



# Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland

A dissertation submitted in partial fulfilment of the requirements for the degree of

**MSc in Pharmaceutical Business & Technology**

**Innopharma Labs Faculty of Science**

**Griffith College**

# Candidate Declaration

Candidate Name: Stephen Devlin

I certify that the dissertation entitled:

Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland, submitted in partial fulfilment of the requirements for the degree of MSc in Pharmaceutical Business & Technology is the result of my own work and that where reference is made to work of others, due acknowledgment is given.

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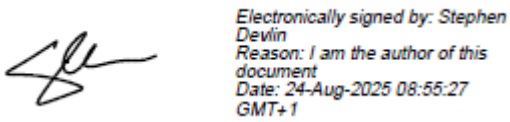


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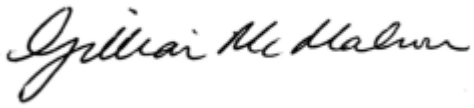

Date: 24 Aug 2025

Acknowledgements

I would like to thank my supervisor Gillian McMahon and the Faculty in Griffith College for their help and guidance in the completion of this dissertation. I would also like to thank all those that participated in the collection of the primary data through interviews to support this work.

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## Acronyms & Abbreviations

| Abb. | Description |
|---|---|
| ACP / ACC | Automation Change Pack / Automation Change Control (site specific change documentation for automation). |
| AI | Artificial Intelligence. |
| ALCOA+ | Attributable, Legible, Contemporaneous, Original, Accurate (+ Complete, Consistent, Enduring, Available). |
| Annex 11 | EU GMP Annex 11 (Computerised Systems). |
| API | Application Programming Interface |
| CAPA | Corrective and Preventive Action. |
| CFR | Code of Federal Regulations (21 CFR Part 11). |
| CMMS | Computerised Maintenance Management System |
| CSV | Computerised System Validation. |
| DCS | Distributed Control System |
| DI | Data Integrity. |
| EBR | Electronic Batch Record. |
| eLogs | Electronic Logbooks. |
| EMA | European Medicines Agency |
| ERES | Electronic Records / Electronic Signatures (21 CFR Part 11 scope). |
| ETL | Extract, Transform, Load (data pipeline process). |
| FDS | Functional Design Specification. |
| FDA | U.S. Food and Drug Administration. |
| GAMP 5 | Good Automated Manufacturing Practice guide (ISPE). |
| GMP | Good Manufacturing Practice. |
| GxP | “Good practice” family (e.g., GMP, GLP, GCP). |
| HDS | Hardware Design Specification. |
| ICH Q9 | International Council for Harmonisation guideline on Quality Risk Management. |
| IQ/OQ/PQ | Installation / Operational / Performance Qualification. |
| ISPE | International Society for Pharmaceutical Engineering. |
| LLM | Large Language Model (type of AI, e.g., chatbots). |
| MES | Manufacturing Execution System. |
| MCS | Manufacturing Control System |
| OT | Operational Technology |
| PI System | (AVEVA/OSIsoft) Plant Information data historian/visualisation platform. |
| QMS | Quality Management System. |
| QRM | Quality Risk Management. |
| QA | Quality Assurance |
| RQ | Research Question |
| SCADA | Supervisory Control and Data Acquisition. |
| SDS | Software Design Specification |
| SLAs | Service Level Agreements. |
| SME | Subject Matter Expert. |
| SOP | Standard Operating Procedure. |
| SSPE | Small Scale Process (Equipment). |
| URS | User Requirements Specification. |

| Abb. | Description |
|---|---|
| Veeva Vault | Cloud QMS platform used for change/deviation/CAPA docs. |
| VPE | Vendor Process Equipment. |
| WI | Work Instruction. |
| XAI | Explainable Artificial Intelligence |

*Table 1- Acronyms & Abbreviations*

# ABSTRACT

Integration of infrastructure and interconnection of computerised systems in pharmaceutical manufacturing in Ireland is ever-increasing. Organisations are collating data from multiple GxP (Good Practice) systems to generate large datasets from computerised systems. This collation of data is to support the drive for increased contextualisation of the entire manufacturing process for the purpose of delivering increased efficiencies and exploring new methods of production. Despite these advances, and to satisfy current regulatory requirements manual review of systems events continue to be the norm, formerly isolated systems critical to the development of pharmaceutical product can interface to archives and historians but the event logs and audit trails, crucial in maintaining compliance and quality are largely required to be manually investigated by trained personnel. This research was undertaken to investigate current practices of this type of review and capture the awareness of professionals tasked with supporting, executing or reviewing these tasks. The research also explores modern solutions, attitudes and concerns to using advanced technologies such as validated scripting tools and AI models to understand how academic research, industry practices and professionals tasked with supporting these logs for regulatory purposes feel about their use. The research also proposes a framework for the implementation of different methods of review to increase the efficiency, consistency and effectiveness of the task, to assign potential owners and distribute actions.

# 1. Introduction

The title of this dissertation is the 'Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland', this title was chosen because of the field the author worked in in the life sciences industry as an automation engineer. Expertise knowledge was gained as an administrator in GxP systems and more formally as a manufacturing data engineer. Working in GxP environments whether it is good manufacturing, documentation, laboratory or clinical practice requires a level of due diligence in every aspect of the administration of computerised systems, the industry adopts GxP to ensure that products are developed, manufactured, and maintained in compliance with regulatory expectations while safeguarding patient safety and product quality. Encompassing GxP frameworks provides a structured approach to controlling processes, ensuring data integrity, and maintaining traceability throughout the product lifecycle (ISPE, 2022). These practices are essential for meeting global regulatory requirements, reducing risk, and ensuring that products are consistently safe, effective, and reliable for patient use. Several years ago, the authors role was to ensure the systems administered provided a consistent performance, that the system maintained compliance and its qualified state, that change management was implemented with full transparency and that the audit requirements were satisfied and retrievable for review purposes whether from the system and its event logs or from the supporting documentation. This task required the constant monitoring of disparate systems connected via computerised infrastructure (accessing file paths, remote access, etc.) but not interconnected to each other. Systems in manufacturing are now required to be interfaced, that all former data 'siloes' communicate their manufacturing data with each other and provide the ability to view and contextualise complete manufacturing datasets to provide better analysis. The 'smart' factory promises the ability to control with a higher precision predictive maintenance, asset tracking, inventory management, quality control, process monitoring, energy efficiency, and supply chain optimisation all built on the ability to harness data from all aspects of the manufacturing process (Soori *et al.*, 2023). But, as in the course of these activities it has been hypothesised that there are aspects of this transformation that have not kept pace with the improvements, regulatory requirements and the personnel responsible for them in the life sciences industry in Ireland.

Many of these systems are small but vital components of the manufacturing process. They test samples from batches to determine cell count or viability, examine filters used in production, or generate purified water for manufacturing. The ability to review the manufacturing or result data generated by these systems is critical to achieving the connected factory vision, while access to the associated audit and event data remains central for maintaining compliance with regulatory responsibilities. These reviews require the expertise of subject matter experts (SMEs) and rely on well-defined workflows to ensure data integrity and regulatory alignment.

Mostly these practices remain rooted in traditional approaches. Manual investigations of ever increasing datasets continue to be the norm, despite growing industry discussions about the role of advanced technologies in review processes. Regulatory guidance, such as that from the FDA, advises caution in adopting emerging technologies like artificial intelligence for these activities (FDA, 2025b). Against this

backdrop, the purpose of this research is to assess the perspectives of SMEs who work with and understand these systems focusing on their views regarding the importance of accuracy and consistency in the review process, their opinions on current practices, their openness to potential digital and automated solutions, and their perceptions of the risks associated with changes to review methodologies.

This background below is to provide an understanding of where the industry was, how it is presently and its future direction of travel.

## 1.1. Background

Industry 3.0, also known as the third industrial revolution, was marked by the introduction and development of digital technology, leading to significant changes in manufacturing and production processes (Dima, 2021). The use of controllers and automation reduced manual intervention in manufacturing, enabling industry to adopt more efficient and faster production methods.

With the advent of Industry 4.0, these automated processes which once operated independently after configuration are now expected to be interconnected with other systems and technologies. This integration is intended to drive greater efficiency, enhance established production methods, and leverage generated data for improved decision making (Xu *et al.*, 2021).

Industry 5.0, still in its early stages, aims to combine advanced technology with human creativity. It emphasises human centric design, sustainability, and resilience. The focus is on meaningful collaboration between humans and machines for more personalised, ethical, and sustainable manufacturing practices (Xu *et al.*, 2021).

The interconnection of what were once isolated control and measurement systems can transform a process and create efficiencies to maximise output and support operations. Reducing the complexity of scheduled activities in manufacturing delivers a better quality of life for end users and helps develop datasets that can be used to further perfect a pharmaceutical product.

Peripheral devices and control systems where data is collected and stored such as bench top laboratory equipment require lifecycle management of data and system performance to maintain the qualified status. As a result of the advancements of industry 4.0 & 5.0, the results generated on these systems are increasingly integrated into governing batch or product control systems to reduce manual transcription, and the burden of responsibility from operators of the process. Even with the increasing availability of data and more integration of these systems, traditional review methods remain prevalent in validation.

These approaches still rely heavily on manual inspection to determine whether a product or system has maintained its validated or qualified state. Periodic or investigative reviews require detailed examination of audit trails, log data, and results to ensure no part or instrument has deviated from qualified change management protocols.

In line with evolving digital capabilities, the concept of RBE (Review by Exception) is becoming increasingly relevant within pharmaceutical validation practices. Rather than manually reviewing all system data, this approach focuses only on investigating flagged anomalies, such as deviations, out of specification results, or critical alarms. When underpinned by validated systems and robust data integrity controls, Review by Exception offers a more efficient and targeted means of ensuring compliance. It aligns well with the growing use of electronic batch records and integrated manufacturing execution systems (MES), allowing quality assurance personnel to prioritise their attention where it matters most. For small scale and vendor supplied process equipment, where manual oversight has traditionally been resource intensive, this method could provide a scalable and risk based alternative provided the supporting infrastructure ensures data accuracy and traceability.

Figure 1 provides a broad overview of key issues in current pharmaceutical manufacturing. Field layer controllers and computerised systems such as the ones shown have the ability to send the manufacturing or result data to a centralised hub, a historian where all the data collated is stored and archived either directly or through a gateway or middleware. Tools for interfacing or communicating this type of data such as industry standards like OPC or XML have been available for most systems in recent years but this rarely extends down to the system log data generated, this data has been traditionally presented in a different format, in human readable .pdf, (Portable Document Format) .txt (Text) or .csv (Comma Separated Values) and available locally or for export to fulfil review purposes and meet regulatory requirements.

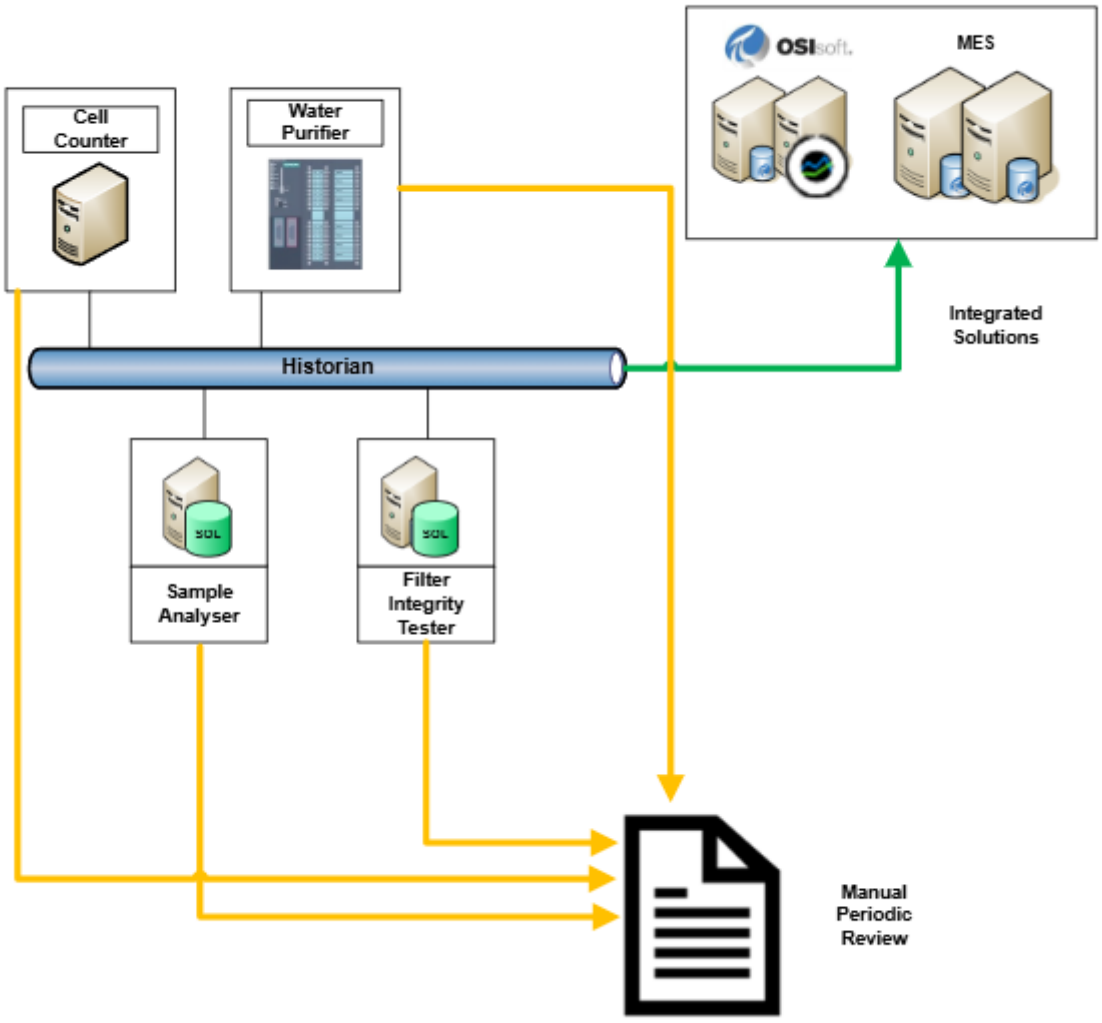


*Figure 1 - Manual Review and Integrated Solutions (authors own)*

## 1.2. Aims and Objectives of the Dissertation

Data collection is growing exponentially within the pharmaceutical industry (Jankovic, 2023) but the periodic review process for many systems is still a manual process for validation engineers required to verify data against source systems and change management updates.

With the advancement of data retrieval and interaction of systems, requalification and periodic reviews of equipment requires different approaches, the traditional method of filtering all events manually to determine the compliance of a system to the use of automated tools such as python scripts to clean & query data based on defined variables or the use of Artificial Intelligence (AI) large language models (LLM) such as Chat GPT to provide via bots the results of any review and identify anomalies. (Rao, 2022)

## 1.3. Aim

To evaluate and propose modern, data driven approaches to periodic review validation practices for small scale and vendor process equipment in pharmaceutical manufacturing, with a focus on improving efficiency, accuracy, and compliance through the use of automation, data querying, and AI technologies.

## 1.4. Objectives

1. To assess current manual periodic review validation practices used in the pharmaceutical industry, particularly for small scale and vendor supplied equipment.

2. To understand the regulatory requirements of performing periodic review in a regulated environment

3. To explore the capabilities of automated data querying tools (e.g., Python scripts) in filtering and validating system data against defined parameters.

4. To investigate the application of artificial intelligence tools, such as large language models and chatbots, in assisting validation review processes.

5. Determine organisational readiness and understand barriers to implementing automated or AI supported validation review practices.

6. Develop a framework or set of recommendations for implementing data driven, scalable validation practices in highly regulated environments, ensuring data integrity and traceability.

## 1.5. Research Questions

How can data automation and AI driven tools be integrated into periodic review validation practices to improve the accuracy, efficiency, and regulatory compliance of reviews for small scale and vendor process equipment in pharmaceutical manufacturing?

1. What are the current challenges and limitations associated with manual periodic review validation practices for small scale and vendor supplied equipment?

2. What are the regulatory and data integrity requirements for performing periodic review specifically towards audit trail review?

