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Harmonization Challenges: Comparing FDA 21 CFR Part 11 and EU GMP Annex 11 Requirements for Audit Trail Review

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Abstract

Background: The pharmaceutical industry operates in an increasingly globalized environment where multinational companies must navigate divergent regulatory frameworks for computerized systems and electronic records. Audit trail review requirements represent a critical component of data integrity assurance, yet significant variations exist between major regulatory authorities.

Objective: This manuscript provides a comprehensive comparative analysis of audit trail review requirements under FDA 21 CFR Part 11 and EU GMP Annex 11, examines the challenges multinational pharmaceutical companies face in establishing unified Global Quality Systems (GQS), and proposes harmonization strategies.

Methods: A systematic review of regulatory guidance documents, industry publications, warning letters, and current literature was conducted. Additional regulatory frameworks from WHO, PIC/S, MHRA, TGA, and PMDA were analyzed to provide a global perspective.

Results: Fundamental differences exist in the scope, frequency, and depth of audit trail review requirements across regulatory jurisdictions. FDA 21 CFR Part 11 mandates comprehensive audit trails for creation, modification, and deletion of electronic records, while EU GMP Annex 11 focuses primarily on modification and deletion of GMP-relevant data. Regulatory interpretations of "regular review" vary significantly, creating implementation challenges for global organizations.

Conclusions: Achieving harmonization requires risk-based approaches, leveraging emerging technologies including artificial intelligence and machine learning, and implementing robust governance frameworks. The manuscript concludes with practical recommendations for establishing effective global audit trail review programs.

Keywords: Audit trail review; 21 CFR Part 11; EU GMP Annex 11; Data integrity; Global quality systems; Pharmaceutical regulation; Computerized systems validation

1. Introduction

The pharmaceutical industry has undergone profound transformation over the past three decades, evolving from predominantly paper-based documentation systems to sophisticated electronic record-keeping environments [1]. This digital revolution, while enhancing operational efficiency and data accessibility, has introduced complex regulatory compliance challenges, particularly concerning the integrity and traceability of electronic records [2]. At the heart of these challenges lies the requirement for comprehensive audit trails—chronological records that document the "who, what, when, and why" of data lifecycle events [1].

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Audit trails serve as the cornerstone of data integrity assurance in pharmaceutical manufacturing, quality control, and clinical research [3]. They enable reconstruction of events, facilitate regulatory inspections, support root cause investigations, and provide evidence of compliance with Good Manufacturing Practice (GMP) requirements [4]. However, the implementation of audit trail systems and the conduct of audit trail reviews have become sources of significant regulatory scrutiny, as evidenced by the increasing number of FDA warning letters and EU inspection findings related to data integrity deficiencies [5, 6].

The regulatory landscape governing audit trails is characterized by parallel but not perfectly aligned frameworks. In the United States, the Food and Drug Administration (FDA) established 21 CFR Part 11 in 1997, setting forth criteria for electronic records and electronic signatures [2, 7]. In the European Union, EudraLex Volume 4 GMP Annex 11 addresses computerized systems, with the current version implemented in 2011 [8, 9]. While both regulations aim to ensure the authenticity, integrity, and reliability of electronic records, their specific requirements—particularly regarding audit trail scope, review frequency, and documentation—differ in substantive ways [10, 11].

For multinational pharmaceutical companies operating across multiple regulatory jurisdictions, these differences create significant operational and compliance challenges [12, 13]. Organizations must either maintain separate systems and procedures for different geographic regions—an approach that is resource-intensive and increases complexity—or develop harmonized global standards that meet the most stringent requirements across all jurisdictions [14]. The latter approach, while conceptually appealing, presents practical difficulties in interpretation and implementation [10].

Recent years have witnessed increasing regulatory emphasis on data integrity, catalyzed by high-profile cases of data manipulation and falsification [5, 6]. This heightened focus has expanded to encompass not merely the existence of audit trails but also the systematic review and evaluation of audit trail data [3, 15]. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance PI 041-1 on Good Practices for Data Management and Integrity explicitly addresses audit trail review as a critical control measure [4]. However, guidance on the practical aspects of review—including frequency, depth, personnel qualifications, and documentation—remains fragmented across different regulatory authorities [16].

The implementation challenge is further compounded by the volume of audit trail data generated by modern pharmaceutical operations [15, 17]. A typical manufacturing facility may operate hundreds of computerized systems, each generating thousands of audit trail entries daily [16]. Manual review of this data is impractical, necessitating risk-based approaches and, increasingly, the deployment of automated tools and artificial intelligence technologies [17, 18]. Yet the regulatory acceptability and validation requirements for such technologies remain areas of ongoing discussion and evolution [18].

This manuscript addresses these critical challenges through a comprehensive comparative analysis of audit trail review requirements across major regulatory frameworks, with primary focus on FDA 21 CFR Part 11 and EU GMP Annex 11. The analysis extends to include perspectives from WHO, PIC/S, MHRA (United Kingdom), TGA (Australia), and PMDA (Japan) to provide a truly global view [13]. Beyond comparative analysis, this work examines the practical challenges multinational companies face in establishing Global Quality Systems, explores emerging technological solutions, and proposes harmonization strategies that balance regulatory compliance with operational efficiency [19].

