aborted or incomplete injections should be captured in audit trails and should be investigated and justified.

FDA期望工艺的设计应使得要求创建和维护的数据在没有修改记录的情况下无法被修改。例如，色谱数据应在每个步骤或进样完成后(例如，峰积分或处理步骤；已完成、未完成或中止的进样)保存至持久介质，而不是在进样序列结束时保存，并且对色谱数据或进样顺序的更改应记录在审计追踪中。中止或未完成的进样应被捕获在审计追踪中，并应进行调查和论证。

It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook (see §§ 211.100(b), 211.160(a), and 211.180(d)). Similarly, it is not acceptable to store electronic records in a manner that allows for manipulation without creating a permanent record.

将数据记录在纸片上、待数据转录至永久实验室笔记本后即丢弃的做法是不可接受的(见211.100(b)、211.160(a) 和 211.180(d))。同样，以允许在不创建永久记录的情况下进行操纵的方式存储电子记录也是不可接受的。

You may employ a combination of technical and procedural controls to meet CGMP documentation practices for electronic systems. For example, a computer system, such as a Laboratory Information Management System (LIMS) or an Electronic Batch Record (EBR) system, can be designed to automatically save after each entry. This would be similar to indelibly recording each entry contemporaneously on a paper batch record to satisfy CGMP requirements. The computer system described above could be combined with a procedure requiring data be keyed in or otherwise entered immediately when generated.

你可以采用技术与程序控制相结合的方式，以满足电子系统的 CGMP 文件记录规范。例如，计算机系统(如实验室信息管理系统(LIMS)或电子批记录(EBR)系统)可设计为在每次录入后自动保存。这类似于在纸质批记录上同步、不可擦除地记录每次录入，以满足 CGMP 要求。上述计算机系统可与要求数据在生成时立即键入或以其他方式录入的程序结合使用。

For PET drugs, see the “Laboratory Controls” section of the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP).*

关于PET药品，见行业指南*PET*药品--现行药品生产质量管理规范*(CGMP)*中的“实验室控制”部分。

[14] Under section 704(a) of the FD&C Act, FDA inspections of manufacturing facilities “shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs [and] nonprescription drugs intended for human use ... are adulterated or misbranded ... or otherwise bearing on violation of this chapter.” Accordingly, FDA routinely requests and reviews records not intended to satisfy a CGMP requirement but which nonetheless contain CGMP information (e.g., shipping or other records that may be used to reconstruct an activity).

[14]根据《FD&C 法案》第 704(a) 条，FDA 对生产设施的检查“应扩展至其中所有与以下事项相关的事物(包括记录、文件、纸张、工艺、控制和设施)：供人使用的处方药[和]非处方药.....是否掺假或贴错标签.....或以其他方式与本 chapter 的违反相关。”因此，FDA 经常要求并审查并非为满足 CGMP 要求而保存、但仍包含 CGMP 信息的记录(例如，可用于重建某项活动的运输记录或其他记录)。

13. Why has FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result (e.g., testing different samples until the desired passing result is obtained). This practice, also referred to as *testing into compliance*, is not consistent with CGMP (see the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*). In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance. FDA considers it a violative practice to use an actual sample in *test*, *prep*, or *equilibration* runs as a means of disguising testing into compliance.

According to the United States Pharmacopeia (USP), system suitability tests must include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied (see USP General Chapter <621> *Chromatography*). System suitability tests should be performed according to the firm's established written procedures—which should include the identity of the preparation to be injected and the rationale for its selection—and the approved application or applicable compendial monograph (§§ 211.160 and 212.60).

If an actual sample is to be used for system suitability testing, it should be a properly characterized secondary standard, written procedures should be established and followed, and the sample should be from a different batch than the sample(s) being tested (§§ 211.160, 211.165, and 212.60). CGMP original records must be complete (e.g., §§ 211.68(b), 211.188, 211.194) and subjected to adequate review (§§ 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)). Transparency is necessary. All data—including obvious errors and failing, passing, and suspect data—must be in the CGMP records that are retained and subject to review and oversight. An investigation with documented, scientifically sound justification is necessary for data to be invalidated and not used in determining conformance to specification for a batch (see §§ 211.160, 211.165, 211.188, and 211.192).