3. What opportunities exist to leverage data automation tools (e.g., Python scripts, dashboards) to improve the filtering, validation, and traceability of periodic review data?

4. How could artificial intelligence tools, such as large language models or chatbots, be applied to support or augment periodic review validation processes?

5. What is the perceived organisational readiness and if there are any barriers to implementing automated and AI supported validation review practices in highly regulated environments?

6. What framework or recommendations can be developed to guide the integration of data automation and AI driven tools into periodic review practices, while ensuring data integrity, traceability, and regulatory compliance?

## 1.6. Structure of Research

### 1.6.1. Chapter 1: Introduction

This chapter gives an overview of industrial revolutions from Industry 3.0, characterised by automation and digital technology, through Industry 4.0, which focuses on interconnected and data driven systems for enhanced efficiency & Industry 5.0 which aims to balance advanced technology with human creativity, sustainability, and collaboration, discussing the integration of data from systems along with the limitations of regulatory requirements and emerging approaches to resolving the current inefficiencies.

### 1.6.2. Chapter 2: Literature Review

This chapter gives an overview of the current practices within the industry and the regulatory requirements to remain compliant, it explores the different aspects of established review processes and emerging practices, and the research already conducted into them. This provides a framework for comparing and contrasting the findings of this study's primary research.

### 1.6.3. Chapter 3: Research Methodology

The aim of this chapter is to describe how the study was carried out. It examines the research paradigms and philosophical approach adopted, then explains the practical aspects of the work, including the target population and the design of the tools used to gather the primary data.

### 1.6.4. Chapter 4: Findings and analysis

In this chapter, the results gathered through primary data collection are presented using data visualisation and analysis techniques to address the research objectives. Quantitative data is analysed using a single method approach.

### 1.6.5. Chapter 5: Conclusion and Recommendations

This chapter summarises the study's conclusions and discusses their implications. It offers practical recommendations for industry stakeholders and regulators, as well as suggestions for future research. Additionally, the chapter addresses the study's limitations.

# 2. Literature Review

# Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland

## 2.1. Research Table

See the below table for an overview of guiding papers and articles supporting the literature review:

| Name | Author | Type | Summary |
|---|---|---|---|
| Part 11, Electronic Records; Electronic Signatures -Scope and Application | FDA, 2003 | Guidance Document | Document describing the requirements from computerised systems, all research has a bearing on this document and similar from EMA |
| Towards enterprise-wide pharma 4.0 adoption | Phiri et al., 2025. | Paper | Provides roadmap for Pharma 4.0, digitising processes, main impact on this research was the introduction of the idea around early collaboration with SMEs |
| Digitalised validation systems as an enabler for quality 4.0 within a medical device manufacturer | McDermott et al., 2024 | Paper | This paper although not around the use of tools and AI was to digitalise paper based validation systems for audit purposes, single source of truth |
| A Harmonized Approach to Performing a Risk-Based Audit Trail Review | Lippke et al., 2022 | Article | This article discussed the risk based approach to audit trail reviews and identification of parameters and determining the rigor of audit trail review as a function of data risk and data impact. |
| ICH Q9 Quality risk management – Scientific guideline | ICH, 2006 | Guideline | This document provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality |
| Review by Exception: Connecting the Dots | Zebib, 2019 | Article | Although MES focussed the analysis of real time review for review by exception, how the process can evolve from paper on glass to RBE using QRM |
| Automation and Data Integrity in Regulatory Submissions: Innovations for Decentralized Clinical Trials | Upputuri, 2025 | Paper | The author explores the data integrity challenges faced by programmers for compliant data processing and assesses the potential use of more automated tools, the conclusions are around getting the balance between advanced technology and security, privacy, data integrity, etc.. |
| AUDIT TRAIL REVIEW: A KEY TOOL TO ENSURE DATA INTEGRITY | eClinical Forum, 2021 | Position Paper | This paper went in-depth to the types of parameters that would need to be assessed in QRM to allow development of automated tools and support better review with visualisation |
| Explainable Artificial Intelligence (XAI) in auditing | Zhang et al., 2022 | Paper | Introduced the concept of explainable AI as a potential way to use models in audit situations. The authors developed tools to support using AI & MLs in audit situations |

*Table 2- Research Table*

## 2.2. Research Topic

This study aims to investigate the current practices of periodic and audit trail review in the Irish Pharmaceutical and Biopharmaceutical industry. It explores current practices, and regulatory concerns, the groundwork that would be required to enable new methods & tools along with newer approaches and the technical and regulatory barriers that may discourage adoption of these advances. The literature review has

been conducted to support the primary research data collection methods and the findings of it will be compared and contrasted with the primary research data captured in chapter 4.

## 2.3. Detailed Literature Review

Reviewed from journal papers, articles and web sites the review explores firstly the current practices and expectations of regulators in review of system event data before talking to the evolution of data and the divergence between integration and compliance activities. To this end, quality review systems are discussed with the focus on rationalising current practices to support the introduction of new methods of data integration. Information on advanced tools and their potential are then discussed before looking at the attitude of regulators to advanced tools for use in the life sciences industry.

## 2.4. Validation Practices in the Pharmaceutical Industry

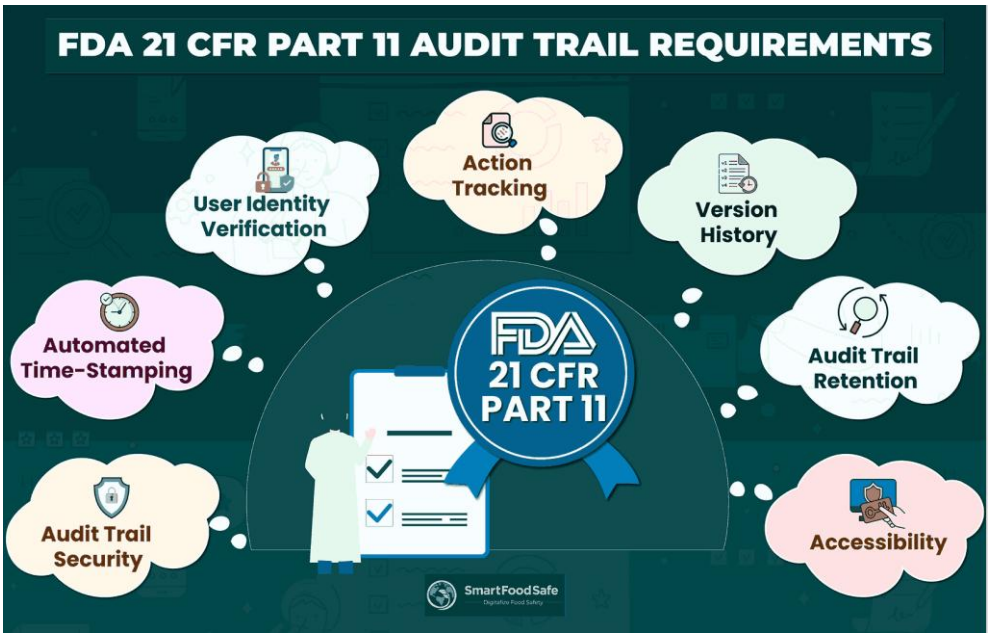


*Figure 2 - 21 CFR Part 11 FDA Audit Trail Requirements (Shabu, 2024)*

Figure 2 above displays the main requirements and considerations for a computer validated system and outlines the key audit trail requirements stipulated under FDA 21 CFR Part 11, which governs the use of electronic records and signatures in regulated environments. These requirements include user identity verification to ensure accountability for actions performed within the system, action tracking to record all operations and changes, and automated timestamping to provide accurate chronological documentation of events (FDA, 2003). Additionally, systems must maintain version history to capture and preserve changes over time, implement audit trail security to safeguard data integrity, and enforce robust audit trail retention policies to ensure long term availability for regulatory review (FDA, 2011). The framework emphasises accessibility, ensuring that audit trails remain readily retrievable and reviewable. These considerations aim to enhance data integrity, transparency, and compliance in electronic record keeping systems used within FDA regulated industries.

Below is an overview of the current validation practices and the regulatory requirements to maintain compliant systems along with some the areas of interest where the 'connected factory' advancements are revolutionising the manufacturing process.

Validation is a fundamental aspect of pharmaceutical manufacturing, ensuring that equipment, systems, and processes consistently operate within predefined parameters to produce products meeting quality standards (FDA, 2011). Periodic review is a critical component of maintaining the validated state of systems over time. Many organisations continue to rely on manual review processes, especially for small scale or vendor supplied equipment, which often lack full integration with enterprise systems (ISPE, 2022).

Audit trails are essential for maintaining data integrity within computerised systems. The FDA mandates that electronic systems must have 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. These audit trails must be retained for a period at least as long as that required for the subject electronic records and must be available for agency review and copying (FDA, 2011). Furthermore, personnel who create, modify, or delete electronic records should not be able to modify the audit trails, ensuring the authenticity and integrity of the data.

The FDA also emphasises the importance of routine audit trail reviews. Audit trails that capture changes to critical data should be reviewed with each record and before final approval of the record. The frequency of audit trail reviews should be based on the complexity of the system and its intended use, ensuring that CGMP requirements are satisfied, and the reliability of the review is proven (FDA, 2018).

Similarly, the EMA's draft revision of Annex 11 underscores the necessity of audit trail functionality in GMP critical systems. The audit trail should automatically log all manual interactions, capturing the identity of the user, the date and time of the change, and the reason for the change. The audit trail functionality should not be editable and all users of the system including users with elevated privileges should not have the ability to disable it, to ensure the integrity of the data. Additionally, the EMA recommends that audit trail reviews should be part of batch release processes, following a risk based approach (EMA, 2021)

These regulatory guidelines highlight the increasing importance of robust audit trail functionalities and periodic reviews in maintaining data integrity and compliance within pharmaceutical manufacturing. The integration of automated systems and adherence to regulatory expectations are crucial for ensuring the reliability and quality of pharmaceutical products.

Traditional validation and review methods, which often rely on extensive manual inspections and rigid processes, can become bottlenecks when applied to modern, data rich environments. As (Sahoo and Lo, 2022) highlight, to fully leverage the benefits of these emerging technologies, regulatory bodies and industry stakeholders must adapt their review processes to maximise efficiency without compromising data integrity, product quality, or patient safety.

## 2.5. The evolving role of data in Validation

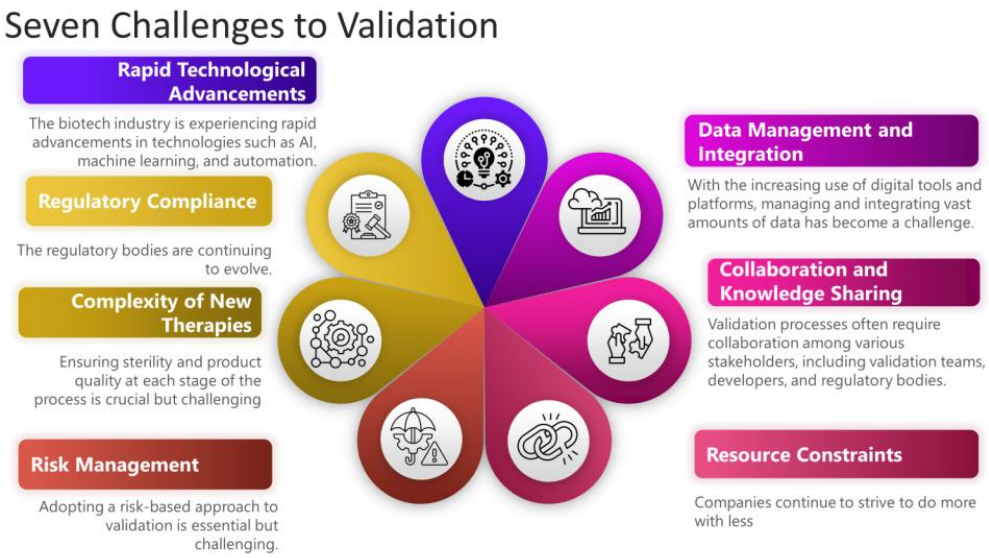


*Figure 3 - Challenges in Validation (Genest, 2024)*

In the above Figure 3 visual - described in the associated article how validation in the biotechnology sector is undergoing a period of significant transformation, driven by a convergence of technological, regulatory, and therapeutic developments. This evolution presents a complex landscape that necessitates new approaches to ensure compliance, product quality, and operational efficiency. As illustrated in Figure 3, seven key challenges define this landscape. Firstly, rapid technological advancements, including AI, machine learning, and automation, are reshaping manufacturing and quality systems, yet require novel validation structures and methodologies to ensure their compliant integration. Secondly, regulatory compliance remains a persistent challenge, with regulatory bodies such as the FDA continually updating guidelines to align with emerging technologies and industry practices. New therapies and the verification of their performance requires attention. In addition, data management and integration have become increasingly complex as the adoption of digital platforms generates vast volumes of data, necessitating advanced analytics and machine learning tools for effective interpretation and risk based decision making. Collaboration and knowledge sharing are also vital, as validation processes require coordinated efforts among diverse stakeholders, including validation teams, developers, and regulators. Compounding these challenges are resource constraints, particularly within smaller biotech organisations, which often face limitations in funding, personnel, and technical expertise. Finally, risk management remains fundamental, demanding robust, lifecycle oriented strategies to identify, assess, and mitigate risks effectively.

The topics covered under this have all relevance for my research but are not mutually exclusive, my focus is on quality and risk management, regulatory compliance, collaboration and technological advances but there is a connecting line bringing these topics together, to understand this the papers researched below attempt to provide a broad view of the status as it is currently in industry.

### 2.5.1. The Intersection of Digital Innovation and Validation in Pharmaceutical Manufacturing

Industry 4.0 and 5.0 have revolutionised manufacturing by integrating advanced digital systems such as automation, real time sensors, and cloud computing to improve productivity, quality, and traceability (Kagermann *et al.*, 2013). The era of the connected factory has enabled the interfacing of data from diverse systems and the capability to harness large sets of previously siloed datasets. This allows manufacturers to compare, contrast, visualise, and leverage data more effectively to support decision making in production. These technologies also provide significant opportunities to strengthen compliance monitoring, including validation processes (Rao, 2022).

However, according to (O'Connor *et al.*, 2025) many validation practices have not evolved at the same pace as these advances in data accessibility. Periodic reviews and, in particular, audit trail review procedures often remain highly manual, resource intensive, and time consuming. This misalignment can result in inefficiencies and the potential for compliance gaps, undermining the benefits of digital transformation.

The pharmaceutical industry is characterised by high profit margins, significant regulatory risk, and costly, complex research and development pipelines, factors which have historically contributed to a conservative approach toward adopting digital innovation. Nonetheless, as described by Phiri *et al.*, the COVID 19 pandemic served as a catalyst for change, accelerating the sector's shift towards digitalisation. As a result, the pharmaceutical industry has emerged as the fastest growing sector in digital adoption since 2020 (Phiri *et al.*, 2025).

Chinmoy describes that integrating advanced technologies across validation and manufacturing processes can support regulatory compliance, improve the identification and resolution of production issues, and enable cost reductions while enhancing collaboration with suppliers and regulatory authorities (Chinmoy, 2024). In this evolving landscape, pharmaceutical organisations must gain a clear understanding of the frameworks, principles, and strategies required for the successful, enterprise wide adoption of advanced data driven tools to maximise their potential benefits (Phiri *et al.*, 2025).

## 2.6. Quality Management Systems

Change can be slow with regard to implementing new technologies, and manufacturers frequently cite regulatory processes as a barrier to innovation (Antony *et al.*, 2021). The introduction of Industry 4.0 technologies, for example, may be perceived as disruptive because they require significant modifications to existing quality management systems and a shift away from traditional QMS structures. Such changes can generate uncertainty and resistance among stakeholders, particularly where established processes are deeply embedded within the manufacturing culture (McDermott *et al.*, 2024).