1.1. Scope and Objectives

This manuscript aims to:

- Provide a detailed comparative analysis of audit trail requirements under FDA 21 CFR Part 11 and EU GMP Annex 11
- Examine requirements and guidance from other major regulatory authorities (WHO, PIC/S, MHRA, TGA, PMDA)
- Analyze the specific challenges multinational pharmaceutical companies face in harmonizing audit trail review practices
- Evaluate the role of emerging technologies, particularly artificial intelligence and machine learning, in audit trail review
- Propose practical frameworks for establishing effective Global Quality Systems that accommodate regional variations while maintaining high data integrity standards
- Identify areas requiring further regulatory clarity and opportunities for international harmonization

1.2. Significance of the Study

This work addresses a critical gap in pharmaceutical regulatory science literature by providing a comprehensive, comparative examination of global audit trail review requirements. While individual regulatory frameworks have been analyzed separately, limited research has systematically compared requirements across multiple jurisdictions or addressed the practical implementation challenges for global organizations [12, 13]. The insights and recommendations presented herein will benefit:

- Regulatory affairs and quality assurance professionals designing and implementing audit trail review programs
- Validation specialists responsible for computerized system compliance
- Senior management making strategic decisions about Global Quality System architecture
- Regulatory authorities considering harmonization initiatives
- Academic researchers studying pharmaceutical regulatory science and data integrity

As the pharmaceutical industry continues its digital transformation journey, and as regulatory agencies worldwide intensify their focus on data integrity, the need for harmonized, risk-based approaches to audit trail review has never been more critical [10, 12].

2. Regulatory Framework Overview

2.1. FDA 21 CFR Part 11: Electronic Records; Electronic Signatures

2.1.1. Historical Context and Development

The FDA published 21 CFR Part 11 in March 1997, with an effective date of August 20, 1997, establishing the regulatory framework for electronic records and electronic signatures [2]. The regulation was promulgated in response to the increasing use of computerized systems in FDA-regulated industries and the need to establish clear criteria for accepting electronic records as equivalent to paper records and handwritten signatures [7].

Following significant industry feedback regarding interpretation and implementation challenges, the FDA issued guidance in 2003 titled "Part 11, Electronic Records; Electronic Signatures - Scope and Application," which clarified the agency's enforcement approach and exercised enforcement discretion regarding certain requirements [7]. This guidance represented a risk-based regulatory philosophy, acknowledging that validation and controls should be proportionate to the impact computerized systems have on predicate rule requirements and record integrity [20].

2.1.2. Scope and Applicability

21 CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations [2]. The regulation also applies to electronic records submitted to the FDA under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in Agency regulations [7].

Importantly, Part 11 requirements apply when organizations choose to use electronic records in lieu of paper records, electronic signatures in lieu of traditional signatures, or when electronic records are used to supplement paper records [20]. The regulation establishes a framework of controls that must be implemented to ensure the trustworthiness, reliability, and general equivalence of electronic records to their paper counterparts [2, 20].

2.1.3. Audit Trail Requirements Under 21 CFR Part 11

The specific audit trail requirement is found in 21 CFR 11.10(e), which mandates: "Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying" [2, 20].

Key components of this requirement include:

- **Scope of Audit Trail:** The regulation explicitly requires audit trails to capture three types of actions: creation, modification, and deletion of electronic records [2]. This comprehensive scope distinguishes FDA requirements

from some other regulatory frameworks and reflects the agency's emphasis on complete traceability of the electronic record lifecycle [20, 21].

- **Security:** Audit trails must be "secure," meaning they must be protected from unauthorized access, modification, or deletion [2, 20]. The security requirement extends to both technical controls (system-level protections) and procedural controls (policies and procedures governing system access and use) [1].
- **Computer-Generated:** Audit trails must be automatically generated by the computerized system, not manually created or entered by users [20]. This requirement ensures objectivity and prevents manipulation of the audit trail itself [1].
- **Time-Stamped:** Each audit trail entry must include date and time information, recorded using a trusted system time [2]. The FDA's 2003 guidance clarified that when systems span multiple time zones, manufacturers may use a single designated time zone (such as UTC) for consistency, rather than recording each user's local time [7].
- **Non-Obscuring:** Changes to records must not obscure or overwrite previously recorded information [2]. Both the original data and the modified data must be preserved and accessible [1, 20].
- **Retention:** Audit trails must be retained for at least as long as the electronic records to which they pertain [2]. For pharmaceutical records, this typically means retention periods of multiple years, depending on the specific record type and regulatory requirements [1].
- **Availability for Review:** Audit trails must be available for FDA review and copying during inspections [2]. This requirement implies that audit trails must be readily accessible and convertible to human-readable format [1, 20].

2.1.4. FDA Guidance on Audit Trail Review

While 21 CFR Part 11 mandates the creation and retention of audit trails, it does not explicitly specify requirements for the frequency or method of audit trail review [7]. However, the FDA has provided clarification through various guidance documents and inspection observations [1].

The 2018 FDA guidance "Data Integrity and Compliance With Drug CGMP Questions and Answers" addresses audit trail review explicitly [1]. Question 6 asks "Who should review audit trails?" and the FDA responds: "Personnel who are responsible for and knowledgeable about the data being recorded in the audit trail, such as process owners, should review the data. Management should review the audit trails as needed" [1].

Question 7 asks "How often should audit trails be reviewed?" The FDA's response indicates: "The review frequency should be based on the criticality of the data and how quickly you need to identify data issues. For example, audit trails for critical process control systems might need to be reviewed 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 access to the data and system" [1].

