Innopharma education

GRIFFITH COLLEGE DUBLIN

Electronic batch records and the process of their design and implementation within a multi-product biopharmaceutical facility in Ireland

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

MSc in Pharmaceutical Business & Technology

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Griffith College

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CANDIDATE DECLARATION

Candidate Name: Jean O'Driscoll

I certify that the dissertation entitled:

Electronic batch records and the process of their design and implementation within multi-product biopharmaceutical facilities 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 acknowledgement is given.

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Date: 27 January 2024

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Date:

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ACRONYMS & ABBREVIATIONS

ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate
BPR	Batch Production Records
BR	Batch Record
cGMP	Current Good Manufacturing Practices
CHO	Chinese Hamster Ovaries
CIPC	Critical In Process Control
CPP	Critical Process Parameters
CSV	Computer System Validation
DI	Data Integrity
DMS	Document Management System
DSP	Downstream Processing
DVI	Detergent Viral Inactivation
eBR	Electronic Batch Record
EC	European Commission
EIS	Enterprise Information Systems
eLog	Electronic Log
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
FIT	Filter Integrity Tester
GAMP	Good Automated Manufacturing Process
GDP	Good Documentation Practices
GMP	Good Manufacturing Practices
HE	Human Error
HEC	Hydrophobic Exchange Chromatography
HSE	Health, Safety & Environmental
ICH	International Committee for Harmonisation
IEX	Ion-Exchange Chromatography

ISPE	The International Society for Pharmaceutical Engineering
IT	Information Technology
LpH	Low pH
mAb	Monoclonal Antibody
MBR	Master Batch Record
MES	Manufacturing Execution Systems
NF	Nanofiltration
NPI	New Product Introduction
NS0	Murine Myeloma
pBR	Paper Batch Record
PQS	Pharmaceutical Quality System
ProA	Protein A
QA	Quality Assurance
QbD	Quality by Design
QMS	Quality Management System
QP	Qualified Person
QRM	Quality Risk Management
RbE	Review by Exception
RFT	Right First Time
SME	Subject Matter Expert
TFF	Tangential Flow Filtration
UF/DF	Ultrafiltration/Diafiltration
USP	Upstream Processing
VI	Viral Inactivation

ABSTRACT

The dissertation relates to electronic batch records and the process of their design and implementation within multi-product biopharmaceutical facilities. This dissertation outlines the position of electronic batch records (eBR) in the current age of digitisation within the biopharmaceutical industry. It presents the benefits that can be obtained through eBR implementation, particularly in the realm of compliance and right-first-time execution. It presents the quantity of paper record reduction within a single biopharmaceutical facility. It also outlines the challenges introduced with eBR implementation and the requirements for companies to adopt practices and processes to realise the associated benefits. This research was focused within a single company comprising of numerous biopharmaceutical facilities on one site located in Ireland.

This dissertation identified the technical hurdles that must be overcome during eBR implementation, and also the organisational barriers that could impede successful implementation. Data was collected across organisational hierarchies via an online survey (N=119). This survey aimed to collect data as it relates to (i) internal attitudes towards eBRs, (ii) eBR familiarity, (iii) ease of eBR adoption, (iv) understanding of eBR processes, (v) understanding of eBRs compared to paper records and, (vi) time/experience impact on eBR attitudes. This data was analysed to identify relationships between organisational role/functional role and the areas of investigation. Qualitative data was also collected via a series of semi-structured interviews (N=11). These interviews were completed with subject matter experts (SMEs) in eBR implementation and participants were either presently or previously involved in an eBR implementation project. They were conducted across technical and management personnel who were identified as either (1) business SMEs, experts in paper batch record content and production processes or, (2) eBR SMEs, personnel familiar with IT requirements to enable the translation of paper process to electronic. The interviews aimed to gather information across the following areas, (i) role in eBR implementation (ii)understanding of drivers for eBR implementation(iii) priority of eBR implementation within the business, (iv) challenges and benefits associated with eBR implementation, (v) structure of eBR implementation, and, (vi) behavioural and technical challenges of eBR implementation. The output from the surveys and interviews was interpreted to establish research findings associated with this dissertation.