To overcome these challenges, it is essential to engage the Quality and any other relevant SMEs at the earliest stages of concept development and planning for digital system implementation. Early engagement can help identify potential quality related impacts, ensure alignment with regulatory expectations, and reduce resistance to change. Equally important is forming a cross functional team and involving all relevant

stakeholders from the outset to secure a shared understanding of objectives, roles, and responsibilities, thereby supporting the successful adoption of a digitalised system. (Phiri *et al.*, 2025)

This comprehensive engagement across the manufacturing process, including risk management and assessment activities, is critical not only for maintaining regulatory compliance but also for realising the benefits of technological advancements in terms of efficiency, data integrity, and sustainability (McDermott *et al.*, 2024). To provide confidence in any new approach, risk assessments together with the consideration of audit trail review requirements should be performed. This risk assessment process can be used to determine the need for procedural controls, with those controls documented in the qualification package for new equipment or captured within the change management system for updates to existing equipment. (Lippke *et al.*, 2022). The paper goes on to describe how a robust risk assessment can also help define data integrity elements for a system where audit trail review is adopted as a risk mitigation strategy. Developing and risk assessing rules for implementing digital tools to support audit trail review, and ensuring appropriate contextualisation of the data, should be considered a foundational step in progressing toward full scale implementation of digital tools for ATR (Audit Trail Review) purposes. By following this structured approach, manufacturers can more confidently adopt advanced technologies while ensuring compliance and maintaining product quality (Ullagaddi, 2024).

Identifying the parameters needed for the implementation of a 'robust' audit trail review depend on the ability to understand and plan for having a consistent approach, Quality Risk Management (QRM) can support the delivery of these ideas  and the vehicle for achieving consistency across multiple systems using a pragmatic approach (ICH, 2006).

## 2.7. Quality Risk Management

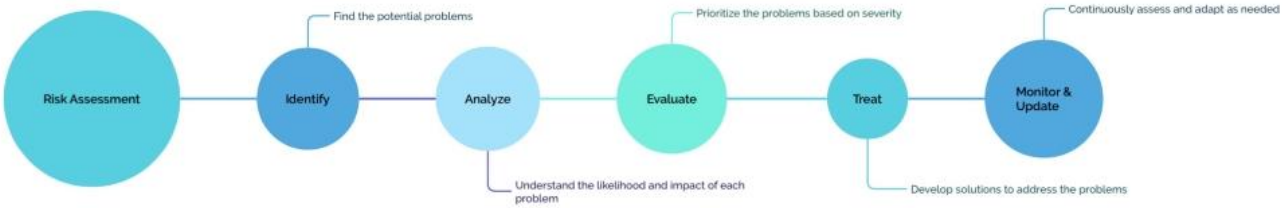


*Figure 4 - Risk Assessment Matrix (Sild, 2024)*

The key elements of the risk assessment (RA) are displayed in

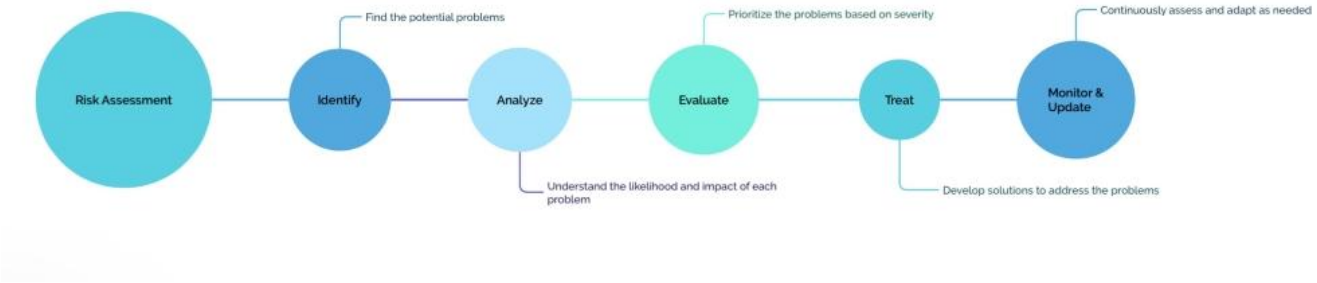


Figure 4, the focus here is on identification of the issues, to then analyse and understand these potential problems and score or evaluate against criteria such as cause of hazard associated with process, the potential harm that could result if hazard occurred, actions or other controls intended to manage, mitigate, defend likelihood of the cause and the controls intended to detect the potential harm or hazard before it impacts data.

QRM is a process of identifying areas of potential risk associated with a product, process, or system, analysing and evaluating risk based on knowledge, appropriately communicating risk, and mitigation of risk when the impact of that risk is unacceptable (Naeem, 2021).

The level of effort, formality and documentation of the QRM process must be commensurate with the level of risk. When the complexity warrants the performance of a formal risk assessment a quality tool designed to facilitate the risk assessment process must be utilised (EMA, 2014). A system must be established to track, control, and archive formal risk assessments performed (FDA, 2023). According to the FDA a framework in which to assess risks in a system would be to initiate the QRM process starting with a risk assessment where the risks are identified, analysed and evaluated, is the first step, secondly work is required to reduce or accept the risk (or value of data being reviewed for audit trail review) to provide the output of the QRM process. Risk review for post batch events can then be scheduled to maintain oversight completing the QRM lifecycle. At each stage communication with stakeholders is required to maintain transparency.(ICH, 2006)

With risks identified, scored and documented review by exception can then be used to increase efficiency in the review process.

## 2.8. Review by Exception as a Strategic Shift


*Figure 5 Review by Exception (Cook, 2025)*

Figure 5 is a graphic based on how the traditional review process is conducted prior to batch release, to ensure the integrity and consistency of the product. Traditional batch review can delay product release by weeks as teams review reports. Live review by exception software such as Emerson's Quality Review Manager identifies issues, enabling auto release and reducing time to market. this approach is accepted as meeting all regulatory requirements and improving outcomes with the benefit of an approved review in almost real time process. (Cook, 2025)

According to a governing organisation like the ISPE, Review by Exception is a modern, risk based validation approach where only flagged anomalies (e.g., deviations or OOS results) are reviewed, rather than all system data (ISPE, 2022). This approach is gaining traction, particularly where systems support reliable data integrity and robust audit trails. For small scale and vendor managed equipment, Review by Exception can reduce the review burden without compromising regulatory compliance (Zebib, 2019).

Large datasets and audit trails for equipment can be extremely hard to review manually, reports and visualisations help reviewers efficiently and effectively examine audit trails by summarising large amounts of detailed data into more easily understood information. Additionally, applying risk thresholds can further enhance the review process by quickly highlighting areas of concern within the audit trail data (eClinical Forum, 2021). Another article from EY refers to Review by Exception (RBE) as representing a strategic evolution in biopharmaceutical manufacturing, addressing rising complexity, workforce challenges, and cost pressures. It talks about traditional paper based review processes being too slow and error prone to support modern lean operations. RBE, supported by electronic batch records and QRM (Quality Review Management), enables faster batch release by focusing human attention on deviations and critical exceptions. This shift reduces review effort, improves data integrity, and supports knowledge transfer in an evolving workforce. (Amery, 2023)

Risk assessment of data or review by exception shares a broadly similar goal, reduce the requirement to investigate full datasets based on an agreed set of parameters determined by analysing the requirements and risk of the activity and the impact of error, the value of reducing menial load on human components of the review process and reducing delays on the approval or release of batch or similar pharmaceutical products (Zebib, 2019). To achieve this the focus must be on the initial phase of any proposed digitalisation or automation process, SMEs must be engaged to understand the risks, review data from a historical context and decide the value of the current review process (Lippke *et al.*, 2022). A baseline of what is required across single systems or having a broad template to administer audit trail reviews on multiple systems is the most important element in the advancement of using automation and data querying tools (Phiri *et al.*, 2025).

## 2.9. Automation and Data Querying Tools in Validation

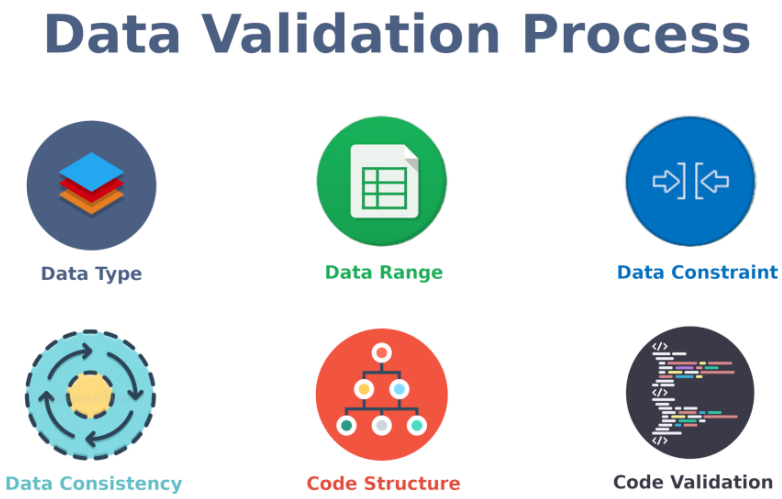


*Figure 6 - The Importance of Data Validation in Data Analysis (Torres, 2024)*

If an agreed set of parameters based on the prioritisation of risk are identified and applied to a dataset such as an audit trail, then consistency on the availability of data, the data itself, its range and type and the method of interaction as displayed in the above Figure 6 become the focus in delivering a digital validation solution.

Numerous studies underscore the potential of using Python scripts themselves as version controlled engines for producing consistent datasets, thereby enabling validation workflows that are inherently reproducible. (Wilson *et al.*, 2017) emphasises script based workflows that begin with raw data and generate outputs through repeatable, documented code minimising variability and maximising transparency. (Ziemann *et al.*, 2023) articulate a framework based on five pillars of computational reproducibility including literate programming, version control, environment capture, and automated execution all of which reinforce the practice of using version controlled Python scripts to deliver consistent results. Additionally, (Schackart III *et al.*, 2024) provide a practical case study in which Python scripts form the reproducible core of a machine learning workflow applied to large biodata sets, tracking both code and execution metadata to ensure deterministic outcomes across analyses

According to (Tupsakhare, 2019) Python has become a foundational tool in the world of automation and scripting, thanks to its exceptional flexibility, user friendliness, and extensive library ecosystem that supports countless tasks. The author examined how Python boosts efficiency in diverse industries by automating repetitive processes, handling complex workflows, and minimising human error. With automation tools using scripting languages like Python being used to streamline validation data analysis, the possibilities can offer a practical bridge between manual reviews and fully AI driven compliance models. These tools can query audit trails, identify system changes, and produce reports based on predefined filters, improving both consistency and efficiency (Upputuri, 2025). With the advantage over AI models in that Python scripts once validated can be managed as per any qualified and compliant system they can then be used to leverage GMP data for analytics giving the end user confidence in their system data (Sartorius, 2022).

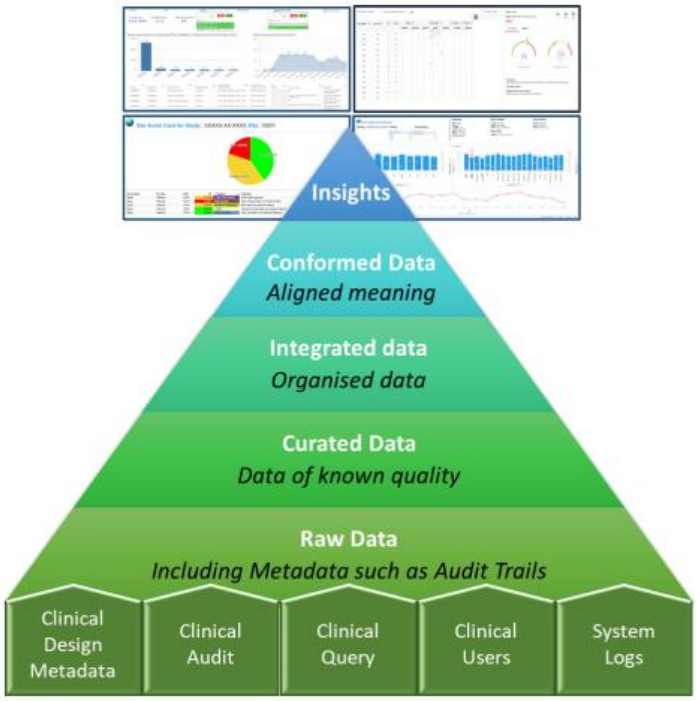


*Figure 7 - Data Maturity Model (eClinical Forum, 2021).*

Figure 7 above displays the 'cleaning' of data and extraction of value to provide insights, when the data is contextualised a greater understanding of underlying issues can be readily assessed, this can only be achieved by rationalising the data (eClinical Forum, 2021). Based on the parameters identified during a QRM process the qualified Python tools can then be used for data cleaning to detect any irrelevant, incorrect, incomplete, inaccurate data in datasets. Data transformation can be implemented to support format change, to allow analysis and aggregation without impacting the source system data but with the ability to make GMP decisions on large data sets.(Gao *et al.*, 2016) . This paper talks to the problems, challenges and issues in not having a clearly defined strategy to use large datasets and increased use of python tools can give the quality assurance in reviewing and use of this data.

### 2.9.1. Lean Six Sigma in Data Validation

To support the introduction of python scripts/tools based on a set of rules with a view to rationalise large datasets, a methodology that could potentially be used is a Lean Six Sigma (LLS) approach. A combination of 'Lean Thinking' a concept coined by John Krafcik in 1987 (Saxena, 2025) developed by the Toyota Motor Corporation which focuses on eliminating non value adding activities, improving efficiency, and fostering a culture of continuous improvement across all organisational levels (Womack and Jones, 1996), and Six Sigma a method of achieving operational excellence by focusing on process improvement and minimising inefficiencies in business (Flint, 2023). Lean Six Sigma (LSS) represents an integrated, data driven methodology designed to enhance process performance by combining the defect reduction focus of Six Sigma with the waste elimination principles of Lean. It employs structured improvement frameworks, most notably the DMAIC cycle (Define, Measure, Analyse, Improve, Control), alongside a range of statistical and analytical tools to systematically identify process inefficiencies and implement sustainable solutions (Womack and Jones, 1996).

The integration of Lean Six Sigma methodologies with Python based data querying and analysis offers a powerful approach to validating large datasets in compliance driven environments. (Pongboonchai-Empl *et al.*, 2025) expand the traditional DMAIC framework by embedding Industry 4.0 technologies such as Python scripts for automated data ingestion, analysis, and reporting into Six Sigma projects, thereby supporting consistent, repeatable outcomes across validation cycles. Similarly, (Fardan, 2023) proposes a unified framework incorporating big data analytics, machine learning, and Lean Six Sigma, in which Python scripting is instrumental in managing large scale data queries under LSS control plans A related case study by (Lambri et al., 2024) highlights how machine learning models driven by Python align with Lean Six Sigma strategies to optimise operational performance through automated analysis of complex datasets. Together, these sources support the thesis that Python scripted workflows, structured within LSS protocols, can ensure consistent, reproducible validation across large datasets a key requirement for high integrity results in regulated manufacturing environments.

## 2.10. Artificial Intelligence, MLs and LLMs in Validation Review

Generative AI has emerged as a powerful solution for optimising audit trail review by helping to prioritise areas of higher risk or concern. (Yao *et al.*, 2024) Not all audit trail data holds equal importance, and even with AI assistance, comprehensive forensic analysis is neither required nor expected by regulators. Instead, companies should align their audit review strategy with broader risk based principles focusing on critical data that directly impacts patient safety or product integrity, identifying potential failure points where data inconsistencies may arise, and highlighting key risk areas that warrant deeper investigation (Lippke *et al.*, 2022). By integrating these priorities, generative AI and other automation approaches can support a more effective review by exception strategy, ensuring that resources are focused where they are most needed while still maintaining regulatory compliance and safeguarding product quality and patient outcomes (Solutions, 2025).