This guidance establishes several important principles:

- Audit trail review should be performed by qualified personnel with knowledge of the processes and data
- Review frequency should be risk-based
- For critical data supporting batch release, audit trail review should occur prior to release
- Risk assessment should consider data criticality, existing controls, and access patterns

2.1.5. FDA Enforcement Trends

Analysis of FDA warning letters from 2019-2024 reveals consistent citations related to audit trail deficiencies [5]. Common observations include:

- Computerized systems lacking audit trail functionality
- Audit trails that were disabled or could be disabled by users
- Failure to review audit trails
- Inadequate audit trail review procedures
- Inability to retrieve or view audit trails during inspections
- Audit trails that could be modified or deleted
- Shared login accounts preventing attribution of actions to specific individuals

A 2024 FDA warning letter to Applied Therapeutics, Inc. highlighted a particularly severe case where electronic data and associated audit trails were deleted from a clinical trial system, preventing FDA investigators from verifying the integrity of critical efficacy data [6]. This case underscores the FDA's expectation that audit trails must be preserved and protected throughout the record retention period [1, 6].

2.2. EU GMP Annex 11: Computerised Systems

2.2.1. Evolution and Current Status

The current version of EU GMP Annex 11 came into effect on June 30, 2011, replacing the previous 1992 version [8]. This revision was undertaken to reflect technological advances, align with international practices, and address emerging data integrity concerns [9, 10]. Annex 11 applies to all forms of computerized systems used as part of GMP-regulated activities, encompassing a broad range of applications from process control systems to laboratory instruments to quality management systems [8].

The European Medicines Agency (EMA) published a Concept Paper in November 2022 outlining plans for revision of Annex 11, acknowledging areas requiring clarification or expansion, particularly regarding audit trails, cloud services, and artificial intelligence [9]. Draft revisions were released for public consultation in July 2025, with final implementation expected in 2026 [10]. These planned revisions signal the regulatory authority's recognition that current requirements need enhancement to address modern technological capabilities and data integrity challenges [10].

2.2.2. Scope and Applicability

Annex 11 applies to all computerized systems that are used as part of GMP-regulated activities [8]. The regulation defines a computerized system as "a system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control" [8]. This broad definition encompasses a wide range of systems, from simple standalone instruments to complex, integrated manufacturing execution systems [8, 10].

Importantly, Annex 11 applies based on a risk assessment approach, with the principle that the application should be validated, and IT infrastructure should be qualified [8]. The regulation emphasizes that where a computerized system replaces a manual operation, there should be no resultant decrease in product quality, process control, or quality assurance, and there should be no increase in the overall risk of the process [8].

2.2.3. Audit Trail Requirements Under EU GMP Annex 11

Section 9 of Annex 11 specifically addresses audit trails [8]. The current regulation states: "Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated 'audit trail'). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed" [8].

Key aspects of this requirement:

- **Risk-Based Approach:** Unlike the FDA's mandatory requirement, Annex 11 uses the language "consideration should be given," indicating that the need for an audit trail should be determined through risk assessment [8]. However, PIC/S guidance PI 041-1 clarifies that audit trails should be implemented for all GMP-relevant data, and regulatory authorities typically expect audit trails for all systems with GMP impact [4].
- **Scope: Changes and Deletions:** The regulation explicitly mentions "changes and deletions" but notably does not mention "creation" of records [8]. This represents a fundamental difference from FDA requirements [2]. The European regulatory philosophy holds that the creation of data is an expected system function, and the focus should be on modifications to data after initial entry [8, 21].
- **GMP-Relevant Data:** The requirement specifically applies to "GMP-relevant" data, requiring organizations to make determinations about which data falls within this category [8]. Generally, data that could impact product quality, patient safety, or regulatory decision-making is considered GMP-relevant [3, 4].
- **Reason for Change:** When data is changed or deleted, the reason must be documented [8]. This may be captured through free-text entry, selection from predefined reason codes, or linked comments [3].
- **Availability and Readability:** Audit trails must be "available and convertible to a generally intelligible form" [8]. This requirement addresses both technical accessibility (the ability to retrieve audit trail data) and usability (the ability to understand and interpret the data) [3, 21].

- **Regular Review:** The requirement for "regularly reviewed" audit trails is stated but not explicitly defined [8]. This lack of specificity has been a source of interpretation challenges and is a focus area for the planned Annex 11 revision [9, 10].

2.2.4. Related EU Guidance and Interpretations

Several documents provide additional context for interpreting Annex 11 audit trail requirements:

- **EU GMP Chapter 4 (Documentation):** Establishes fundamental documentation principles, including the requirement that any change to a document entry should be signed and dated, and the original information should remain legible [8]. These paper-based documentation principles form the conceptual foundation for electronic audit trail requirements [8, 21].
- **EudraLex Volume 4 Annex 11, Section 8 (Printouts):** States that "for records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry" [8]. This requirement establishes a clear expectation for audit trail review prior to batch release [4].
- **MHRA GXP Data Integrity Guidance (2018):** While not specific to the EU, this MHRA guidance is widely referenced and provides detailed interpretation of data integrity principles, including audit trails [3]. The guidance emphasizes that audit trails should always be switched on, users should not be able to amend or switch off audit trails, and periodic checks should verify that audit trails remain enabled and effective [3].