The research found that the implementation of eBRs is a complex process, and its success is not depending on a single variable. Findings showed that both technical and organisational challenges

exist, and improvements can be made by addressing both areas. The research revealed the compliance benefits obtained through eBR implementation. It also demonstrated the significant time saving and streamlining effect of eBR in the process of batch release. However, this research also showed a need for an internal mindset change to the eBR implementation approach. It indicated a requirement for processes and practices to evolve to enable both eBR implementation and maintenance into the future. This research demonstrated the importance of understanding gaps within the current process and potential risks associated with knowledge management and training in eBRs. This dissertation's research findings present an opportunity to adapt current approaches to eBR implementation to enable the benefits of eBR implementation within the organisation.

CHAPTER ONE

1. INTRODUCTION

The biopharmaceutical industry, along with the wider pharmaceutical industry, is primarily concerned with the manufacture and release of (bio)pharmaceutical materials for the treatment of human illnesses. The ability of a facility to produce and release batches efficiently, and compliantly, impacts the ability of a company to access market share to obtain profits and funding of further research and development efforts. Within the facilities studied in this dissertation the efficient production and release of batches is of concern as batch production times decrease there is an increasing the number of batches requiring release which can result in a pinch point. This places significant demand on production personnel, in particular Quality Assurance and Technical Services. Paper records require significant manual interactions, both during creation, execution, and review. As a result, paper systems are prone to human error factors at all stages in their lifecycle. Additionally, the requirement to create new product-specific paper batch records for each new molecule places additional demands during new product introduction and the technology transfer process. Manual execution also poses data integrity challenges, an issue which is presently to the fore of regulatory focus during good manufacturing practice inspections. The implementation of electronic batch records enables the opportunity to implement a "review-by-exception" approach, whereby records do not require manual intervention or review unless an event has occurred causing the record to deviate from the designed path of execution or pre-determined parameters.

The use of electronic batch records offers distinct advantages over paper records where data integrity is concerned. The record will enforce completion of steps sequentially ensuring that regulatory compliance expectations are met by system design. Electronic records also enable the interfacing of electronic batch records with external systems, such as in-process analytical equipment, enabling automation data retrieval and removing the potential for transcription errors. Real time assessment of information collected can be compared against pre-determined specifications within the electronic batch record ensuring any process discrepancies are detected in real-time allowing appropriate response. The removal of manual execution streamlines production processes, prevents rework, and removes the potential for an issue to go undetected.

The ability to interface with the source system ensures that checks are performed at point-of-use. Where issues are detected, electronic records will identify this issue to operations personnel preventing continued execution and do not require interpretation of results, that may also be prone to human error. Electronic records have the ability to perform complex calculations without human intervention, this represents another risk mitigation with the introduction of electronic records.

In addition to the many technical challenges in the migration from paper to electronic records the transition from manual execution to electronic systems represents a period of significant change within an organisation that may be met with resistance. To maximise the benefits associated with electronic records, organisational barriers to such change must be understood and navigated to enable the seamless integration of these systems without internal disruption (de Wit, 2020). The implementation of electronic records is a necessary change required to keep the organisation in line with the changing pharmaceutical landscape. The alignment of prioritisation of electronic record adoption across management hierarchies is required to ensure consistent messaging throughout the organisation. In order to achieve buy-in to such a significant change understanding the internal mindsets and cognitive maps of the organisation is necessary to enact change.

The adoption of electronic record systems represents a significant opportunity within the pharmaceutical industry. The adoption of electronic batch records forms part of a 'digital plant' concept within the biopharmaceutical industry. However, the highly regulated aspect of the pharmaceutical industry has led to a slower adoption of continuous improvements processes for the reduction of inefficiencies when compared to other industries, such as the automotive industry. Adherence to stringent regulatory requirements has often resulted in surplus capacity, non-value-added tasks and significant waste within the life sciences industries (Gabriel *et al.*, 2020). These regulatory requirements must be integral to the electronic record design to ensure compliance.