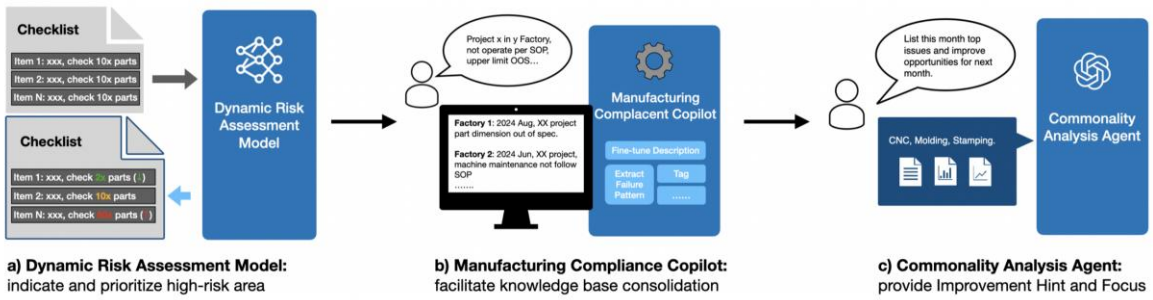


*Figure 8 - Smart audit systems (Yao et al., 2024)*

Early case studies suggest that LLMs can assist in interpreting structured data, summarising reports, and answering user queries through conversational interfaces (Mulla Syed *et al.*, 2024) Regulatory agencies like the FDA are cautiously supportive but stress the importance of validation, transparency, and auditability when AI tools are introduced in GxP environments (FDA, 2025a). (Mundhra *et al.*, 2024) emphasise that AI technologies enhance data integrity by automating the collection and analysis of data, thereby reducing human error as a key aspect of compliance in regulated industries. According to the authors, machine learning algorithms can evaluate production data in real time, allowing manufacturers to detect deviations from expected performance promptly. This functionality supports rapid corrective measures and bolsters the entire quality assurance process. Other potential possibilities can be to arrange and assess large amounts of data to support review by regulating agencies in certain audit situations (Abid *et al.*, 2024).

Apart from validation, transparency, explainability and auditability are factors in using AI to support audit review as are AI reliability to reproduce results, robustness and the concern about the security of sensitive or propriety data (Kokina *et al.*, 2025). These concerns have been explored in papers, articles and books, in relation to the term transparency and explainability in relation to AI is explained as the sharing of information regarding datasets, processes, applications, and outcomes among various stakeholders. On the other hand, AI explainability involves the ability to comprehend how the output of an AI system is generated.(ICAEW, 2023) Explainability is closely linked to interpretability, which focuses on understanding the interactions within a system, including the training processes, data, and learned elements relating to information from datasets and processes. (Ammanath, 2022). The need to communicate how a system returns values when prompted is a concern when required to explain to a regulator (Kokina *et al.*, 2025), to this end the idea of an 'explainable AI'(XAI) (van Lent *et al.*, 2004) would need to be understood. For audit requirements to be sufficient in regard to XAI where sufficiency refers to the amount of audit evidence, while appropriateness pertains to its quality, encompassing factors such as relevance and reliability. Auditors typically cannot rely on definitive evidence but instead use convincing evidence, which is corroborated by information from multiple sources.(Zhang *et al.*, 2022). Another challenge is maintaining the robustness and reliability of machine learning models over time, as models can 'drift' when training data no longer reflects current conditions. Some organisations are experimenting with continuous learning systems to automatically retrain models when drift is detected. In the life sciences industry human oversight still plays a critical role in model recalibration (Falticeanu *et al.*, 2022). Another paper from (Yan *et al.*, 2025) details

the concerns around the potential to leak sensitive data as a result of using LLMs or ML and what security mechanisms would be required to be enabled to mitigate against the risk of sensitive data being shared with unintended entities. A range of options from hardware protections, maintaining data locally with connections to cloud for computational processes to filtering and session isolation where an AI agent security is configured preventing information leakage and model pollution (Yan *et al.*, 2025)

## 2.11. Regulatory and Compliance Considerations

Regulatory agencies such as the FDA, EMA, and PIC/S require that automated systems used in validation processes uphold rigorous standards for data integrity, traceability, and reliability (FDA, 2011; EMA, 2021). Tools leveraged in periodic review must be validated and supported by comprehensive lifecycle documentation, which includes risk assessments, training of users, and clear definitions of intended use. (ISPE, 2022).

According to the FDA's draft guidance on AI, it is crucial to establish credibility for automated tools by planning and documenting the context of use, performance criteria, and maintenance activities to ensure the tools remain fit for purpose across their lifecycle (Niazi, 2025). This is particularly important when using innovative technologies like artificial intelligence or data processing scripts, which must be continuously monitored and periodically re-evaluated to confirm their performance stays aligned with current GxP requirements. Maintaining a traceable, well documented approach enables consistent and defendable compliance with these evolving regulatory expectations. (FDA, 2025). Likewise, new guidance in the form of the new Annex 22 from the EMA attempts to outline the requirements for applying AI and machine learning in the production of active substances and medicinal products. It specifies expectations for model selection, training, and validation. Key focus areas include clearly defining the model's intended purpose, establishing performance criteria, ensuring the quality of training data, and managing the handling of test data. Annex 22 also requires ongoing oversight of AI systems, covering change control, performance monitoring, and processes to enable human review when needed. (EMA, 2025)

From the outset, the annex makes clear that it applies only to static AI models used in GMP systems where product safety, efficacy, and quality could be affected. In other words, it covers AI systems that remain fixed after their initial construction and training. While machine learning may be applied during development to build functionality, once finalised, the system does not continue to evolve. According to the annex, such static systems may be used in GMP critical applications. The annex describes this safeguard as maintaining 'human in the loop' (HITL). Additionally, the principles established for static models should still be considered and applied where relevant. (Calcott, 2025)

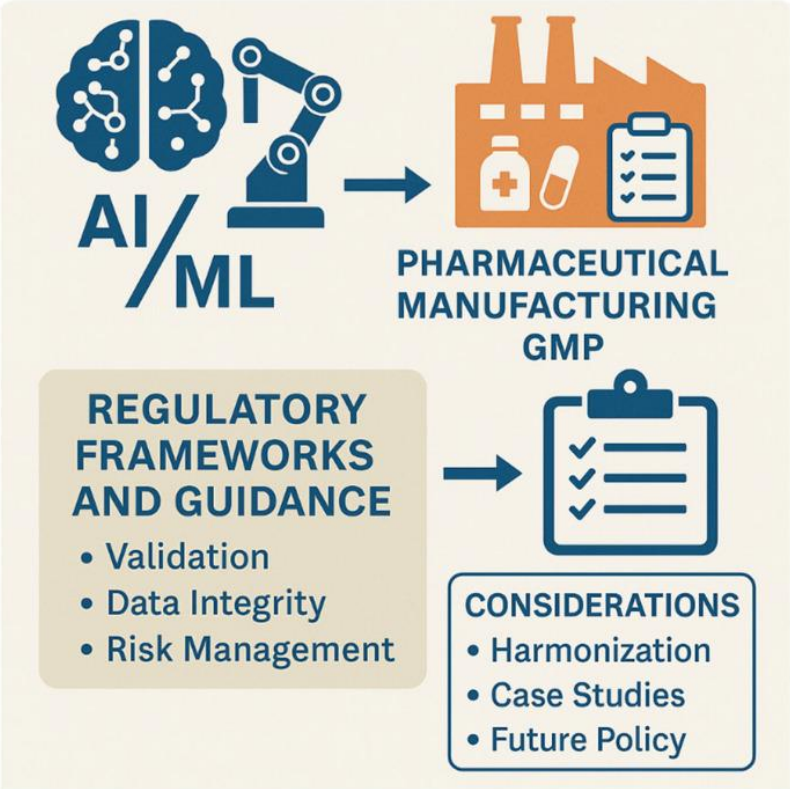


*Figure 9 - Prospective framework for the AI/ML integration in GMP manufacturing (Niazi, 2025)*

The enormous benefits of using tools like AI to develop solutions for the life sciences industry is indisputable but in order to make use of the potentially transformational power of AI, it is critical to establish the correct framework around its use (Ahmed *et al.*, 2020).

Although the landscape for all technology is changing in the era of AI the lack of transparency, validation and consistency across ML algorithms and AI models is a cause for concern(Lambri et al., 2024). Keeping pace with the constantly evolving landscape is a major challenge for regulators and these factors can stunt the progress for some technological solutions developed. This absence of well-defined practices and guidelines, a cautious and risk averse mindset, and the perception that AI technology is unproven and unreliable are key factors hindering broader adoption of AI solutions within the pharmaceutical industry (Vrdoljak, 2022).

## 2.12. Literature Review Findings

As explored in section 2.5 validation in pharmaceutical manufacturing is in a major transition, shaped by converging technological, regulatory, and therapeutic shifts. The landscape is complex and calls for new validation approaches to protect quality, ensure compliance, and boost efficiency. Industry 4.0/5.0 has created connected factories where automation, real-time sensors, and cloud data improve productivity, traceability, and opportunities to strengthen validation and compliance. In section 2.5.1 the research looked at why validation practices especially periodic and audit-trail reviews still lag as manual, resource heavy tasks, creating inefficiencies and potential compliance gaps. This was shown as the historically cautious stance taken by highly regulated industries like pharma but that since COVID-19 have accelerated adoption, the research showed that by integrating advanced tools across validation and manufacturing can boost

compliance, speed issue resolution, cut costs, and enhance collaboration provided organisations adopt clear, enterprise wide frameworks and strategies for scaling data driven solutions. These frameworks and strategies were then reviewed with a focus on Quality Management Systems in section 2.6, the papers reviewed here talked to the engagement of Quality and other SMEs during concept and planning is crucial for digital system implementation surfacing quality impacts, aligning with regulators, and reducing resistance to change. Forming a cross-functional team from the outset secures shared objectives, roles, and responsibilities, enabling smoother adoption. As a factor of this the research then explored different methods of identifying risk, section 2.7 looked at quality risk management. QRM, is a method used to identify areas of potential risk associated with a product, process, or system, analysing and evaluating risk based on knowledge, appropriately communicating risk, and mitigation of risk when the impact of that risk is unacceptable. QRM can be a proactive method of implementing a framework for all digital integrations on GxP systems by identifying the risk events in large datasets and determining their priority. As an off shoot of this and something that is more prevalent in life sciences is Review by Exception, RBE as explored in section 2.8 is that by setting agreed, risk-based parameters for what must be checked guided by activity requirements and error impact, large datasets can be rationalised to provide the reviewer with the relevant data based on value to increase efficiency and support batch release and approval and release. With the basis of understanding of what requirements are needed from quality management perspective and maintain regulatory compliance the research then studied the use of automated or scripted tools in section 2.9, version-controlled Python scripts can generate reproducible, transparent datasets and workflows applying practices like literate programming, environment capture, and automated execution. Once validated, these scripts can query audit trails, flag system changes, and produce filtered reports, cutting manual effort and variability. Governed like any qualified system, they form a practical bridge between manual reviews and fully AI-driven compliance, enabling confident use of GMP data. In the course of understanding how these tools might perform and interesting method of using lean methodologies (section 2.9.1)on large datasets may provide a structure to support the generation of validated scripts and the ability to scale these tools across other equipment based on the consistent approach of LSS. From here section 2.10 investigated the use of generative AI, MLs or LLMs for optimising audit trail review by helping to prioritise areas of higher risk or concern. Although still in its early phases with a lack of use cases implemented in compliant environments, the potential to reduce inefficiency in the review process can be achieved using explainable AI models which like scripted tools can be controlled and governed to reproduce results. A common theme from the research was the ability of these models to reproduce results generated and a lack of transparency or control in their governance, that maintaining the robustness and reliability of machine learning models over time, and as models can ‘drift’ when training data no longer reflects current conditions, some organisations are experimenting with continuous learning systems to automatically retrain models when drift is detected. The ‘human in the loop’ is consistent across the research in that AI and other LLMs are as an addendum to humans for the purpose of review. The research then looked at a regulatory standpoint, section 2.11 showed that automated tools fall under current guidance and that once they are validated and supported by comprehensive lifecycle documentation, which includes risk assessments, training of users,

and have clear definitions of intended use, then the use of such tools was acceptable. In regard to AI only draft guidance from the FDA talking to draft guidance stresses building credibility for automated tools by documenting context of use, performance criteria, and lifecycle maintenance, with continuous monitoring and periodic re-evaluation to stay aligned with GxP. The EMA have released Annex 22 which sets expectations for AI in manufacturing: clear purpose, model selection, training and validation, data quality, test data handling, and ongoing oversight through change control, performance monitoring, and human review. Importantly this annex only applies to static models governed under the same criteria as other software applications in the industry.

# 3. Primary Research

## 3.1. Research Philosophy

The research is underpinned by an interpretivist philosophical approach, which is appropriate for qualitative research aiming to understand the lived experiences, practices, and perceptions of individuals within a specific context (Saunders and Bristow, 2023). Interpretivism holds that knowledge is socially constructed and best explored through dialogue and detailed inquiry, making it suitable for this study's aim to investigate how validation professionals navigate periodic reviews and data integration challenges. (Rahman, 2016)

The interpretivist philosophical approach has its advantages and disadvantages, disadvantages in that it can be subjective, leaving room for bias on behalf of the researcher. Primary data in interpretive studies is hard to generalise as the data is impacted by personal opinions and viewpoints with the potential to undermine the reliability and representativeness of the data. (Dudovskiy, 2025) Advantages of an interpretivist approach can be that the findings can be from cross functional departments of an organisation and that the data can be of a high level of quality as these studies tend to be accurate and reliable.(Clark *et al.*, 2002)

The research approach is inductive, interviewing subject matter experts to understand specific processes, an important factor when examining manual validation efforts, system limitations, and emerging attitudes toward automation and AI tools. It acknowledges that participants experiences are shaped by their work environments, roles, and interpretations of regulatory expectations, all of which are key to understanding the barriers and opportunities for innovation in validation practices.

## 3.2. Research Strategy and Data Collection

This study will employ a qualitative research strategy, using semi-structured interviews as the primary data collection method to obtain detailed accounts from professionals engaged in periodic review validation within pharmaceutical manufacturing. Semi-structured interviews are particularly suited for exploring complex and context dependent processes, as they allow researchers to guide the discussion while also providing flexibility to probe emergent themes (Kallio *et al.*, 2016). This approach enables participants to express their experiences, perspectives, and interpretations in their own words, which is essential for understanding the current practices and decision making processes underlying validation activities. (DiCicco-Bloom and Crabtree, 2006).

In the context of pharmaceutical manufacturing where validation activities must comply with regulatory frameworks such as those outlined by the EMA and the FDA qualitative methods can capture the tacit knowledge, organisational factors, and inter-departmental collaboration that quantitative measures may overlook. The use of semi-structured interviews supports the interpretivist paradigm underpinning this research, as it prioritises contextual understanding over generalisability (Bryman, 2016).

## 3.3. Data Collection Method

Mono-method, interviews will explore current practices, challenges in reviewing small scale or vendor equipment, and perspectives on adopting tools like Python scripts or AI driven review assistants. The semi-structured format allows for consistency across interviews while still enabling participants to elaborate on relevant experiences or ideas (Bryman, 2016). The differing opinions on how this data should be captured and how current practices are implemented will have a wide range of opinion, but a commonality between all participants is the understanding of the regulatory requirements and value of maintaining compliance throughout the review, the ability to revisit the reviewed data, the transparency of the activity and the capacity to explain to a regulatory body the findings.

## 3.4. Participant Selection

Participants were selected through purposive sampling, focusing on professionals with direct experience in CSV, QA, automation, or engineering roles within pharmaceutical companies operating in Ireland. This sampling strategy is appropriate for qualitative research as it enables the selection of individuals who possess in-depth knowledge and practical experience relevant to the research topic (Palinkas *et al.*, 2015). The target sample size was 11 participants, which aligns with empirical research indicating that qualitative saturation is often achieved within 9–17 interviews for studies with a relatively homogeneous participant group and focused objectives (Hennink and Kaiser, 2022).

All selected participants have a vested interest in maintaining the qualified state of the equipment under periodic review. Whether in a supporting capacity or in the direct execution of the review, they are accountable for its findings and responsible for addressing any associated data integrity concerns. This ensures that the data collected will reflect both technical and procedural expertise, as well as the organisational perspectives influencing periodic review validation practices.