For more information, see the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* and VICH guidances for industry *GL1 Validation of Analytical Procedures: Definition and Terminology* and *GL2 Validation of Analytical Procedures: Methodology*.[15]

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

No. Analytical methods should be accurate and precise.[16] For most lab analyses, reprocessing data should not be regularly needed. If chromatography is reprocessed, written procedures must be established and followed and each result retained for review (see §§ 211.160, 211.165(c), 211.194(a)(4), and 212.60(a)). FDA requires complete data in laboratory records, which includes

[15] VICH=Veterinary International Conference on Harmonisation.

[16] See ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology*.

13. FDA为何在警告信中引用在"系统适用性"或测试、制备或平衡运行中使用实际样品的情况?

FDA 禁止以取得特定结果或克服不可接受结果为目的进行取样和检测(例如，检测不同样品直至获得所需的合格结果)。这种做法也称为检测至合规，不符合 CGMP(见行业指南药品生产中超标*(OOS)*检测结果的调查)。在某些情况下，使用实际样品进行系统适用性检测已被用作检测至合规的手段。FDA 认为，在检测、制备或平衡运行中使用实际样品以掩盖检测至合规的行为，属于违规做法。

根据《美国药典》(USP)，系统适用性试验必须包括标准制备液或其他标准溶液的重复进样，以确定是否满足精密度要求(见 USP 通则<621>色谱法)。系统适用性试验应按照企业既定的书面程序进行--该程序应包括待进样制备液的身份及其选择理由--以及已批准的申请或适用的药典各论(211.160 和 212.60)。

如果实际样品将用于系统适用性测试，则该样品应为经过适当表征的二级标准品，应建立并遵循书面程序，且该样品应来自与被检样品不同的批次(211.160, 211.165, and 212.60).CGMP original records must be complete(e.g., 211.68(b)、211.188、211.194)，并经过充分审核(211.68(b), 211.186(a), 211.192, and 211.194(a)(8)).Transparency is necessary.All data-including obvious errors and failing, passing, and suspect data-must be in the CGMP records that are retained and subject to review and oversight.An investigation with documented, scientifically sound justification is necessary for data to be invalidated and not used in determining conformance to specification for a batch(see 211.160、211.165、211.188 和 211.192)。

更多信息，见ICH行业指南*Q2(R1)* 分析方法的验证：文本和方法以及VICH行业指南*GL1* 分析方法的验证：定义和术语和*GL2* 分析方法的验证：方法学。[15]

14. 仅保存重新处理的实验室色谱分析的最终结果是否可以接受?

不可以。分析方法应准确且精密。[16]对于大多数实验室分析，通常不应需要重新处理数据。如果对色谱数据进行重新处理，必须建立并遵循书面程序，且每项结果均应保留以供审核(见 211.160、211.165(c)、211.194(a)(4) 和 212.60(a))。FDA要求实验室记录中包含完整数据，包括

[15] VICH=兽药国际协调会议。

[16]见ICH行业指南*Q2(R1)* 分析方法的验证：文本和方法。

but is not limited to notebooks, worksheets, graphs, charts, spectra, and other types of data from laboratory instruments (§§ 211.194(a) and 212.60(g)(3)).

15. Can an internal tip or information regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?

No. Regardless of intent or how or from whom the information was received, suspected or known falsification or alteration of records required under parts 210, 211, and 212 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken (see §§ 211.22(a), 211.125(c), 211.192, 211.198, 211.204, and 212.100).

FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. "CGMP data integrity" should be included in the subject line of the email. This reporting method is not intended to supersede other FDA reports (e.g., field alert reports or biological product deviation reports that help identify drug products that pose potential safety threats).

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

Yes. Training personnel to prevent and detect data integrity issues is consistent with the personnel requirements under §§ 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

17. Is FDA allowed to look at electronic records?

Yes. All records required under CGMP are subject to FDA inspection. This applies to records generated and maintained on computerized systems, including electronic communications that support CGMP activities. For example, an email to authorize batch release is a CGMP record that FDA may review.