The design of electronic batch records for multi-product facilities poses a challenge due to the unique requirements for each product produced. The design of the records needs to be flexible to accommodate such variations without becoming exceedingly complex. Once created these records need to be managed, including change management, the ability to initiate changes within

these systems after implementation is a key consideration in the design phase. The resource requirements within an organisation on the introduction of electronic records must be considered to ensure ongoing maintenance and updates are possible. While electronic records offer significant benefits, they also require a robust IT infrastructure and dedicated IT expertise to ensure knowledge management requirements can be met. Such a significant change to batch record design and execution also poses a potential challenge in the realm of training and adaptation to these new processes. Identifying and executing a clear plan to ensure the same subject matter expert knowledge present with paper records is also translated to electronic records is critical to their adoption.

The research undertaken as part of this dissertation aims to identify some of the challenges, organisational and technical, faced when designing and implementing electronic batch records within operational multi-product facilities. This research also aims to quantify the reduction in paper records achieved with the implementation of electronic records within a biotech facility. While there exists a significant body of research with regard to these records there is a lack of documented research into their practical implementation at commercial facilities. Records must be designed and implemented seamlessly such that batch release, and product supply, are not negatively impacted as a result. This research also aims to identify the organisational and technical pre-requisites required to enable such a change. The adoption of electronic records represents a paradigm shift within a facility and without the required pre-requisites cannot be implemented successfully.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Monoclonal Antibodies in the Biopharmaceutical Industry

Biopharmaceuticals refers to pharmaceuticals produced in a biotechnological process using molecular biology methods (Kesik-Brodacka, 2018). While chemically synthesised drugs are the products of chemical processes, biopharmaceuticals are produced in living cells. Biopharmaceuticals differ to chemically synthesised products in most arenas from manufacturing methods to legal regulations and marketing rules (Kesik-Brodacka, 2018). The number of biopharmaceutical products available on the market has increased drastically in the last decade (Figure 1). Mammalian cell culture is the predominant platform utilised for the manufacture of these products. (Ecker *et al.*, 2022)

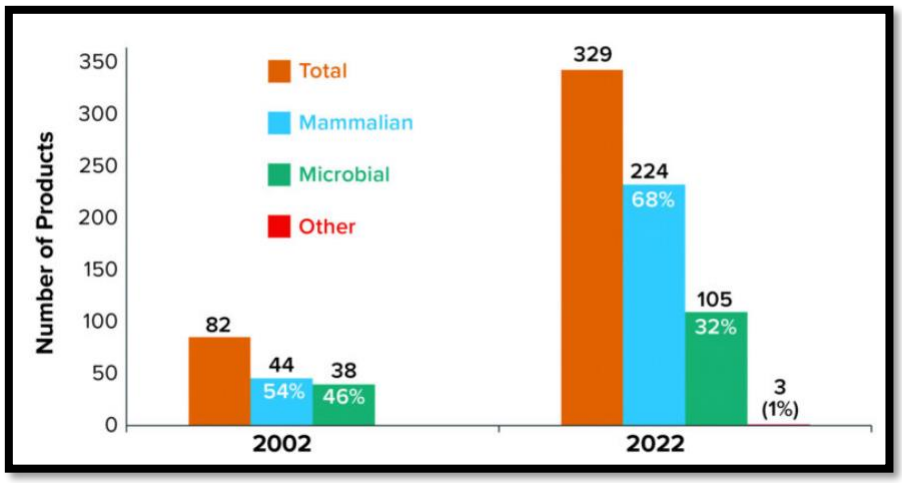


Figure 1 Biopharmaceutical Products and Associated Manufacturing Processes (Ecker et al.*, 2022)*