2.2.5. Planned Revisions to Annex 11

The draft Annex 11 revision (2025) includes significantly expanded requirements for audit trails [10]. Proposed changes include:

- Explicit requirement that audit trails must not be editable by users
- Requirement that audit trails cannot be switched off by normal users
- Specific guidance on audit trail review frequency based on system criticality
- Clarification that audit trail data should be sortable and filterable to facilitate review
- Requirements for validation of audit trail functionality
- Guidance on differentiating between audit trails (GMP-relevant changes) and system logs (technical system events)

These proposed revisions, if adopted, would bring EU requirements more closely aligned with FDA expectations and address long-standing ambiguities [10, 21].

2.3. PIC/S PI 041-1: Good Practices for Data Management and Integrity

2.3.1. Overview and Significance

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) represents a collaborative effort among over 50 pharmaceutical regulatory authorities worldwide to harmonize GMP inspection approaches [4, 13]. PIC/S guidance PI 041-1, "Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments," was finalized in July 2021 following extensive stakeholder consultation [4].

While PIC/S guidances are not legally binding regulations, they are highly influential, as they represent the consensus view of global regulatory authorities and are used to train inspectors [4]. PI 041-1 has become a de facto international standard for data integrity expectations [4, 13].

2.3.2. Audit Trail Guidance in PI 041-1

Section 9.4 of PI 041-1 specifically addresses "Audit trails for computerised systems" [4]. The guidance provides detailed expectations:

- **Audit Trail Functionality:** "Companies should select software that includes appropriate electronic audit trail functionality. Companies should endeavour to purchase and upgrade older systems to implement software that includes electronic audit trail functionality" [4].
- This statement establishes a clear expectation that audit trails are not optional and that organizations should actively work to implement them, even in legacy systems [4, 21].

- **Audit Trail Review:** "9.4 Critical audit trails related to each operation should be independently reviewed with all other relevant record reviews, such as batch record reviews, prior to batch release, so as to ensure that critical data and changes to it are acceptable" [4].
- This requirement is particularly significant as it explicitly links audit trail review to the batch release process for critical systems [4, 15]. The guidance clarifies that audit trail review should not be an isolated activity but should be integrated with other quality control reviews [3, 4].
- **Review by Exception:** The guidance acknowledges the impracticality of reviewing all audit trail entries and supports a risk-based "review by exception" approach [4]. Organizations are expected to configure systems and develop procedures that enable focusing review efforts on anomalies, exceptions, and high-risk activities [4, 19].
- **Frequency of Review:** While PI 041-1 does not mandate a specific review frequency applicable to all situations, it establishes the principle that review frequency should be determined based on the criticality of the data and the associated risk [4].

2.3.3. Data Governance Expectations

PI 041-1 establishes that audit trail review should be governed within the organization's broader data governance framework [4]. This includes:

- Clear assignment of roles and responsibilities for audit trail review
- Documented procedures specifying what to review, when, how, and by whom
- Training of personnel on audit trail review expectations and techniques
- Oversight and monitoring of audit trail review effectiveness
- Escalation procedures when issues are identified
- Documentation of audit trail reviews

2.4. Other Global Regulatory Perspectives

2.4.1. WHO (World Health Organization)

The WHO provides guidance for member states, particularly those with developing regulatory systems [13]. WHO Technical Report Series (TRS) publications address computerized systems and data integrity but do not provide the same level of prescriptive detail as FDA or EU regulations [13]. WHO guidance generally aligns with ICH and PIC/S principles, emphasizing:

- Risk-based approaches to computerized system controls
- Data integrity throughout the data lifecycle (ALCOA+ principles)
- Audit trails as key controls for electronic records
- The importance of validation and ongoing system monitoring

WHO's Guidance on Good Data and Record Management Practices emphasizes that regulatory authorities should verify that audit trails are available, routinely reviewed, and maintained throughout the record retention period [13].

2.4.2. MHRA (Medicines and Healthcare products Regulatory Agency - United Kingdom)

The MHRA's "GXP Data Integrity Guidance and Definitions" (March 2018) is widely regarded as one of the most comprehensive regulatory documents on data integrity [3]. While the UK has formally exited the EU, MHRA guidance remains highly influential globally [3, 13].

Key MHRA expectations regarding audit trails include:

- Audit trails should always be switched on and locked; users should not be able to amend or deactivate them
- Where system administrators have the ability to amend or switch off audit trails, such actions should themselves be recorded
- The relevance of data retained in audit trails should be considered to permit robust data review/verification
- Audit trails should be reviewed as part of the Second Person Review of data
- The frequency of audit trail review should be based on data criticality and risk [3]

The MHRA has been particularly active in issuing inspection findings related to inadequate audit trail review, reinforcing that this is a high-priority enforcement area [3].

2.4.3. TGA, PMDA, and Health Canada

The Australian TGA adopts PIC/S guidelines and incorporates them into national requirements [13]. Australia is a PIC/S member and actively participates in international harmonization efforts. TGA expectations for audit trails generally align with PIC/S PI 041-1 and EU Annex 11 [13].

Japan's PMDA has been working toward greater international harmonization, particularly through participation in ICH and PIC/S [13]. Japanese GMP requirements (J-GMP) address computerized systems and data integrity, with expectations generally consistent with international norms [13].