Participants were approached through professional networks and industry contacts and all interviews were conducted online via Microsoft Teams (MS) and transcribed (with consent) for analysis. All transcriptions stored in the raw data folder in Moodle

## 3.5. Interview Questions

The interview questions were developed with SMEs in mind and not likely to be understood outside of the targeted group, although there is a general understanding throughout the industry in the need for risk management and review of GxP systems, there is very little understanding of the process of that review, particularly in the detail and attention it requires. Questions were developed under the following themes:

### 3.5.1. Section 1: Background & Role Context

Questions relating to the participants role, their role in periodic reviews and types of systems they would usually support/execute reviews

This question does not directly relate to the research objectives (RO), participants were selected based on their role, this question was to establish what type of role they had in the execution of

reviews, age and experience were not a factor as many junior members can be tasked with the review of audit trails and therefore possess the same understanding as senior colleagues.

### 3.5.2. Section 2: Current Practices

This section is to allow the interviewee to explain the current process for review, tools used to review data, limitations experienced and if the process is manual or requires time and effort:

This question aligns with RO1 in asking the participants to explain the review process and establish the manual nature of the tasks, the expected response of these reviews was to allow the interviewee to describe the activity and to generate a problem statement.

### 3.5.3. Section 3: Regulatory Compliance & Audit Trails

Questions on understanding of regulatory requirements, accessibility and frequency of audit trails specifically:

The research needed to identify how the interviewees dealt with the challenges of maintaining data integrity during review and decided intervals of work conducted in a highly regulated environment. This section directly relates to RO2

### 3.5.4. Section 4: Technology & Automation

Awareness and opinions/attitudes on using scripted or AI tools to support reviews:

The objective of this question was to gain an understanding of where the participants knowledge base of how scripts and/or AI might be used to support the review process and if they felt assessing systems and identifying parameters might provide a consistent defendable review. This section aligned with RO3 & RO4.

### 3.5.5. Section 5: Organisational Readiness & Barriers

This section was to gauge how the interviewee thought about the readiness of the business in terms of a digital strategy and what type of training would need to be deployed and what responsibility would be expected from relevant departments:

The objective this section aligned with was RO5 and was asked to understand from the interviewees the barriers to introducing new methods, the ownership of new technologies and any potential skills gaps they felt might need to be addressed.

### 3.5.6. Section 6: Final Thoughts

Opportunity for participants to give some expert opinions, to try and capture new vantage points on the research

Developing a framework and having the thoughts on how this roadmap might be perceived by colleagues was important in developing out the ideas to generating the requirements for RO6.

The final list of questions presented to all participants are available to reference in Appendix A

## 3.6. Uncertainties and Challenges

A potential difficulty is limited participant availability due to the busy schedules of pharmaceutical professionals. To mitigate this, interviews will be conducted remotely via MS Teams and scheduled flexibly.

There is also a risk of response bias, especially if participants feel their processes are under scrutiny. This will be addressed by clearly communicating that the purpose of the research is improvement and understanding, not evaluation or judgment.

Ethical approval will be sought through the appropriate academic channels before beginning primary data collection.

## 3.7. Ethical Considerations

Primary data collection, synthesis, and interpretation were conducted ethically. Participants were fully informed of the study's purpose, methods, potential uses, and any risks; all data were kept confidential, and identities anonymised. The research was independent with no researcher conflicts to declare. If a participant had a conflict of interest, they could withdraw; if they remained, the conflict was declared. Participants could withdraw at any time for any reason. Each invite included a Participant Information Leaflet (PIL) outlining background, risks/benefits, and confidentiality, and participants signed an Informed Consent Form (ICF). Privacy was respected and findings will be appropriately disseminated. An ethics assessment and application were completed, and since no confidential organisational information is disclosed, formal ethics committee approval was not required. This information is stored in the raw data folder in Moodle, and a copy available for reference in Appendix B & C.

## 3.8. Qualitative Analysis

Interview data was transcribed and analysed using thematic analysis, following (Braun and Clarke, 2006) six step framework. This involves familiarisation, coding, identifying themes, reviewing and defining themes, and producing a final analysis. Manual coding in Excel was used to assist in categorising recurring concepts such as:

- Current review practices
- Regulatory requirements
- Audit trail access
- Emerging Tool Use
- Attitudes towards Automation
- AI Readiness
- Organisational culture
- Barriers to modernisation

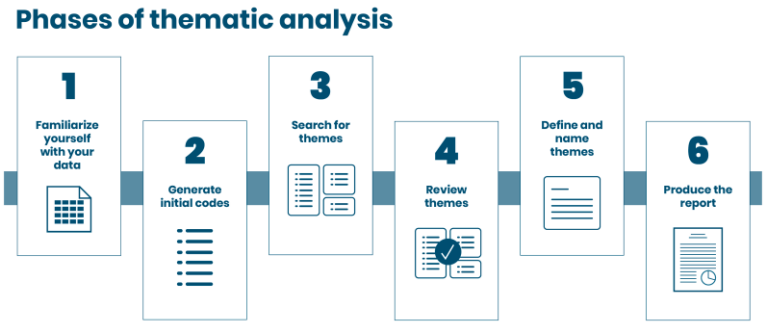


*Figure 10 - Phases of thematic analysis (Fleming, 2023)*

## 3.9. Conceptual Framework

The conceptual framework underpinning this research is built around several key themes that influence both the current state and future potential of validation practices in pharmaceutical manufacturing. Central to the framework are the regulatory requirements governing GxP systems and the integrity of the data they generate, as outlined by agencies such as the EMA and FDA. This foundation sets the expectations for how periodic reviews should be conducted.

The framework also considers current industry practices, particularly the continued reliance on manual data reviews, and the practical limitations experienced by personnel responsible for ensuring compliance. These may include time constraints, limited access to audit trail data, or fragmented vendor systems.

As digital tools and technologies such as automation scripts and AI models become more feasible for aiding in validation, the framework examines organisational readiness and attitudes toward adoption. Understanding how validation professionals perceive these tools is crucial, especially when considering potential skill gaps and training needs related to digital literacy.

Finally, the framework addresses barriers to implementation, such as questions of system ownership, cross-functional coordination, and the requirement that any digital tool used in GxP environments must itself be validated and compliant with data integrity principles. These interconnected factors help shape the research questions and guide the analysis of both primary and secondary data.

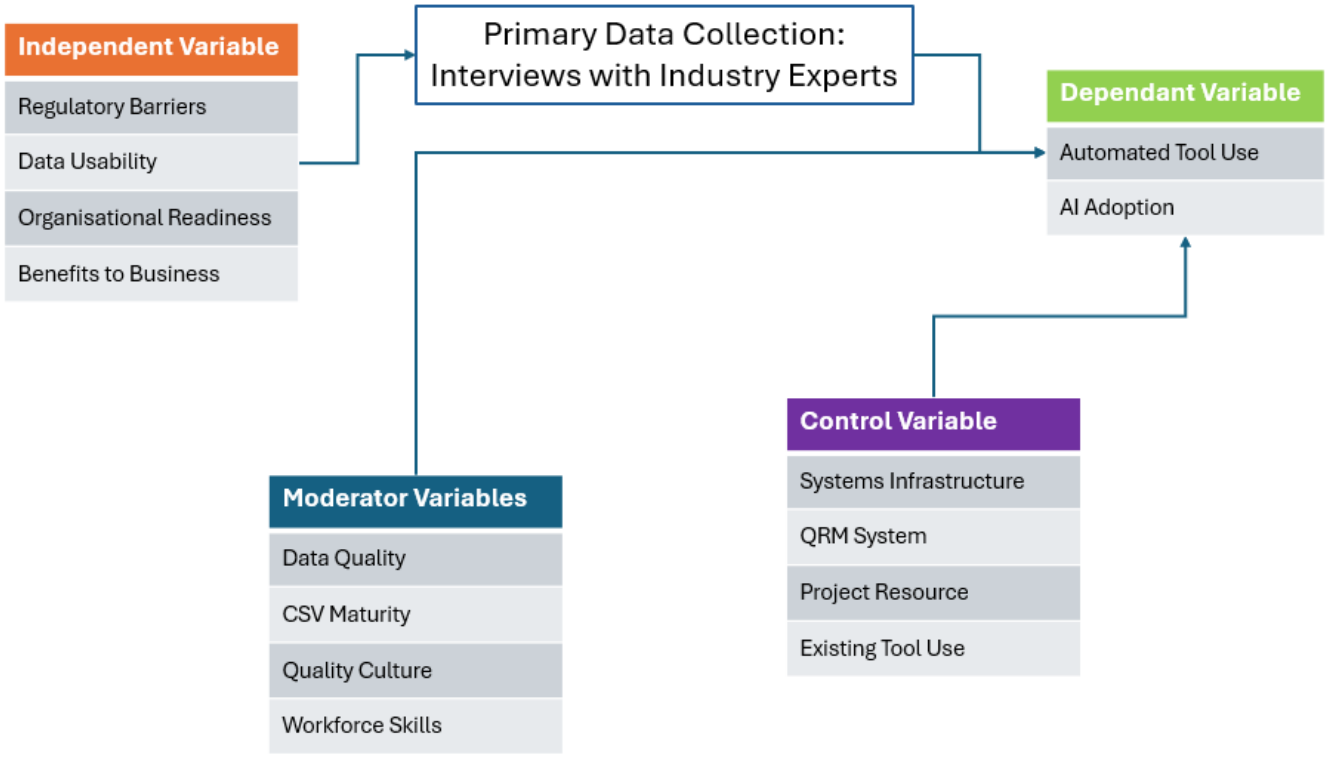


*Figure 11 - Conceptual Framework*

# 4. Findings & Analysis

## 4.1. Overview

This chapter presents the findings from eleven semi-structured interviews conducted with validation, automation, and data integrity professionals working in pharmaceutical manufacturing in Ireland. The purpose of these interviews was to explore current practices, challenges, and opportunities in the periodic review validation of small scale and vendor supplied process equipment. All participants interviewed were selected because of their familiarity with the data, their understanding of the regulatory requirements and their experience with audit trail and log data generated by not only small scale process equipment and vendor process equipment but with a wider arrange of GxP systems used for larger aspects of the pharmaceutical manufacturing process such as distributed control systems (DCS).

## 4.2. Interview Population

Interviewees asked to participate were from different aspects of the periodic and audit trail review process, Quality and validation personnel, engineers responsible for data interconnectivity and engineers responsible for process control change. All have experience with review of audit trails and/or have supported periodic reviews as part of their work.

The participant roles were purposively selected to ensure that each individual could contribute informed, experience based perspectives relevant to the study objectives. The distribution of roles is outlined below:

| Role | Description | Ref |
|---|---|---|
| Automation Engineer | Responsible for implementing and managing control system changes, ensuring continued operation and compliance of GxP-regulated automated systems. | P1 Auto<br>P2 Auto |
| Computer Systems Validation | Responsible for verifying and maintaining the validated state of computerised systems in accordance with regulatory requirements and internal procedures. | P3 CSV<br>P4 CSV<br>P5 CSV<br>P6 CSV |
| Manufacturing Data Engineer | Responsible for designing, developing, and maintaining data flows from source systems to end users, ensuring accuracy, integrity, and usability of manufacturing data. | P7 MDE<br>P8 MDE<br>P9 MDE<br>P10 MDE |
| Quality Assurance | Responsible for reviewing and approving changes, deviations, and documentation that may impact the qualified state of equipment or systems, ensuring compliance with GxP and quality standards. | P11 QA |

*Table 3- Table description of roles and count*

*Note: The reference code will be used to refer to individuals quoted in the transcripts*

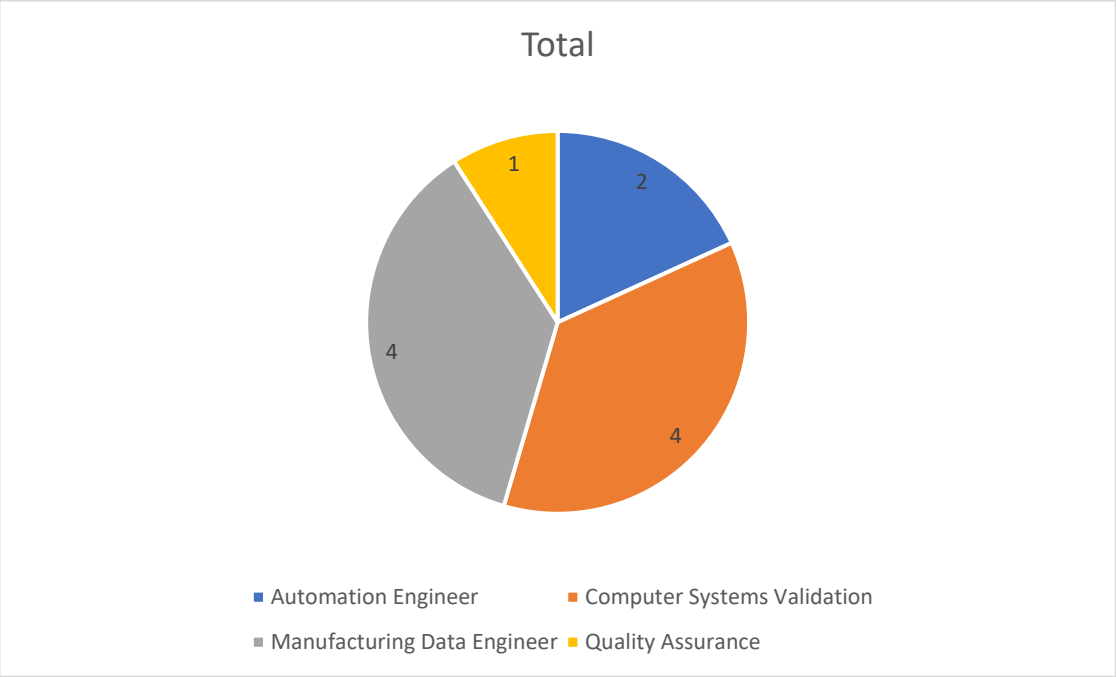


*Figure 12 - Roles of interviewees (authors own)*

## 4.3. Participant overview in relation to Research Topic

The research topic investigated in this work is that of periodic review validation practices for small scale and vendor supplied process equipment in the Irish pharmaceutical manufacturing industry. While periodic reviews are an established regulatory expectation, it is assumed that the processes used for small scale and vendor supplied systems are often manual, inconsistent, and dependent on vendor provided outputs. It is also assumed that the efficiency, standardisation, and automation readiness of periodic review processes vary significantly between functional areas, with Automation and IT teams generally having more technical capability to streamline reviews compared to Process Engineering, Quality Assurance, Validation, and Operations teams.

The significance of this is that robust and efficient periodic review practices are critical to ensuring data integrity, regulatory compliance, and operational efficiency. For periodic reviews to consistently deliver value across all system types, it is necessary for diverse functional groups to engage with, understand, and adopt best practices. This research aims to identify the current challenges, including manual workload, data access issues, and lack of system integration, as well as the potential role of automation, scripting, and AI tools in improving the process.

By examining perspectives across multiple functional areas, this study seeks to determine where skills gaps, procedural inconsistencies, and technology adoption barriers exist. The findings can inform the need for targeted training, investment in enabling technologies, and clearer ownership of review processes. Furthermore, the research holds significance for both industry and regulators, as it can guide the development of frameworks, validation approaches, and oversight practices that encourage more standardised, efficient, and defensible periodic review methods for small scale and vendor supplied systems.