Monoclonal Antibodies (MAbs) represent approximately 70% of total biopharmaceutical sales (Ecker *et al.*, 2020). As illustrated in Figure 2 the number of MAb therapeutics being approved by the regulators has continued to increase since the first approval, muromonab-CD3, in 1986 (Lu *et al.*, 2020). Therapeutic MAbs and antibody related products include Fc-fusion proteins, antibody fragments, and antibody-drug conjugates (Jin *et al.*, 2022). Mammalian cell lines, such as murine myeloma (NS0), murine hybridomas and Chinese Hamster Ovary (CHO) are utilised for mAb

production. The selection of expression system is determined by its capability to deliver high productivity with suitable product quality attributes (Selişteanu *et al.*, 2015).

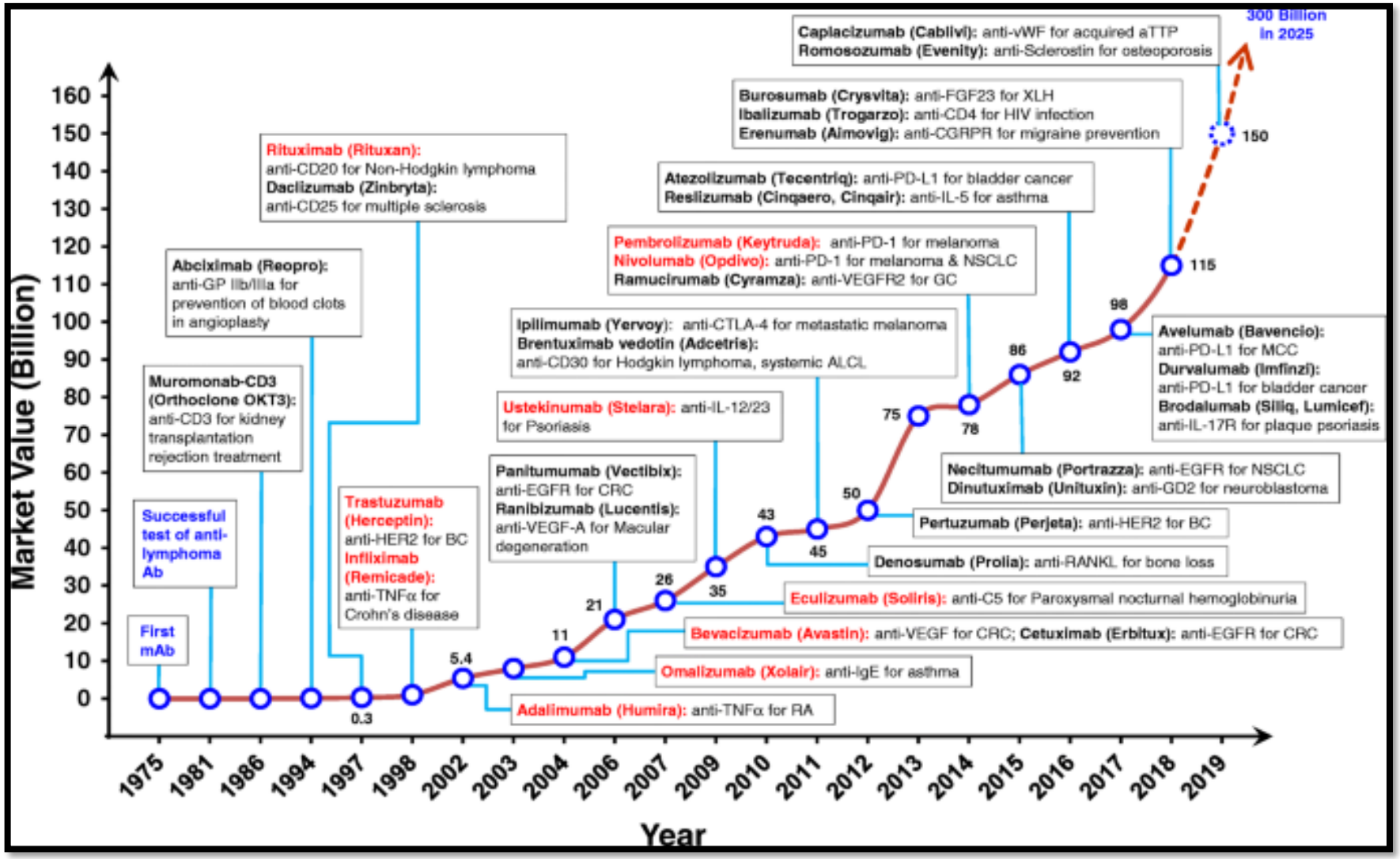


Figure 2 Timeline of FDA mAb Approvals (Lu et al., 2020)

MAbs produced in Mammalian cell culture process are typically separated into two distinct areas, upstream (USP) and downstream (DSP) processing (Figure 3). Upstream processing consists of the cell growth phase, where genetically modified cells are thawed and expanded from shakeflask to production scale bioreactors. During growth phase the cells are fed with media, providing optimum conditions for exponential cell growth. Once cell growth has reached a predefined level, determined based on cell viability and density criteria, the material is harvested, typically using a centrifuge, to split the cells from the expressed protein of interest. A series of filtration steps are performed following centrifugation to further clarify the broth.

Once centrifugation is completed the downstream purification process can commence. Downstream processing typically consists of a capture chromatography step, often Protein A (ProA) Chromatography, followed by a series of viral inactivation and clarifying chromatography steps. Viral inactivation (VI) can be achieved by using a Low pH (LpH) step or a detergent viral inactivation (DVI) step, depending on the characteristics of the product in question. Viral filtration, typically using nanofiltration (NF) is also performed as a viral load reduction step in most downstream mammalian cell culture processes. Ion exchange (IEX) Chromatography is often used as clarifying chromatography steps and exploits the charges associated with the desired products and/or impurities to purify the product stream. Hydrophobic interactions can also be exploited to purify the process stream utilizing Hydrophobic Exchange Chromatography (HEC). During downstream processing a number of buffer exchange steps may be required to transform the matrix to optimize the subsequent protein purification steps, this is performed using an Ultrafiltration/Diafiltration (UF/DF), or Tangential Flow Filtration (TFF), process.