Health Canada's "Good Manufacturing Practices (GMP) Guidelines" address computerized systems in Sections 3 and 11 [13]. Canada is a PIC/S member and generally aligns with ICH and PIC/S guidance. Health Canada has participated in developing Good Machine Learning Practice (GMLP) principles in collaboration with FDA and MHRA, signaling attention to emerging technologies in the regulatory space [18].

3. Comparative Analysis: Key Differences and Similarities

3.1. Scope of Audit Trail: Create, Modify, Delete

- **FDA 21 CFR Part 11:** Explicitly requires audit trails to capture actions that "create, modify, or delete" electronic records [2]. This comprehensive scope ensures complete traceability of the entire record lifecycle [2, 20].
- **EU GMP Annex 11:** Requires audit trails for "changes and deletions" but does not explicitly mention creation [8]. The European interpretation is that data creation is a normal system function and the focus should be on subsequent modifications [8, 21].
- **Implication for Global Companies:** To meet both requirements, organizations typically implement audit trails that capture all three actions (create, modify, delete), as this represents the most stringent requirement [21]. However, this decision should be documented in the validation or configuration rationale [14].
- **Risk-Based Perspective:** From a data integrity standpoint, capturing creation provides additional context and can be valuable for investigations [3]. The risk-based argument for not capturing creation is that it generates significant audit trail volume without necessarily adding proportionate value, particularly for high-volume transactional systems [19].

The risk-based approach should consider not only regulatory requirements but also the organization's specific data integrity risk profile [19]. Their research demonstrates that companies with robust initial data entry controls may achieve equivalent data integrity assurance with or without audit trails of creation events, provided that modification and deletion audit trails are comprehensive [19].

3.2. Mandatory vs. Risk-Based Implementation

- **FDA 21 CFR Part 11:** Once an organization chooses to use electronic records in lieu of paper records, audit trail requirements become mandatory [2]. There is no discretion about whether to implement audit trails for systems covered by Part 11 [7, 20].
- **EU GMP Annex 11:** Uses the language "consideration should be given, based on a risk assessment," suggesting that audit trail implementation is not universally mandatory but should be determined through risk assessment [8].
- **Regulatory Interpretation:** In practice, EU/PIC/S inspectors typically expect audit trails for all GMP-relevant computerized systems [3, 4]. The "risk-based" language is generally interpreted to mean that the extent, detail, and review frequency of audit trails should be risk-based, not whether audit trails exist at all [4].
- **PIC/S PI 041-1:** Clarifies that companies should "select software that includes appropriate electronic audit trail functionality" and should "endeavour to purchase and upgrade older systems to implement software that includes electronic audit trail functionality" [4]. This guidance effectively establishes audit trails as an expected standard [13].
- **Implication for Global Companies:** In practice, organizations should plan to implement audit trails for all GMP-relevant systems regardless of geographic location [12, 14]. The risk assessment should inform decisions about audit trail scope, detail, review frequency, and retention, not whether to have an audit trail [12, 19].

3.3. Review Frequency: Specificity vs. Flexibility

- **FDA Guidance:** The FDA's data integrity guidance provides risk-based principles but does not mandate specific review frequencies [1]. The guidance indicates that critical data supporting batch release should have audit trails reviewed before release, and other systems should have review frequency determined through risk assessment [1].
- **EU GMP Annex 11:** Requires "regular review" but does not define what "regular" means [8]. This lack of specificity has been widely criticized as creating ambiguity [9, 10].
- **PIC/S PI 041-1:** Establishes that "critical audit trails related to each operation should be independently reviewed... prior to batch release" [4]. This creates a clearer expectation for at least one category of systems [15].
- **Draft EU Annex 11 Revision:** Proposes to add guidance stating that the higher the criticality of the system, the more frequently audit trails should be reviewed [10]. While this represents improvement, it still leaves room for interpretation [10].

Industry Practice: Many organizations have adopted a tiered approach [12, 19]:

- **Tier 1 (Critical systems):** Review before batch release or product disposition
- **Tier 2 (Important systems):** Monthly or quarterly review
- **Tier 3 (Supporting systems):** Semi-annual or annual review
- **Tier 4 (Minimal GMP impact):** Review triggered by events or audits

The specific categorization and frequencies should be based on documented risk assessment considering factors such as data criticality, system reliability, access controls, and historical compliance record [12, 19].

3.4. Review Personnel: Qualifications and Roles

- **FDA Guidance:** States that "personnel who are responsible for and knowledgeable about the data being recorded in the audit trail, such as process owners, should review the data" [1]. Management should review audit trails as needed [1].
- **EU/MHRA Interpretation:** The MHRA guidance discusses "Second Person Review" and indicates that audit trail review should be part of this process [3]. There is emphasis on independence—the person reviewing audit trails should not be the same person who generated the data [3].
- **PIC/S PI 041-1:** Indicates that audit trail review should be "independent" and conducted as part of broader record review processes [4].
- **Quality Unit Involvement:** Both FDA and EU regulations emphasize the role of the quality unit in ensuring data integrity [1, 4]. Quality unit oversight of audit trail review programs, including periodic assessment of review effectiveness, is expected [4, 14].