## 4.4. Results according to Themes

Upon completion of the interviews the transcripts were analysed separately and a process of identifying initial codes was initiated, from this the themes were developed, refined and eventually condensed to six themes developed to support the responses from the interviewees collated from the data:

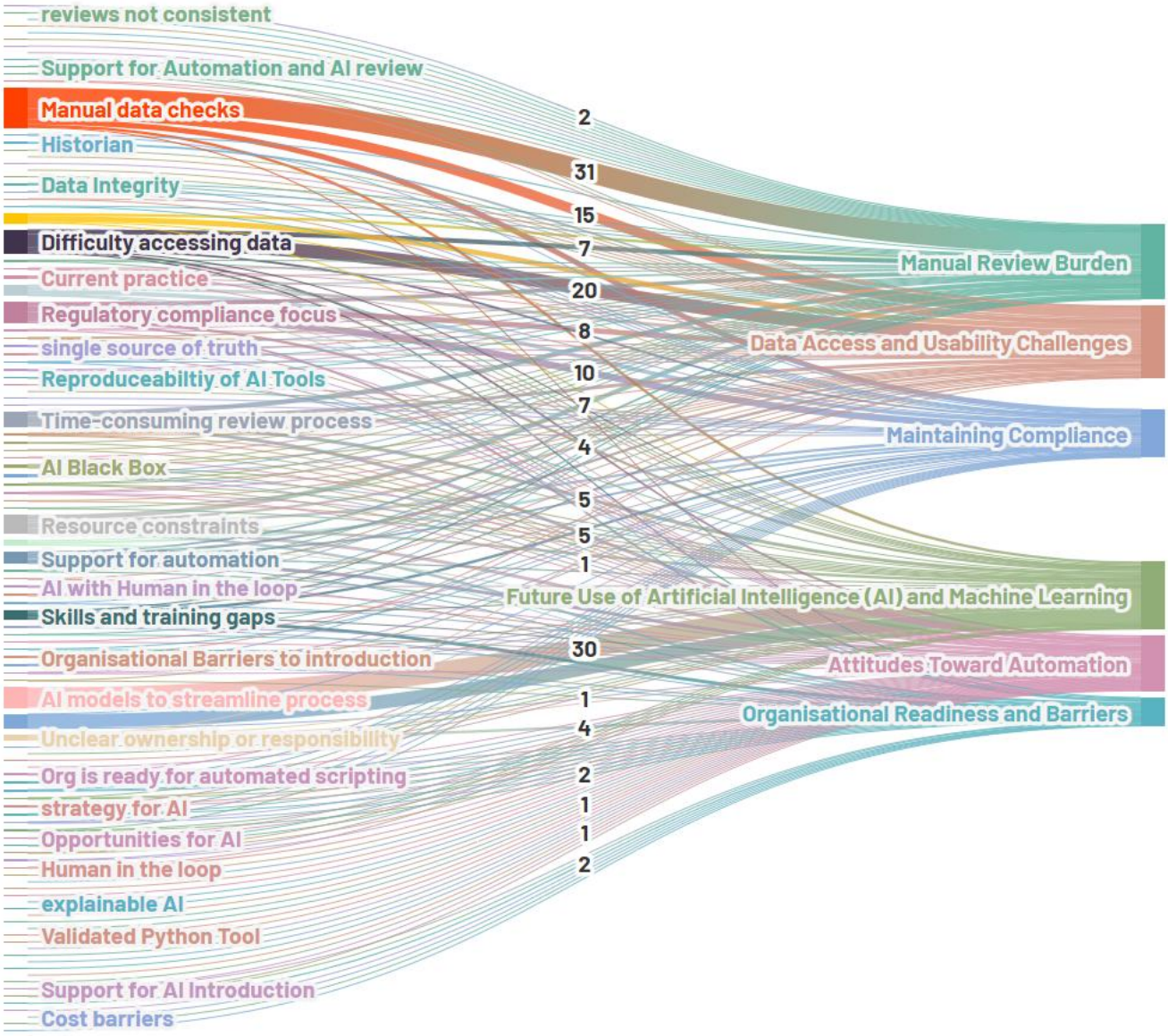


*Figure 13 - Codes associated per theme (authors own, developed in flourish)*

- **Manual Review Burden**
- **Maintaining Compliance**
- **Data Access and Usability Challenges**
- **Attitudes Toward Automation**
- **Future Use of Artificial Intelligence (AI) and Machine Learning**
- **Organisational Barriers**

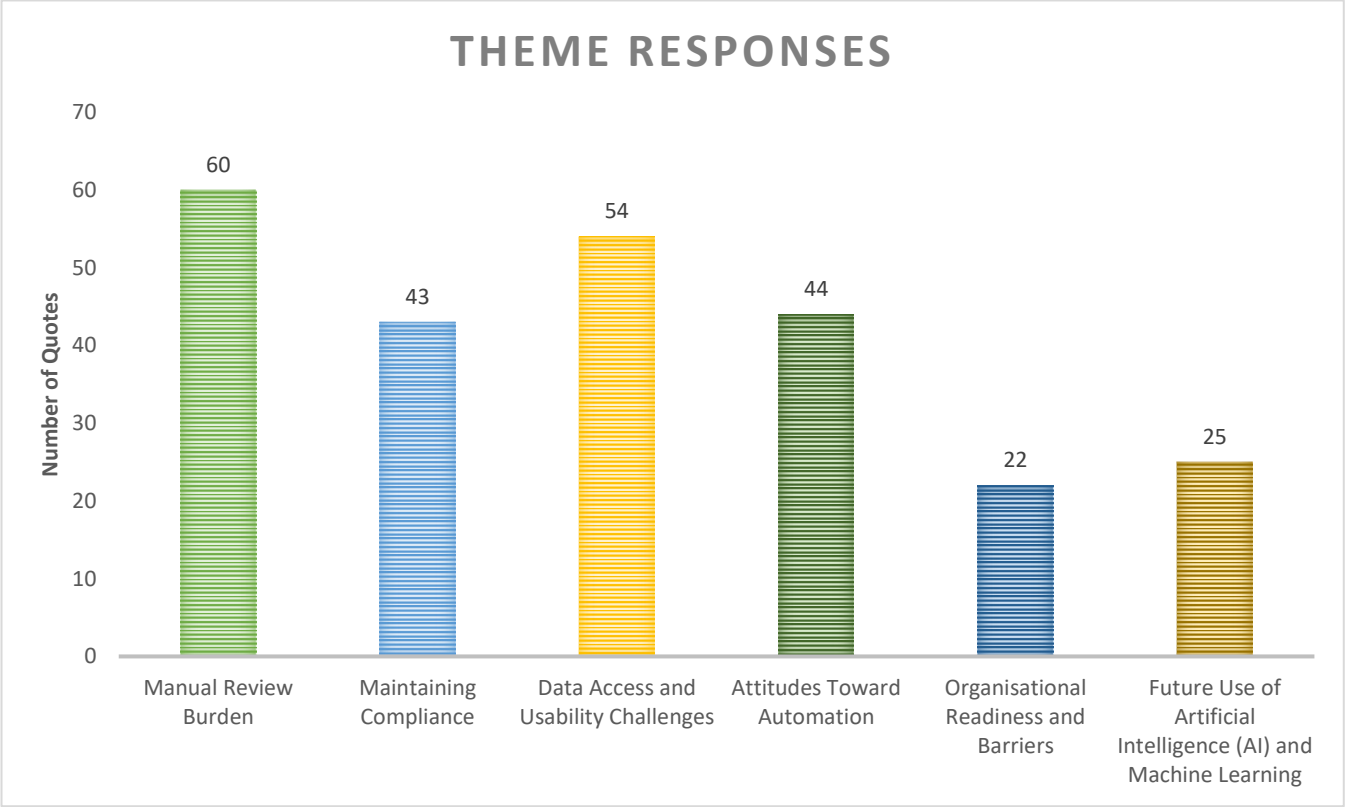


*Figure 14 - Responses per theme recorded (authors own)*

Manual Review Burden and Data Access/Usability Challenges together represented 46.0% of all coded extracts, evidencing that scale and format issues, not lack of reviewer intent are the primary drivers of inefficiency.

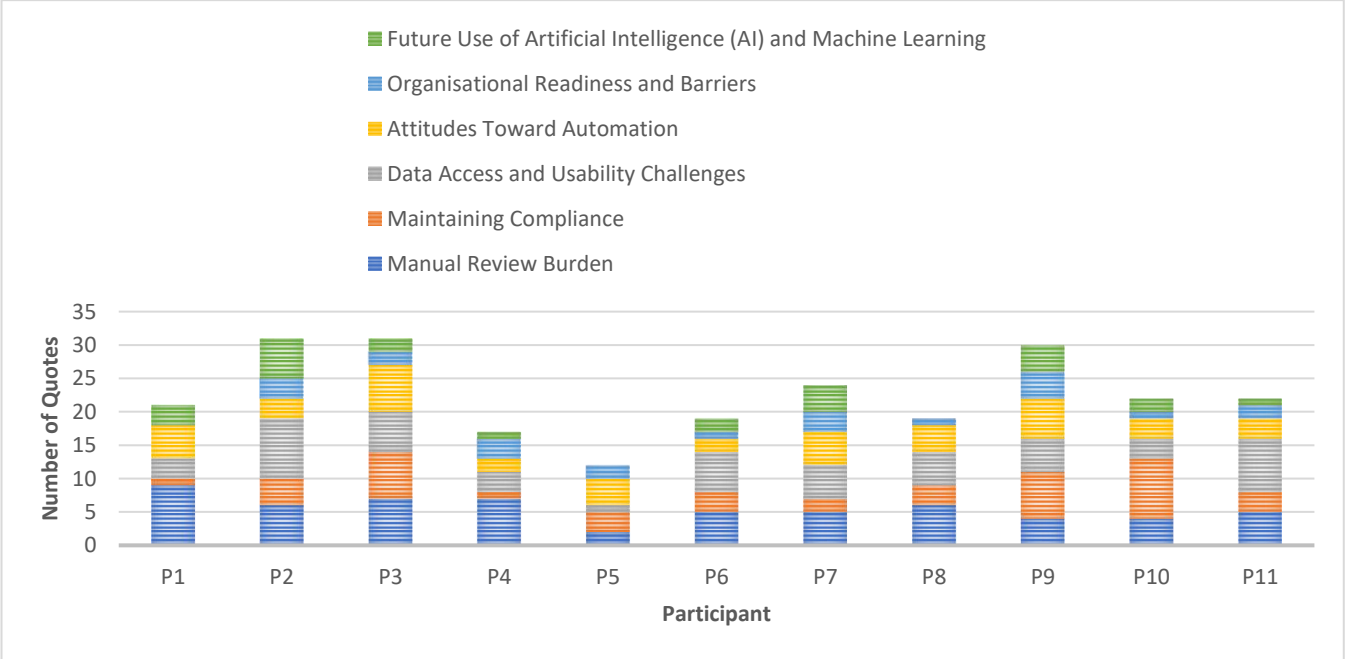


*Figure 15 - Coverage per theme across participants (authors own)*

All eleven interviewees contributed evidence to the four central themes, underscoring their cross-functional relevance; conversely, AI/ML and organisational readiness topics, while present (90% coverage), were more contingent on role exposure and perceived adoption prospects.

Each theme is presented below with supporting extracts from participants, anonymised and identified by role. Interpretive commentary is provided to situate the findings in relation to the research objectives.

### 4.4.1. Theme 1 - Manual Review Burden

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Manual review burden | 60 | 9 | 6 | 7 | 7 | 2 | 5 | 5 | 6 | 4 | 4 | 5 |

*Table 4 - Manual Review Burden participant response scores per theme*

From the interview questions asked to participants theme 1 was developed from the responses to interview questions 6 & 7 from section 2, this question was designed to understand the actual review process, to determine how much of the review process is manual and if there were specific challenges and limitations in performing the review on SSPE or VPE

A consistent finding across all participants was the reliance on manual processes for audit trail review. Periodic reviews are typically conducted by exporting audit trail data into spreadsheet software and visually scanning for anomalies. This process is described as labour intensive, repetitive, and prone to error. All interviewees described the current process as manual and time consuming.

Accessibility was a major concern for some of the participants from a review supporting role in automation or in the manufacturing data team interviewed where a continuing theme was the accessibility in retrieving files for review. The management and permissions required to be sought to access the system and export/view event logs and audit trail files was often a source of frustration.

**P3 CSV:** 'Gathering the data from different systems takes a lot of time before we even start the review'

**P7 MDE:** 'Having to go in and pull the audit trails off or that someone has to go into the equipment in the first place, such as the wave rocker or similar and export the audit trails'

**P5 CSV:** 'Not very, not very accessible or usable. A lot of the exports are in kind of PDF format, so not filterable. We're trawling through trawling through data so.'

**P4 CSV:** 'We don't have access to them. So, we have to request them from the automation team to export them for us to review.'

Another code identified was 'Manual audit trail review' which was associated with the same theme, this was repeated across all interviewees and covered under themes such as 'Excel Based Review, 'time consuming review' and 'Audit trail review is fully manual'.

**P3 CSV:** 'The audit trail review, that's mostly manual. We're manually checking entries for anomalies or unauthorised access. So, you're going through the logs line by line.'

**P10 MDE:** 'Mostly manual exporting data from each system, applying filters in Excel, then reviewing entries one by one.'

**P7 MDE:** 'Literally open it on Excel and you can either filter or you could just scroll through and be looking out for anything abnormal or of note'…. I suppose the height of it would be that exact function we use in Excel just to make sure everything matches

**P9 MDE**: 'At the most basic level, Excel and notepads, because that's what usually is used to open the files themselves'

Other codes such as 'No standard process across systems' & 'Manual review of heterogeneous small scale equipment audit trails' talks to the lack of commonality across some of these systems and how each individual unit must be accessed, data retrieved, and data reviewed.

**P1 Auto:** 'So many systems, especially small scale process equipment, aren't identical... you have to be guided by a work instruction per piece of equipment.'

#### 4.4.1.1. Theme 1 - Conclusions

Although expected from the transcripts and obvious from a data integration standpoint, having the interviewees describe the current process of review as a time consuming manual and inconsistent confirmed that the current methods of determining activity on these systems requires further investigation.

### 4.4.2. Theme 2 - Maintaining Compliance

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Maintaining Compliance | 43 | 4 | 7 | 1 | 1 | 3 | 3 | 2 | 3 | 7 | 9 | 3 |

*Table 5 - Maintaining Compliance participant response scores per theme*

Interview questions 8 & 10 from section 3 is directly related to Theme 2, the anticipated response from the interviewees was to describe the environment in which the review is performed. All participants talked to the importance of transparency, of adhering to procedure and the cadence of the review cycle in maintaining compliance.

Maintaining compliance was identified as a central driver for periodic review activities, with participants stressing adherence to ALCOA+ principles and regulatory frameworks such as 21 CFR Part 11 and EU Annex 11. Codes developed were 'Regulatory compliance focus', 'ALCOA+ adherence' & 'Data Integrity'. Reviewers reported that their processes were designed not only to identify deviations but also to confirm that systems remained in a validated state. This often involved verifying that user access rights matched current roles, ensuring audit trails were intact and unaltered, and confirming that changes were appropriately documented through change control. Participants described implementing event driven reviews in addition to periodic checks, particularly following system upgrades, incident investigations, or infrastructure changes.

**P9 MDE:** 'Extensive testing and validation but also utilising our documentation through Kneat. (Electronic review) Also the review process from our peers. This allows us to ensure that everything is as expected'

**P2 Auto:** 'The CSV team would take a sample of data. I think they have an SOP that guides them on what that sample size should be. Then they assess that sample size to verify that any of the user interactions with the system are happening under the umbrella of the appropriate GMP record, and if they have any query'

**P8 MDE:** 'The other systems or documents that are related to the work orders or the change controls that I mentioned they this is basically use it to have traceability across them.'

**P6 CSV:** 'Data integrity is assessed during our periodic reviews, so we look at we look at the regulatory guidelines and assess if there's any been any updates during the periodic review period. And if there's been any change or updates in terms of data integrity guidance, we also make sure during the periodic review that appropriate data controls are in place'

Maintaining compliance was not seen as an isolated task, but one closely linked to organisational quality systems, staff training, and procedural control to ensure consistency. The emphasis on traceability and documented evidence reflects established regulatory expectations and underscores the critical role of periodic review in sustaining data integrity in GxP environments.

**P8 MDE:** 'It's our responsibility to keep the auditory of system up and running, which is basically. Providing context on which action was performed in the system, by who and when. So, I think from an ALCOA+ plus perspective were ensuring the integrity on the audit trails'

**P3 CSV:** 'The systems are validated, so all the data in those systems is coming from a validated source, so whatever we pull down from those systems would be integral and traceable back to the source system. Those systems will be checked to be compliant with the regulations 21 CFR Part 11 and Annex 11'

#### 4.4.2.1. Theme 2 - Conclusions

Although not talking to any particular research question the commitment to maintaining the data integrity standards across the different aspects of the wider review group emphasises the importance of finding a compliant way of interrogating large datasets.

From the dataset and possibly as a result of maintaining data integrity more codes were generated under the 'Maintaining Compliance' theme from the automation and data engineers (35/43), this is probably as a result of administrator duties tasked with the responsibility of ensuring consistent data across all systems.