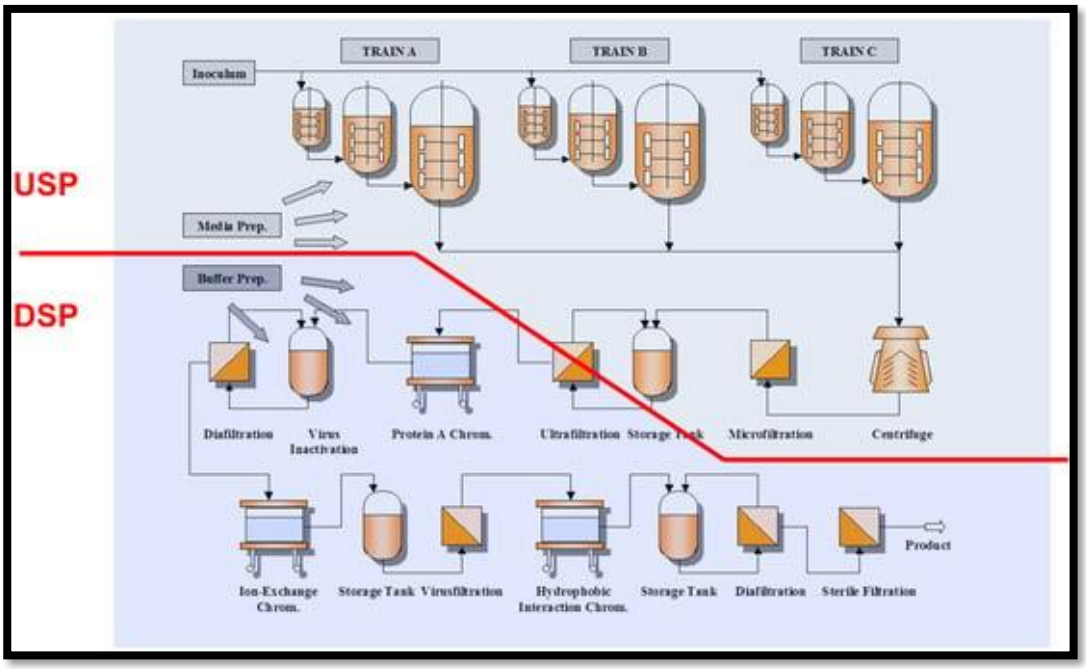


Figure 3 Example of Upstream and Downstream Manufacturing Process for a mAb (Gronemeyer et al.*, 2014)*

2.2 Regulatory Requirements and Good Manufacturing Practices for the Biopharmaceutical Industry

The pharmaceutical industry is governed by stringent regulatory expectations. Failure to adhere to regulatory expectations may result in poor audit outcomes, compromised product quality, product recalls, license revocation or cessation of manufacture. GMP documentation requirements are outlined in Chapter 4 of EudraLex Volume 4. (European Commission, 2011b) Documentation systems are required to "establish control, monitor and record all activities which directly or indirectly impact all aspects of the quality of medicinal products" (European Commission, 2011b). As outlined in EU regulation No 1252/2014 manufacturers are responsible for retaining written records of all activities performed during manufacture of active substances (European Commission, 2014). These records must be handled in accordance with the regulations and issuance, revision, replacement, and withdrawal of documents must be controlled (European Commission, 2014).

The requirements for the production of medicinal products for human use are contained within European Commission Directive 2003/94/EC (European Commission, 2003). Good Manufacturing Practices (GMP) form the cornerstone of pharmaceutical compliance. Article 9, Documentation,

stipulates that “documents shall enable the history of the manufacture of each batch….to be traced” (European Commission, 2003, p.94). This documentation must be available for inspection during regulatory audits and represents a core element of the quality assurance (QA) process. The execution of documentation is an element of the Quality by design (QbD) process, whereby quality is integral to the process and cannot be achieved through release testing alone. Failure to appropriately document the steps performed in a manufacturing process represents risks to batch release (Ahmad et al., 2022).

Current Good Manufacturing Practices (cGMP) represents the most up to date regulations pertaining to GMP and indicates that organisations must ensure systems are up-to-date and employ technologies to enable this. (ISPE, 2023b)

2.3 Computerised System Validation in the Biopharmaceutical Industry

Validation activities are necessary to demonstrate that the process, when operated within established parameters can perform effectively and reproducibly (ICH, 2012). Computerised systems that have an impact on product quality, patient health and data integrity must be validated to ensure the integrity and traceability of information and product quality (QBD Group, 2023). Annex 11 of EudraLex Volume 4 outlines the regulatory requirements for computerised systems.

"A computerised system is a set of software and hardware components which together fulfil certain functionalities."

(European Commission, 2011a)

The primary concern when transitioning from manual to computerised system is the associated risk, there must not be any resultant decrease in product quality, process quality or quality assurance (European Commission, 2011a).

Good Automated Manufacturing Practice (GAMP) was established to provide industry guidance that aims to achieve compliant computerised systems fit for intended use. GAMP 5, Figure 4, is a risk-based approach that provides pragmatic and practical guidance that promotes efficiency and enables innovation and further technical advances (ISPE, 2023a). GAMP is applicable to Manufacturing Execution Systems, MES, which are utilised for eBR execution.