You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§§ 211.180(c) and 212.110(a) and (b)). See also the guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* and section 704 of the FD&C Act. Procedures governing the review of electronic records are described in chapter 5 of the *Investigations Operations Manual* (IOM) at https://www.fda.gov/iceci/inspections/iom/default.htm.

18. How does FDA recommend data integrity problems be addressed?

FDA encourages you to demonstrate that you have effectively remediated your problems by investigating to determine the problem's scope and root causes, conducting a scientifically sound risk assessment of its potential effects (including impact on data used to support submissions to

但不限于笔记本、工作表格、图表、图形、光谱以及来自实验室仪器的其他类型数据(211.194(a) 和 212.60(g)(3))。

15. **关于质量问题的内部举报或信息(例如潜在的数据伪造)能否在已记录的CGMP质量体系之外非正式处理?**

不可以。无论意图如何，或信息如何收到、从何人处收到，疑似或已知的210、211和212部分所要求记录的伪造或篡改必须在CGMP质量体系下进行全面调查，以确定该事件对患者安全、产品质量和数据可靠性的影响；确定根本原因；并确保采取必要的纠正措施(见 211.22(a)、211.125(c)、211.192、211.198、211.204 和 212.100)。

FDA邀请个人通过DrugInfo@fda.hhs.gov报告可能影响药品安全性、鉴别、规格、质量或纯度的疑似数据完整性问题。电子邮件主题行中应包含"CGMP数据完整性"。此报告方式不旨在取代其他FDA报告(例如，有助于识别构成潜在安全威胁的药品的现场警报报告或生物制品偏差报告)。

16. **是否应作为常规CGMP培训计划的一部分，对人员进行预防和发现数据完整性问题的培训?**

是的。对人员进行预防和发现数据完整性问题的培训符合 211.25 和 212.10 中的人员要求，该要求规定人员必须具备教育、培训和经验，或任何组合，以履行其分配的职责。

17. **FDA 是否允许查看电子记录?**

是的。CGMP要求的所有记录均须接受FDA检查。这适用于在计算机化系统上生成和维护的记录，包括支持CGMP活动的电子通信。例如，用于授权批次放行的电子邮件是FDA可审核的CGMP记录。

您必须允许授权检查、审核和复制记录，包括复制电子数据(211.180(c) and 212.110(a) and(b)).See also the guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug inspection* and section 704 of the FD&C Act.Procedures governing the review of electronic records are described in chapter 5 of the *Investigations Operations Manual*(IOM) at https://www.fda.gov/iceci/inspections/iom/default.htm.

18. **FDA 建议如何解决数据完整性问题?**

FDA鼓励您通过以下方式证明您已有效解决问题：进行调查以确定问题的范围和根本原因，对其潜在影响进行科学合理的风险评估(包括对用于支持提交至

FDA), and implementing a management strategy, including a global corrective action plan that addresses the root causes. This may include retaining a third-party auditor and removing individuals responsible for data integrity lapses from positions where they can influence CGMP-related or drug application data at your firm. It also may include improvements in quality oversight, enhanced computer systems, and creation of mechanisms to prevent recurrences and address data integrity breaches (e.g., anonymous reporting system, data governance officials and guidelines).

These expectations mirror those developed for the Application Integrity Policy. For more detailed information, see *Points To Consider for Internal Reviews and Corrective Action Operating Plans* at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm.

FDA)，并实施一项管理策略，包括针对根本原因制定全球纠正措施计划。这可能包括聘请第三方审计员，并将对数据完整性失误负有责任的人员从能够影响贵公司 CGMP 相关数据或药品申报数据的岗位上调离。还可能包括改进质量监督、增强计算机系统，以及建立防止问题复发和处理数据完整性违规的机制(例如匿名报告系统、数据治理官员和指南)。

这些期望与为“申请完整性政策”制定的期望相一致。有关更详细的信息，请参见http://www.fda.gov/ICECI/EnforcementActions/Application Integrity Policy/ucm134744.htm.处的内部审查与纠正措施操作计划应考虑的要点。

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