### 4.4.3. Theme 3 - Data Access and Usability Challenges

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Data Access and Usability Challenges | 54 | 9 | 6 | 3 | 3 | 1 | 6 | 5 | 5 | 5 | 3 | 8 |

*Table 6 - Data Access and Usability Challenges participant response scores per theme*

This theme was developed from codes associated mostly with interview questions 5 & 7 from section 2 and question 9 from section 3, participants discussed the limited tools currently in use and how accessible the data was in terms of format and actual accessibility.

Data access and usability emerged as significant obstacles to efficient periodic review. Participants reported restrictions on system permissions, which in some cases limited their ability to extract complete or searchable datasets. Older SSPE or VPE often produced audit trail exports in non-searchable PDF or proprietary formats, complicating analysis and slowing review. Inconsistent data schemas and heterogeneous export options between systems complicated attempts to standardise review approaches. Even when data could be exported, missing metadata such as precise timestamps or change reasons was cited as a challenge for establishing context. These issues contribute directly to the manual review burden and limit opportunities for automation. The literature on data integration in regulated environments mirrors these concerns, emphasising the need for standardised, interoperable formats to improve efficiency and reduce compliance risk. Without addressing these access and usability barriers, the benefits of advanced review tools remain constrained by data quality and availability.

**P2 Auto: '**I think there's two aspects that take time. I think for the CSV team, its manually going through the sample. So, the sample could be of significant size as well. It could be hundreds or thousands of line items and then they have to manually match that against a list of, I suppose, authorised users. So, in terms of segregate. And duty. So, is any download or any import being done by an engineer that has appropriate engineering level access and then if they find that they're that that they pass that gate, the second gate is a what? What GMP Records did that activity occur under so can they match that, and they would normally come to us then and again for us that's quite manual. So, we would have to see, right, go into the alarmed events, see when that activity happened. Typically, it's something a download and then we would go and see right during that time what change records were we working on and then look.'

**P10 MDE:** 'Access restrictions, inconsistent data formats, and the sheer volume of events to sift through'

**P5 CSV:** 'Not very, accessible or usable. A lot of the exports are in kind of PDF format, so not filterable'

**P1 Auto:** 'The audit trails look different by their very nature. The entries you're interested in are different. A filter integrity tester [for example]. If you're looking for. audit trail entries which are out of the norm. You know, they'll be by their nature a water integrity failure. Thats different than the entries you'll be looking up for on other pieces of equipment. So, you need a level of equipment understanding to really conduct that. And the problem is that very often audit trail reviews are carried out by automation engineers by CSV engineers, and there probably isn't the validation inputs that you require.'

**P4 CSV:** 'Well, as we don't have access to the systems to view the auto trails, were dependent on an export of them and each system export is different. So, there's no, there's no consistency for each system.'

Specific examples include data silos that can only be accessed manually and exported for review

**P10 MDE:** 'Charge recorders were difficult to get a proper audit trail for them. I think they came in just PDF format as well. So, it's not really, it's not very easy to, it's not easy to analyse'

#### 4.4.3.1. Theme 3 - Conclusions

Participants questioned the ability to physically access data from some of the systems and the ability to safely review the data based on the outputted files available for review. Participants felt that any tool would have a major task in accessing this data and the ability to leverage from it.

All interviewees responded to this issue with an even spread across all the data, emphasising the burden of review for SSPE & VPE disparate systems. Again data & automation engineers account for 41/54 showing the level of support required from departments outside of CSV

### 4.4.4. Theme 4 - Attitudes Toward Automation

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Attitudes Toward Automation | 44 | 5 | 3 | 7 | 2 | 4 | 2 | 5 | 4 | 6 | 3 | 3 |

*Table 7 - Attitudes Toward Automation participant response scores per theme*

The interview questions in section 4 provided the codes to allow this theme to be defined, the questions were designed to allow the participants to give their opinion and insight into automated tools or the integration of AI related solutions. What set this theme apart from theme 5 was both the question 11 where the interviewee was asked about previous automated tool experience and the specific reference to 'Python' in question 12.

Attitudes toward automation were generally positive, provided that any tools introduced were validated and produced transparent, reproducible results. Participants welcomed the idea of scripts, dashboards to pre-filter audit trail data and highlight exceptions, noting that this could significantly reduce review times. There was unanimous agreement that automation should serve as an aid rather than a replacement for human judgement. Trust in automated tools was closely tied to their perceived reliability, the clarity of their outputs, and their alignment with compliance requirements. In practice, many participants viewed automation as a means to reprioritise effort, allowing reviewers to focus on investigating flagged anomalies rather than manually scanning entire datasets. This perspective reflects the broader GxP guidance that positions automation as a complement to, rather than a substitute for, qualified human review, ensuring that regulatory accountability and critical thinking remain central to the validation process.

**P8 MDE:** 'Not just automatising but kind of getting automatic insights from that, for example as opposed to manual review every single audit entry that you might have, if your automated script, it's not just looking for that, but for the change controls the work orders as well and can already maybe generate a report'

**P3 CSV:** 'Let's suppose if any of those repetitive tasks were automated, that would be great. Just to make it more efficient'

**P2 Auto:** 'I think that would be really positive as long as you're validating what your Python script is or your risk assessing, you know the use of the script for that purpose, then I think that would be a good thing. Anything that automates repetitive manual tasks and can throw up. You know exceptions or errors to that I think is a positive thing.'

**P8 MDE:** 'I think it'll be a really good idea. I did something under codes easy to be develop it and you can have control on the rules what the code is actually doing as opposed to, for example an AI'

**P4 CSV:** 'I would be delighted to use that script and to automate the review process. It does. It will be at the initial setup will be quite time consuming to ensure what you are scripting for is correct and you're not missing anything.'

**P9 MDE:** 'So mostly scripts, PowerShell or Python, you can build robust scripts to assist you in your reviews and also PI system because it acts as a single source of truth for everything coming in and most of the things in PI are already per vendor validated and you can qualify your solution'

**P6 CSV:** 'I definitely think there's a role for that script tools that to use, particularly an audit trail review process, some of those audit trailer reviews can be, you know, extremely long length and for a human review. It's probably not really effective, so I would imagine a scripting tool will probably do a better job at that. And then maybe with human review afterwards, based on the findings that the scripting tool might find. I think there's a role for both.'

**P11 QA:** 'we should be going after what's important as an industry, it all starts with your quality indicators of what's actually in the audit trail and what is the problem as opposed to everything.'

#### 4.4.4.1. Theme 4 - Conclusions

The understanding of both the validation requirements and the qualification implications for the respective script or automation of review process was widely understood by the interview group and this cross-consensus on the positive use and implementation of these tools because of the transparency, control and repeatability would make them a valuable method of assessing large datasets capable of rationalising data and providing context. Having the confidence to leverage off a controlled script with risk assessed pre-determined rules to analyse is the basis for these scripts.

### 4.4.5. Theme 5 - Future Use of Artificial Intelligence (AI) and Machine Learning

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Future Use of Artificial Intelligence (AI) and Machine Learning | 25 | 3 | 6 | 2 | 1 | 0 | 2 | 4 | 0 | 4 | 2 | 1 |

*Table 8 - Future Use of Artificial Intelligence (AI) and Machine Learning participant response scores per theme*

Question 13 from section 4 provided the codes for theme 5, each interviewee responded specifically to this question as it required a response to be explored on whether the participant was in favour or not, with a distinctive amount of responses to this issue, it was decide that 2 themes could be generated from the data

in relation to attitudes towards automation and this Future Use of Artificial Intelligence (AI) and Machine Learning

Participants expressed cautious optimism regarding the future application of AI and machine learning in periodic review processes. Potential use cases included anomaly detection, automated categorisation of audit trail events, and predictive analytics to flag systems at higher risk of non-compliance. There was strong consensus that any AI implementation must be explainable, validated, and continuously monitored for performance drift. Concerns were raised about the transparency of some machine learning models, particularly in contexts where regulatory auditors require clear, documented decision logic. AI was generally viewed as an assistive technology capable of enhancing human review rather than replacing it by pre-screening large datasets and highlighting areas of interest. This reflects emerging guidance in AI governance, which emphasises transparency, accountability, and human oversight in high stakes applications. To realise these benefits, participants stressed the importance of pilot projects, phased adoption, and alignment with existing compliance frameworks before full scale deployment.

**P1 Auto:** 'absolutely. I mean especially you know, you say chatbots and large language models are, they're almost built for it. I mean, pattern recognition and machine learning are what they're good for. So maybe they refined. But again, were going back into explainable AI'

**P7 MDE:** 'So its own new and there isn't this kind of processes in place to validate. It's very easy to say it would be great to have this set up, but say for example you set up an AI to be checking your periodic reviews, that's all well and good, but how are you going to explain to an auditor and what specifically? What the AI is doing? … it shouldn't be a black box, but still, I think that the process isn't set up yet for these kinds of things.'

**P2 Auto:** 'I think with AI the current challenge would be is how you define the use cases for an AI model. If that AMI if that AI model drifts or changes over time and you don't know what the configuration of that model is. So, I think it would depend on how you'd validate the model, and you probably have too periodically. Stress test that model again to make sure that it's capturing the false positives or false negatives and getting the type of detecting the type of discrepancy or noncompliance that you're trying to find'

**P1 Auto:** 'I think that will come into effect more and more within the industry. It's just quality (QA), are still understandably nervous about AI and I guess that's where you get into explainable AI and those are all quite new concepts…. So, maybe they refine it, but then again, were going back into explainable AI and if that's a stumbling block, maybe the model doesn't refine itself, but you can certainly still use it to pick out keywords and phrases, but it's going back to you. You almost have to develop that out yourself, because how do you defend that to an auditor?'

**P6 CSV:** 'Maybe AI tools access to that data, because maybe a lot of that data is sensitive, so I'd imagine there'd be small. It might be hard to convince them of its true effectiveness. And maybe there might be. It might be a bit slow in terms of integration as well. And obviously at the minute with the current environment

in terms of pharma and bit of a slowdown, Id imagine costs would probably be a factor there as well and maybe they [Directors] might not see that as a priority.'

P9 MDE, a manufacturing data engineer went further then the other interviewees in saying that they'd prefer a scripted approach over and LLM or ML, and while still in favour for using AI to conduct review they should be purely from an informational or diagnostic perspective.

**P9 MDE:** 'I believe they could support but I am not 100% in favour as the scripting tools just for the simple reason that the scripting tools you're developing you're testing, you're validating an AI tool. Tools GPTs or chat bots, they are a black box, so you need to be very cautious into what is your query, what the outcome of that query is and making sure that you're using the tool as information, but not something that will make the decisions so people need to be extremely, extremely aware of the risks of false information that AI and chat bots can output.'

#### 4.4.5.1. Theme 5 - Conclusions

All participants bar one CSV and one data engineer, and all expressed an opinion that AI would be introduced across all systems eventually but remained cautious about the ability to leverage GxP decisions. The understanding also varied between groups; more technical interviewees expressed more detail about how these tools could be implemented and how they would need to have a level of qualification and control to enable them to supplement human activities, whereas the review participants (CSV & QA) seemed to group both AI and scripting tools as a similar technology.

### 4.4.6. Theme 6 – Organisational Readiness and Barriers

| Theme | Total | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Organisational Barriers | 22 | 1 | 2 | 3 | 3 | 2 | 1 | 3 | 1 | 3 | 1 | 2 |

*Table 9 - Organisational Readiness and Barriers participant response scores per theme*

Section 5 from the interview questions was designed to elicit a response from each of the interviewee's areas in the review process to understand the awareness and ownership of the industry 4.0 technologies becoming more prevalent in pharmaceutical manufacturing. The intension was to establish codes from the different perspectives indirectly related to each other.

Organisational readiness and barriers to automation adoption were recurring themes, with participants identifying resource constraints, unclear ownership, and varying levels of technical expertise as key inhibitors. While technical feasibility was rarely questioned, securing budget and stakeholder buy in was reported as more challenging. Quality and compliance departments were often described as cautious adopters, requiring extensive validation evidence before approving new tools.

Training gaps also posed risks, with concerns that without adequate user competence, automated solutions could be misunderstood or misapplied. Change management processes, particularly in larger or more regulated organisations, were perceived as lengthy and sometimes resistant to disruptive technologies. These findings align with the literature on technology adoption in regulated sectors, which underscores the

interplay between organisational culture, resource allocation, and regulatory conservatism. Addressing these barriers requires not only technical solutions but also strategic planning, communication, and leadership commitment to integrating automation into established quality systems.

**P11 QA: '**So, this the people like you come along at this stage and make things a lot easier. When you when you're in that transition, so we're kind of moving from that. So, you would have seen, we've seen this in other companies where they move into that sustaining period process and things get better because we're doing the same thing over and over and over again. So, people like you can make life a lot easier for QA, for OPS and reduce it and. Get all of the time savings and cost savings and stuff like that'

**P2 Auto:** 'I think there's an appetite for among the technical teams, in automation and maybe some of the other related teams. I don't know if there's an appetite there because it does require investment and time. I don't think that just using a company enabled AI and feeding data into that without defined strategy and guidance on how you use those tools for validation cheques. I think within the organisation there's definitely demand from the technical people and maybe demand from senior management, but I'm not sure that they fully understand that that requires a level of investment and willing to provide time to resources to develop that.'

**P3 CSV:** 'None, I think they're probably interested in improving efficiency, but I'm not sure how ready they are to be honest, and we think they're open to it, but I think, well, I only know from a CSV point of view. I think there's a skills gap I wouldn't have much experience with scripting languages, or you know, how to query data and things like that.'

**P8 MDE:** 'I think it the organisation pretty much open, especially for automated solutions. I think the organisation understands that its really time consuming this process currently, but at the same point. The organisation might be a bit reluctant on in terms of moving from something automatised. It seems that was always the way to go. So, there is let's say a barrier in terms of change management to culture to have it adopted. But I do see the organisation open for that.'

**P1 Auto: '**I think that it depends on the function within the organisation. I think that engineering global technical operations are certainly. The business and finance arms are interested because they could see the benefits it's, I guess the other side of the coin is probably quality and more compliance focused grips are going to be a bit more nervous. Around it, about using it to support things batch. I mean, you know, using it to support batch release, they might be happy to use it as a tool. You know, but. Are they still going to want, you know, second person verification, objective evidence?'

#### 4.4.6.1. Theme 6 - Conclusions

Again, broad consensus for the organisations being ready to embrace digital solutions although concern about how the certain elements of the organisation might underestimate workload for implementation and maintenance. The automation and manufacturing data SMEs interviewed seemed to understand this aspect and talked to ownership and responsibility of models.

## 4.5. Research according to Objectives

### 4.5.1. Objective 1: Assess current manual periodic review practices (SSPE/Vendor equipment)

#### 4.5.1.1. Research Question 1

What are the current challenges and limitations associated with manual periodic review validation practices for small scale and vendor supplied equipment?

#### 4.5.1.2. Objective 1 Findings

Reviews are predominantly manual, fragmented, and format constrained. Audit trails are exported per system (often .pdfs or txt), then filtered or scanned in Excel. Matching events to authorised users and to change records is manual and error prone. Dissimilar audit trail designs across equipment prevent a common review approach and increase reliance on local work instructions.

The current state confirms the premise of the research that manual review is time intensive, inconsistent across SSPE/VPE, and in large datasets exposes reviewers to miss anomalies potentially compromising the compliance of the system undergoing review.

### 4.5.2. Objective 2: Understand Regulatory Requirements in Audit Trail Review

#### 4.5.2.1. Research Question 2

What are the regulatory and data integrity requirements for performing periodic review specifically towards audit trail review?

#### 4.5.2.2. Objective 2 Findings

As explored in Theme 2, maintaining compliance of a GxP system was described by all participants and was not seen as an isolated task, but one closely linked to organisational quality systems, staff training, and procedural control to ensure consistency. The emphasis on traceability and documented evidence reflects established regulatory expectations and underscores the critical role of periodic review in sustaining data integrity in GxP environments.

### 4.5.3. Objective 3: Explore opportunities for data automation (scripts/dashboards)

#### 4.5.3.1. Research Question 3

What opportunities exist to leverage data automation tools (e.g., Python scripts, dashboards) to improve the filtering, validation, and traceability of periodic review data?