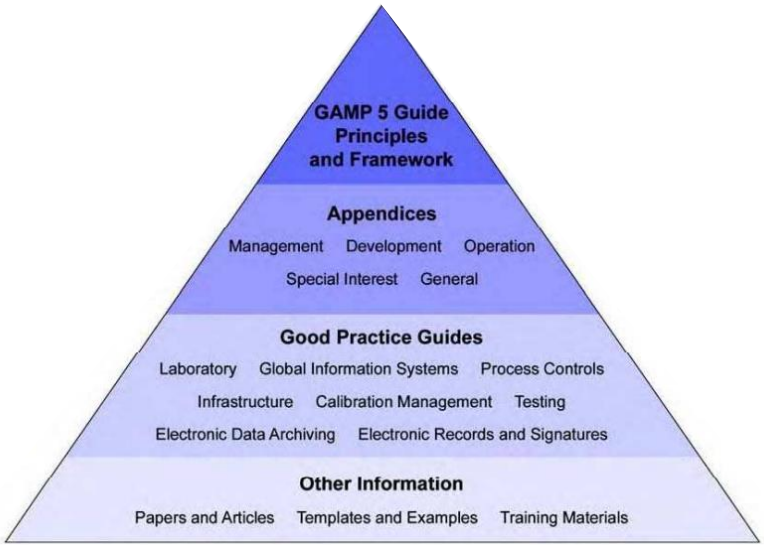


Figure 4 GAMP Document Structure(Shields, 2013)

2.4 Paper and Electronic Batch Records

A Master Batch Record (MBR) contains the overall requirements that each batch record must contain. Batch records (BRs), also referred to as Batch Manufacturing Records (BMRs) or Batch Production Records (BPRs), are batch specific copes of the MBR. Batch record regulatory requirements are detailed within EudraLex Volume 4, Chapter 4: Documentation, and these requirements pertain to both electronic and paper batch records (European Commission, 2011b). Each BR contains a single execution run documenting who, when, where and, how each production step was executed for a single lot. Each BR will also contain the in-process and release tests that are completed to assure the quality of an individual lot and will document any deviations from the defined process.

Electronic batch records can be considered part of digitalisation within the pharmaceutical industry. The process of digitalization is defined by Hole et. al as the increased use of robotics, automatization solutions and computerization to enable reduced costs and improved efficiency and productivity (2021). Digitalization has gained increased attention in the life sciences industry through the release of initiatives such as the FDAs guidance for industry on process analytical technology and ICH guidelines related to Quality Risk Management (QRM) and Quality by Design (QbD) methodologies. (FDA, 2004; International Conference on Harmonisation, 2005; International Conference on Harmonisation, 2009)

Regardless of the form a batch record may take, electronic or otherwise, it should be based on required elements of the approved Manufacturing Formula and Processing Instructions (Figure 5)