Implication for Global Companies: Organizations need to clearly define [14]:

- Who performs initial audit trail review (typically process owners or data reviewers)
- What constitutes adequate "knowledge about the data"
- How independence is demonstrated when required
- The role of the quality unit in oversight and spot-checking
- Mechanisms for escalation when issues are found

Training requirements for audit trail reviewers should be documented and personnel should be qualified through a combination of education, experience, and specific training on the systems and processes under review [1, 4].

3.5. Technology and Tools: Manual vs. Automated Review

- **Regulatory Flexibility:** Neither FDA 21 CFR Part 11 nor EU GMP Annex 11 prescribes specific methods or tools for audit trail review [2, 8]. Organizations have flexibility to use manual review, automated tools, or hybrid approaches [16, 17].
- **Practical Necessity:** Given the volume of audit trail data in modern pharmaceutical operations, purely manual review is increasingly impractical [15, 16]. Risk-based approaches and automated tools have become operational necessities [17].

- **Validation Considerations:** When automated tools are used for audit trail review, regulatory authorities expect [1, 4]:
  - The tools themselves should be validated according to their intended use and risk
  - Algorithms and filtering logic should be documented and justified
  - Users should be trained on proper tool use
  - The tools should be maintained under change control
  - Periodic verification that tools are functioning as intended
- **Emerging AI/ML Applications:** Artificial intelligence and machine learning technologies are increasingly being explored for audit trail analysis [17, 18]. These technologies offer potential to identify patterns, anomalies, and risks that would be difficult or impossible to detect through manual review [17, 19]. However, their use raises questions about validation, explainability, and regulatory acceptance [18].

4. Challenges for Multinational Pharmaceutical Companies

4.1. Operational Complexity and Resource Requirements

Multinational pharmaceutical companies face extraordinary complexity in implementing and maintaining audit trail review programs across global operations [12, 13, 14].

4.1.1. Scale of the Challenge

A typical large pharmaceutical company may operate [12, 16]:

- 50-100 manufacturing sites across multiple continents
- 500-1,000 GMP-relevant computerized systems per major site
- 10,000-100,000 audit trail entries generated per system per day
- Multiple enterprise systems (ERP, QMS, LIMS) with global scope
- Diverse technology platforms and vendors

This scale creates significant resource requirements for audit trail review [12, 16]. If each system requires periodic review, and each review requires qualified personnel time, the cumulative burden can be substantial [14].

4.1.2. Staffing and Competency

Organizations must ensure adequate staffing with appropriate qualifications to conduct audit trail reviews [1, 14]. Challenges include:

Skill Requirements: Reviewers need knowledge of [1, 4]:

- The specific system being reviewed
- The process or operation the system supports
- Data integrity principles and regulatory requirements
- How to interpret audit trail data and identify anomalies
- Escalation procedures when issues are found

Training Burden: As systems evolve and personnel turnover occurs, ongoing training is required [4, 14]. For global organizations, training must be developed, translated, and delivered across multiple languages and time zones [13, 14].

Competing Priorities: Quality control and operational personnel who are expected to review audit trails have many competing responsibilities [14]. Audit trail review can be viewed as a compliance burden rather than a value-added activity, potentially affecting the quality and thoroughness of reviews [19].

4.1.3. Technology Infrastructure

Effective audit trail review requires supporting technology infrastructure [16, 17]:

- **System Capabilities:** Not all legacy systems have robust audit trail functionality or user-friendly review interfaces [16]. Organizations may need to invest in upgrades, replacement systems, or third-party audit trail management tools [16, 17].

- **Data Analytics Platforms:** To manage the volume of audit trail data and enable risk-based review, organizations increasingly implement data analytics platforms that aggregate audit trail data from multiple systems [16, 17]. These platforms require:
  - Integration with source systems
  - Data warehousing capabilities
  - Analytical and reporting tools
  - Security and access controls
  - Validation and ongoing maintenance [16]
- **Global Accessibility:** For global organizations, audit trail data must be accessible to reviewers in different geographic locations while maintaining appropriate security and data privacy controls [13]. Cloud-based solutions and global data centers present both opportunities and challenges [17].

4.2. Inconsistent Regulatory Interpretations

4.2.1. Agency Variations

Different regulatory agencies, even within the same geographic region, may have varying interpretations and enforcement approaches [5, 13]:

- **FDA District Offices:** While FDA headquarters provides guidance, individual district offices and investigators may have different interpretations or areas of focus [5]. Some may emphasize audit trail review frequency, others may focus on the qualifications of reviewers, and others may be particularly concerned with evidence of follow-up on identified issues [5].
- **EU Member States:** Although EU GMP Annex 11 applies across the European Union, individual member state authorities may emphasize different aspects during inspections [13]. Some are known for particular rigor regarding data integrity, while others may focus more on process validation or quality systems [3].
- **Cultural and Language Factors:** In global operations, regulatory interpretations may be influenced by local cultural norms, language differences, and translation challenges [13]. What is considered a "regular review" in one culture may have different connotations in another [12, 13].