#### 4.5.3.2. Objective 3 Findings

Strong support for scripted tools (Python/PowerShell) and central dashboards to pre-filter events, link actions to change records, and produce exception based summaries. Participants emphasise validation of code, clear intended use, and reproducibility. Data engineers highlight the value of routing logs into PI/historian for a single source, from which GMP data can be filtered, considered and reproduced on request.

Interviewees talked to the implementation of these tools could allow SMEs to shift effort from exhaustive scanning to targeted investigation, improving consistency and allowing higher review frequency (i.e. weekly/daily summaries vs annual reviews).

### 4.5.4. Objective 4: Investigate AI/LLM applications for review support

#### 4.5.4.1. Research Question 4

How could artificial intelligence tools, such as large language models or chatbots, be applied to support or augment periodic review validation processes?

#### 4.5.4.2. Objective 4 Findings

Cautious optimism was expressed by all the participants, they saw the potential in anomaly detection, clustering, and query/summary assistance, but insisted that explainability, performance monitoring, and human oversight would need to be considered. Other concerns included that AI models were a 'black box' that would potentially impact auditor defensibility.

AI can support (not replace) reviewers best as an assistive layer to support validated data pipelines, with human in the loop and documented model governance.

### 4.5.5. Objective 5: Determine organisational readiness and perceived barriers

#### 4.5.5.1. Research Question 5

What is the perceived organisational readiness and if there are any barriers to implementing automated and AI supported validation review practices in highly regulated environments?

#### 4.5.5.2. Objective 5 Findings

Participants described a lack of understanding that would require upskilling and training to maintain, stress test and execute reviews based on scripted tools. They also talked to resource constraints and the ownership of the tools themselves. Process owners would be required and convincing a traditional conservative QA stance would be among the challenges to be faced.

The business case is strong, but adoption hinges on governance, clear process ownership, training, qualification, and risk management.

### 4.5.6. Objective 6: Develop a framework/recommendation for integrating automation/AI while ensuring DI/traceability/compliance

#### 4.5.6.1. Research Question 6

What framework or recommendations can be developed to guide the integration of data automation and AI driven tools into periodic review practices, while ensuring data integrity, traceability, and regulatory compliance?

#### 4.5.6.2. Objective 6 Findings

Based on participant consensus and context, adopt a staged, risk based pathway:

| Stages | Actions | Owners |
|---|---|---|
| Data foundation & standardisation | Where possible create a single source of truth (e.g., PI/historian) for SSPE/VPE logs | Data Engineers |
| | Update isolated systems/audit logs to make data accessible | Automation & Data Engineers |
| Standard Operating Procedure & QRM | Define review parameters (e.g., admin actions outside change window, disabled audit trail flags, role anomalies). | CSV, QA |
| | Catalogue systems by risk/criticality; prioritise high impact equipment. | QA |
| | Document intended use, limits, and acceptance criteria under QRM. | CSV, QA |
| Validated scripting layer | Build version controlled scripts to ingest, normalise, link events to users/change records, generate exception reports. | Automation & Data Engineers |
| | Qualify scripts (design traceability, unit/functional tests, challenge datasets, IQ/OQ/PQ style evidence). Lock configurations and manage under change control. | CSV, QA, Automation & Data Engineers |
| Review by Exception operations | Move from annual/biennial bulk reviews to periodic exception dashboards (daily/weekly/monthly). | CSV |
| | Maintain human in the loop for triage, impact assessment, and CAPA. | QA |
| Optional AI assist (narrow, auditable) | Start with explainable use cases (e.g., clustering similar exceptions, natural language summaries of pre validated exception sets). | CSV, QA, Automation & Data Engineers |
| | Define model governance: data lineage, performance thresholds, drift checks, periodic re verification, and rollback plans. | CSV, QA, Automation & Data Engineers |
| People & ownership | Assign a process owner for the automated review pipeline; train CSV/QA on reading exception outputs and defending the process to auditors. | CSV, QA, Automation & Data Engineers |
| | Build a skills uplift plan (intro Python for CSV; governance for Data/Automation). | CSV, QA, Automation & Data Engineers |

| Stages | Actions | Owners |
|---|---|---|
| Lifecycle & evidence | Maintain validation packs (intended use, risk assessment, verification results, SOP/WI, training records). | CSV |
| | Log periodic performance checks (e.g., stress tests) to demonstrate ongoing fitness for purpose. | CSV |

*Table 10 - Proposed roadmap for automation and AI integration*

# 5. Conclusions and Recommendations

## 5.1. Industry Recommendations

The use of advanced technologies for audit review in a highly regulated environment requires a multi-faceted approach from every core group tasked with providing, extracting, reviewing and verifying the system logs of GxP systems. Vendors/System/Software manufacturers should be tasked with providing systems enabled to supply complete datasets easily ingested or interpreted by third party software, i.e. database access, application programming interfaces (API). Secondly, quality departments with support from validation and automation/data engineering could potentially project manage in assessing risks of the events in the system logs by developing a QRM strategy to rationalise log items to remove noise from large datasets. Based on the accepted baseline parameters scripts could then be developed through change management procedures and the development of automated tools from the engineering SMEs could then be validated, qualified and verified as such by CSV members. Training and competencies could then be presented to affected areas and a more efficient method of review based off current regulatory requirements could be implemented. Dashboards displaying critical data and reviews could be achieved in real time to allow an RBE approach. The use of AI would require a similar industry path to widespread use but would require the regulatory bodies tasked with defining the guidelines for GxP manufacturing to broaden its scope and move from a definitive method of determining activity on a system to a more corroborative method with periodic stress testing to identify any model drift.

## 5.2. Future Academic Research Recommendations

To further the research and gain a greater understanding of both awareness of new technologies and the potential of both automated solutions and AI models, I propose that a wider population study that includes professionals from multiple organisations in life science or another highly regulated industry to identify more codes and develop more themes to enrich the current research. I also propose that case studies broadly in line with the proposed roadmap are undertaken to evaluate whether the intended framework could be introduced and what potential bottlenecks not foreseen in the study might come to light.

## 5.3. Contributions

This study extends the literature by evidencing how audit trails from small scale and vendor process equipment (SSPE/VPE) drive review burden and compliance risk on large datasets, it also offers practical

suggestions into where explainable AI can be defensible in GxP contexts namely as an assistive layer for anomaly surfacing rather than autonomous decision making and proposes a structured, staged framework that reconciles ALCOA+, 21 CFR Part 11, EU Annex 11, and GAMP 5 expectations with modern data practices. Practically, the findings demonstrate that validated scripting tools and standardised exports can yield substantial efficiency and quality gains without the use of AI, and that review by exception workflows improve cadence and traceability, enabling earlier detection and remediation.

## 5.4. Limitations

Having a single organisation focus for the research limits the understanding to one company and doesn't give a broader context on how the same issue challenges other pharma plants and what potential issues they have faced and how they may have mitigated against them. The qualitive scope of the study means that the research was author lead and interpretation of interview data and questions asked may have impacted the study. Although a wide group responsible for the review process within the organisation was interviewed, regulator perspectives and external auditors were not involved. The research also had no case studies to baseline and test an audit trail so as to understand the practical challenges that might be faced

## 5.5. Conclusions

The primary and secondary data share broad similarities and are on a comparable trajectory. From the manual review constraints and concerns whether they were the manual review of the data, the cleaning of the data to have it presentable or the consistency of the review with ever increasing datasets are borne out in both the interviews (4.4.1.1) and the literature (2.5.1). The data collated defines the issues and answers RO1/RQ1 This type of review requires a different approach to satisfy regulatory compliance and to ensure the safety of the manufacturing process. The regulatory perspective and what it has produced to date in respect to modernising the review process lag behind what the primary data revealed (2.11), users (proportionally more from supporting departments rather than task owners) familiar with the GxP requirements talked to data integrity concerns (4.4.2.1) impacting the current expectations from regulators. An understanding was gained through the research to answer RO2/RQ2. Data accessibility was another concern for this group (4.4.3.1) with a correlation with the secondary data (2.5.1), the ability to interface systems and move away from isolated review is not sustainable. In terms of achieving a different method of review, the primary and secondary data aligned, the literature review explored requirements, how QRM and general risk assessment are key components in delivering a framework for enabling advanced technologies play a role in the review process (2.6, 2.7, 2.8), while the primary research subjects gave a more developmental, constructive proposals on the methods of review themselves, the participants understood that having risk assessed pre-determined rules to analyse is the basis for (4.4.4.1) automated review via scripted tools. This completed the objectives of RO3/RQ3. For the use of AI for regulatory practices the primary data revealed a more cautious approach should be considered when assessing the potential of AI or MLs. The understanding also varied between participants more technical interviewees expressed more detail about how these tools could be implemented and how they would need to have a level of qualification and control to enable them to supplement human activities, whereas the review participants (CSV & QA)

seemed to group both AI and scripting tools as a similar technology (4.4.5). Likewise, the secondary data (2.10) expressed caution but did provide some basis on which the reviews could be conducted to alleviate the workload but maintain the human component. The data collated from both primary and secondary research supported the objectives of RO4/RQ4. Lastly, the concept of ownership and organisational readiness from the primary data was definitely weighted towards the more technical aspects of the interview groups (4.4.6.1), who from a supporting perspective understood the accountability of providing accurate datasets and the responsibility of the organisation to resource the infrastructure. The secondary data clearly defined ownership and responsibility throughout sections 2.6, 2.7, 2.8, 2.9. Again, the data reviewed supported the objective RO5/RQ5 and provide an understanding of where the organisation is currently at (primary) and the possibilities that could be achieved from a considered approach (secondary).

## Appendix A


Interview Questions

**Research Title:** Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland

**Interview Type:** Semi-Structured

**Section 1: Background & Role Context**

1. Can you briefly describe your role and responsibilities within your organisation?
2. How are you involved in the periodic review or requalification of equipment or systems?
3. What types of equipment or systems do you typically review (e.g., small-scale, vendor-supplied, stand-alone systems)?

**Section 2: Current Practices**

4. Can you describe your current process for conducting periodic reviews?
5. What systems or tools do you use to access and review data (e.g., audit trails, logs, change records)?
6. How much of the periodic review process is manual? What specific tasks require the most effort or time?
7. Are there specific challenges or limitations you experience when reviewing small-scale or vendor equipment?

**Section 3: Regulatory Compliance & Audit Trails**

8. How do you ensure data integrity and traceability during periodic reviews?
9. How accessible and usable are audit trails in the systems you work with?
10. Are audit trail reviews part of your routine validation or only triggered by events (e.g., deviations, CAPAs)?

**Section 4: Technology & Automation**

11. Have you or your team used any automated tools (e.g., scripts, dashboards) to support data review or validation?
12. What is your view on using scripting tools like Python to automate parts of the validation review process?
13. Do you believe tools like AI or chatbots could support periodic review activities in the future? Why or why not?

**Section 5: Organisational Readiness & Barriers**

14. How ready do you think your organisation is to adopt more automated or AI-supported validation tools?
15. What barriers do you see to implementing such tools (e.g., system ownership, validation of the tools themselves, skills gap)?
16. Do you think additional training would be needed for your team to use these technologies effectively?

**Section 6: Final Thoughts**

17. In your opinion, what would make periodic review processes more efficient or effective in your organisation?
18. Is there anything else you'd like to add about your experience with validation or digital tools?

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

Name: **Stephen Devlin**

Institution: **Griffith College Dublin**

Email: stephen.devlin4@gmail.com

Phone: **0872510972**

**Thank you for taking the time to consider participating in this interview.**

# Appendix B

Informed Consent Form:

GRIFFITH COLLEGE

**Consent to take part in research**

**Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland**

The researcher retains one copy signed by both themselves and the participant. The participant should also receive a copy of consent form as a record of what they have signed up to.

- I _____ voluntarily agree to participate in this research study
- I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind
- I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study
- I understand that participation involves answering questions related to current methods of validated computer system review and potential use of automated tools
- I understand that I will not benefit directly from participating in this research
- I understand that all information I provide for this study will be treated confidentially
- I understand that in any report on the results of this research my identity will remain anonymous. This will be done by changing my name and disguising any details of my interview which may reveal my identity or the identity of people I speak about.
- I agree to my interview being audio-recorded.
- I understand that disguised extracts from my interview may be quoted in my Masters dissertation
- If data is coming from within one company or specifically pertaining to the one company -I understand that I will adhere to all of the codes of conduct and employee confidentiality for Alexion AZ and there is no expectation to breach these by partaking in this research. Include a signed confidentiality statement between researcher and company if deemed necessary.
- I understand that if I inform the researcher that myself or someone else is at risk of harm, they may have to report this to the relevant authorities - they will discuss this with me first but may be required to report with or without my permission

- I understand that signed consent forms and original audio recordings will be retained securely in a password-protected folder on a private device until after my degree has been conferred.
- I understand that a transcript of my interview with all identifying information removed will be stored for two years the recording.
- I understand that under freedom of information legalisation I am entitled to access the information I have provided at any time while it is in storage as specified above.
- I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

**Researcher Details**

Name: **Stephen Devlin**

Degree Programme: **MSc in Pharmaceutical Business & Technology**

College Details: **Griffith College Dublin**

Contact number: **0872510972**

Contact mail: **stephen.devlin4@gmail.com**

***Signature of participant***

Name (Printed)

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Signature of research participant

---------- ---------- Date

***Signature of researcher***

I believe the participant is giving informed consent to participate in this study

---------- ---------- Date

Signature of researcher

Participant Information Letter:


## Participant Information Letter

**Investigation of Periodic Review Validation Practices on Small Scale and Vendor Process Equipment in Pharmaceutical Manufacturing in Ireland**

I would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not to take part.

### WHO I AM AND WHAT THIS STUDY IS ABOUT

My name is Stephen Devlin, and I am currently undertaking a master's dissertation as part of my academic programme. This study aims to explore and evaluate current practices in periodic review validation of small-scale and vendor-supplied equipment in pharmaceutical manufacturing in Ireland. The objective is to understand the challenges, limitations, and emerging opportunities for automation and digital tools within validation processes. This research forms part of my master's degree programme and will contribute to the completion of my dissertation.

### WHAT WOULD TAKING PART INVOLVE?

If you agree to take part, you will be invited to participate in a one-to-one interview lasting approximately 30 minutes. The interview will be audio-recorded (with your permission) and later transcribed for analysis. You will be asked questions about your experiences, opinions, and practices relating to validation and data review. You are free to skip any question or stop the interview at any time.

### WHY HAVE YOU BEEN INVITED TO TAKE PART?

You have been invited to take part because you are involved in validation, quality assurance, or compliance activities within a pharmaceutical manufacturing environment in Ireland. You were identified through professional networks or referrals based on your relevant expertise.

### DO YOU HAVE TO TAKE PART?

- Please note:
  - that participation is voluntary
  - that a decision not to consent will have no adverse consequences
  - that consent can be withdrawn at any time
  - If you wish to withdraw, please contact **Stephen Devlin** at **0872510972**

## WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF TAKING PART?

There are minimal risks involved in participating. All data will be anonymised and handled confidentially. You may benefit by contributing to research that may improve industry practices and inform future developments in validation processes. If at any point you feel uncomfortable, you may decline to answer any question or end the interview.

## WILL TAKING PART BE CONFIDENTIAL?

Yes. Your identity will remain confidential. All personal identifiers will be removed from transcripts and replaced with participant codes. Company-specific information will only be included with prior written permission. However, confidentiality may be breached if there is a serious risk of harm to you or others, or disclosure of criminal activity. Non-anonymised data such as consent forms and audio recordings will be securely stored.

## HOW WILL INFORMATION YOU PROVIDE BE STORED AND PROTECTED?

Signed consent forms and original audio recordings will be retained securely in a password-protected folder on a private device until after my degree has been conferred. Transcripts with all identifying information removed will be stored for two years after this. Under freedom of information legislation, you are entitled to access the information you have provided at any time.

## WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of this study will be submitted as part of my dissertation. The dissertation will be made available in the college library and may be included in an online academic repository, if applicable. There are no current plans for publication or conference presentation.

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

Name: **Stephen Devlin**

Institution: **Griffith College Dublin**

Email: stephen.devlin4@gmail.com

Phone: **0872510972**

**Thank you for taking the time to consider participating in this research.**

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