4.2.2. Evolution Over Time

Regulatory expectations regarding audit trail review have evolved significantly over the past decade [5]:

- **Increased Scrutiny:** In the early years following 21 CFR Part 11 and Annex 11 implementation, regulatory focus was primarily on whether audit trails existed [5]. Current focus has shifted to whether audit trails are reviewed, how effectively they are reviewed, and what actions are taken in response to findings [1, 3, 5].
- **Data Integrity Emphasis:** High-profile data integrity cases have led to heightened regulatory attention globally [5, 6]. What might have been considered a minor observation several years ago may now result in warning letters or import alerts [5, 6].
- **Expectation Creep:** There is a perception in industry that regulatory expectations have increased beyond what is explicitly stated in regulations [12]. For example, while regulations require "regular review," some inspectors may question why reviews are quarterly rather than monthly, or why certain categories of systems are reviewed less frequently than others [12, 19].
- **Keeping Pace:** Organizations must continuously monitor regulatory trends, inspection observations, warning letters, and industry guidance to ensure their programs remain current [5, 14]. This requires dedicated resources and mechanisms for communicating updates across global operations [14].

5. Emerging Technologies and Future Trends

5.1. Artificial Intelligence and Machine Learning in Audit Trail Review

The volume and complexity of audit trail data in modern pharmaceutical manufacturing has created an environment where artificial intelligence (AI) and machine learning (ML) technologies offer significant potential value [17, 18].

5.1.1. Current Applications

- **Anomaly Detection:** ML algorithms can be trained to identify unusual patterns in audit trail data that may indicate data integrity issues, system malfunctions, or procedural non-compliance [17]. For example:
  - Multiple users logging in with same credentials

  - Data entries outside normal working hours
  - Unusual patterns of data modification or deletion
  - Rapid sequences of changes inconsistent with normal workflow [17]
- **Pattern Recognition:** AI can identify patterns across large datasets that would be impossible for human reviewers to detect [17, 18]. This includes:
  - Correlation of audit trail events with process deviations or quality events
  - Identification of users or systems with higher rates of modifications
  - Detection of systematic issues affecting multiple products or batches [17]
- **Predictive Analytics:** ML models can predict where data integrity risks are highest, enabling focused review efforts [17, 18]:
  - Systems or users with elevated risk based on historical patterns
  - Time periods when issues are more likely (e.g., month-end, quarter-end)
  - Processes or products with higher variability

5.1.2. Benefits and Value Proposition

- **Efficiency:** AI/ML tools can process vast amounts of audit trail data in minutes that would take human reviewers days or weeks [17, 18]. This enables more comprehensive review with less resource investment [17, 19].
- **Effectiveness:** Automated systems can detect subtle patterns and anomalies that humans might miss, particularly in large, complex datasets [17]. This potentially improves detection rates for data integrity issues [18, 19].
- **Consistency:** Automated review is consistent and not subject to human factors like fatigue, bias, or varying interpretation [17].
- **Scalability:** Once developed and validated, AI/ML tools can be deployed across multiple sites and systems with relatively low marginal cost [17, 18].
- **Real-Time Monitoring:** AI systems can operate continuously, providing real-time or near-real-time monitoring and alerting rather than periodic retrospective review [17].

Current research have demonstrated that risk-based approaches enhanced by AI/ML technologies can provide superior data integrity assurance compared to traditional manual review methods, while simultaneously reducing resource burden. Study of multiple pharmaceutical companies showed that AI-augmented audit trail review identified 300% more potential data integrity issues while reducing review time by 60% [19].

5.1.3. Challenges and Considerations

- **Validation:** AI/ML systems used in GMP environments require validation [18]. However, traditional computerized system validation approaches may not be fully adequate for AI/ML systems that learn and evolve [18]. Key validation challenges include:
  - Demonstrating that the algorithm performs as intended across the full range of expected inputs
  - Ensuring that model updates or retraining don't introduce unintended consequences
  - Validating the quality and representativeness of training data
  - Testing edge cases and failure modes [18]

Regulatory guidance on AI/ML validation in pharmaceutical manufacturing is emerging but not yet comprehensive [18]. The 2025 EU GMP Annex 22 draft on Artificial Intelligence represents a significant step in providing regulatory framework [10, 18].

- **Explainability:** Many advanced ML techniques (deep learning, neural networks) operate as "black boxes" where the reasoning behind specific outputs is not transparent [18]. Regulatory authorities and quality professionals may be uncomfortable relying on systems they cannot fully understand or explain [18].

The concept of "explainable AI" (XAI) has emerged to address this concern, with techniques that provide interpretable explanations for AI decisions [18]. For pharmaceutical applications, explainability is particularly important for:

  - Demonstrating compliance during regulatory inspections
  - Investigating specific findings or alerts
  - Building user trust and acceptance
  - Enabling continuous improvement [18]

- **Regulatory Acceptance:** While there is growing regulatory interest in AI/ML for pharmaceutical applications, explicit guidance on acceptable use cases, validation requirements, and documentation is still developing [18]. Organizations implementing AI/ML for audit trail review should:
  - Engage early with regulatory authorities through pre-submission meetings or pilot programs
  - Document thoroughly the rationale, design, validation, and performance monitoring
  - Maintain human oversight and decision-making authority
  - Be prepared to demonstrate that AI/ML augments rather than replaces appropriate human review [18]

5.2. Proposed Harmonization Framework

Based on the comparative analysis and identified challenges, a practical framework for harmonizing audit trail review practices across global operations should include [12, 14, 19]:

5.2.1. Risk-Based System Categorization

Implement consistent methodology for categorizing systems [12, 19]:

- **Tier 1 (Critical):** Systems directly impacting product quality or patient safety
  - Review frequency: Before batch release [1, 4]
  - Reviewer: Process owner + QC review
  - Documentation: Electronic sign-off in batch record
- **Tier 2 (Important):** Systems with significant GMP impact
  - Review frequency: Monthly [19]
  - Reviewer: Process owner or designee
  - Documentation: Review checklist or report
- **Tier 3 (Supporting):** Systems with indirect GMP impact
  - Review frequency: Quarterly [19]
  - Reviewer: System owner
  - Documentation: Summary report
- **Tier 4 (Minimal):** Systems with minimal GMP relevance
  - Review frequency: Annual or triggered by events [19]
  - Reviewer: IT or system administrator
  - Documentation: Annual certification

5.2.2. Global Standards with Regional Flexibility

- **Core Global Requirements [12, 14]:**
  - All GMP-relevant systems must have audit trails [2, 4, 8]
  - Audit trails must capture modifications and deletions (and preferably creation) [2, 8]
  - Risk-based categorization using consistent methodology [12, 19]
  - Minimum review frequencies by tier [1, 4, 19]
  - Qualified reviewers with documented training [1, 4]
  - Documentation of reviews and findings [1, 4]
  - Quality unit oversight [1, 4]
- **Regional/Site Flexibility [12, 14]:**
  - Specific procedures adapted to local context
  - Local language and terminology [13]
  - Integration with local systems and processes
  - Timing of reviews within defined frequency ranges

5.2.3. Technology Enablement Strategy

- **Short-Term (1-2 years) [16, 17]:**
  - Deploy enterprise audit trail management platform
  - Implement automated data aggregation
  - Develop standard reports and dashboards
  - Begin pilot of AI/ML capabilities [17, 18]
- **Medium-Term (3-5 years) [17, 18]:**
  - Scale AI/ML from pilot to production
  - Implement real-time monitoring for critical systems

- Optimize based on performance metrics
- Enhance user experience and adoption

- **Long-Term (5+ years) [17, 18]:**
  - Achieve "data integrity by design" maturity
  - Full integration of AI/ML across all tiers
  - Predictive analytics and proactive risk management
  - Continuous evolution with technology advances

6. Recommendations and Conclusions

6.1. Recommendations for Industry

6.1.1. Strategic Recommendations:

- **Adopt Global Standards Meeting Highest Requirements** - Implement audit trails capturing create/modify/delete globally to satisfy both FDA and EU requirements [2, 8, 12]
- **Invest in Technology Enablement** - Deploy audit trail management platforms and AI/ML capabilities to enable effective, efficient review at scale [16, 17, 18]
- **Implement Risk-Based Approaches** - Focus resources on highest-risk systems and data using documented, consistent risk methodology [4, 12, 19]
- **Build Data Integrity Culture** - Reinforce that technology and procedures alone are insufficient; sustainable compliance requires organizational culture change [14, 19]
- **Establish Governance and Continuous Improvement** - Create cross-functional oversight with clear accountability and metrics-driven improvement [4, 14]

6.1.2. Tactical Recommendations [1, 4, 20]:

- Include comprehensive audit trail requirements in user requirements specifications
- Validate audit trail functionality as part of system qualification
- Ensure audit trails are enabled and locked before production use
- Provide role-based training with competency assessment
- Document reviews consistently using standardized templates
- Investigate findings promptly and share lessons learned

6.2. Recommendations for Regulatory Authorities

- **Enhance Clarity on Review Frequency** - Provide more specific guidance with examples while maintaining risk-based flexibility [1, 8, 10]
- **Provide Guidance on Emerging Technologies** - Develop comprehensive guidance on AI/ML validation, acceptable applications, and documentation requirements [10, 18]
- **Harmonize Core Requirements** - Continue international collaboration through ICH and PIC/S toward greater alignment on fundamental requirements [4, 13]
- **Leverage Mutual Recognition** - Expand programs allowing regulatory reliance to reduce duplication [13]
- **Provide Regulatory Flexibility for Innovation** - Establish pilot programs and pre-submission pathways for novel approaches [18]

7. Conclusion

This comprehensive analysis reveals both significant challenges and promising opportunities in harmonizing global audit trail review practices. While fundamental regulatory differences exist between FDA 21 CFR Part 11 and EU GMP Annex 11—particularly regarding scope (create vs. modify/delete), mandatory vs. risk-based implementation, and review frequency specifications—practical harmonization is achievable through strategic approaches that meet the most stringent requirements.

The path forward requires:

- Risk-based frameworks that focus resources on highest-value activities
- Technology investments that enable comprehensive review at practical cost
- Governance structures ensuring accountability and continuous improvement

- Quality culture where data integrity is embedded in organizational DNA
- Ongoing regulatory intelligence and adaptation to evolving expectations

Emerging technologies, particularly AI and machine learning, offer transformative potential for audit trail review. However, their implementation must be thoughtful, well-validated, and accompanied by appropriate human oversight [18]. Research has shown that organizations adopting these technologies strategically can achieve superior compliance outcomes while reducing resource burden.

As the pharmaceutical industry continues its digital transformation, audit trail review will remain a critical control in the data integrity framework. Organizations that view this not as a compliance burden but as an opportunity to strengthen systems, processes, and culture will be best positioned for success in an increasingly complex global regulatory environment. Through continued collaboration—within organizations, across industry, and with regulatory authorities—the sector can establish harmonized, effective, and efficient programs that truly protect data integrity and, ultimately, patient safety.

Compliance with ethical standards

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The authors declare no conflicts of interest

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