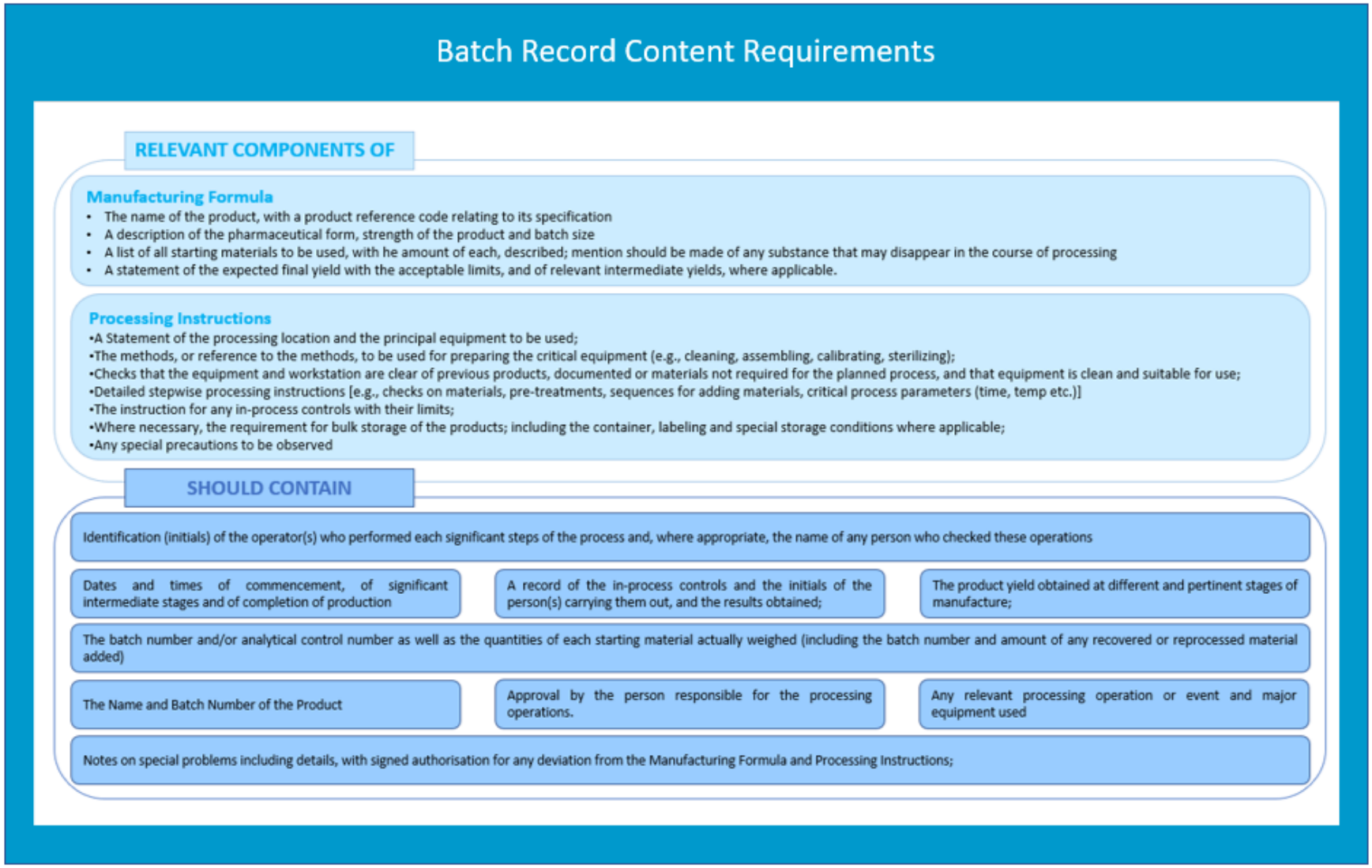


Figure 5 Batch Record Content Requirements (European Commission, 2011b)

Electronic batch records (eBRs) are tools that digitally track all the elements associated with a batch manufacturing process. While there are benefits associated with the transition to electronic systems there are a number of considerations where eBRs are involved. Significant time and monetary investment is required to transition a paper-based process to eBR. Productivity gains associated with the transition are long term goals and there may been a negative impact to productivity during the transition period. Appropriate supplier agreements needs to be put in place with the software vendor to ensure adequate support is available for system maintenance, update, and response to issues, to prevent an impact to production. (Lemay, 2023)

Manufacturing execution systems (MES), incorporating electronic batch records (eBRs) represent an opportunity to reduce manual steps associated with the production and release of batches. Manufacturing Execution Systems, MES, are an element of Enterprise Information Systems (EIS). Developed in the 1970's MES bridges the gap between planning systems and controlling systems while using manufacturing information to support manufacturing processes. (Mantravadi and Møller, 2019)

2.5 Data Integrity and Batch Records

GMP regulations require documented evidence that the manufacturing process was completed as per pre-determined expectations. Throughout the lifecycle of pharmaceutical production information is constantly being generated, this information must be documented in accordance with good documentation practices (GDP).

"If it's not written down it didn't happen."

(Patel and Chotai, 2011)

Data integrity within this documentation is paramount. Data integrity (DI) refers to the completeness, consistency, and accuracy of data. All data collected should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA) (FDA, 2016). The ALCOA principles initially proposed have now been extended to ALCOA+, as indicated in Figure 6 . Data integrity violations are increasing during audit inspections prompting regulators to double-down on required controls and indicating that DI is the main issue the pharmaceutical industry is currently dealing with (Charoo *et al.*, 2023).

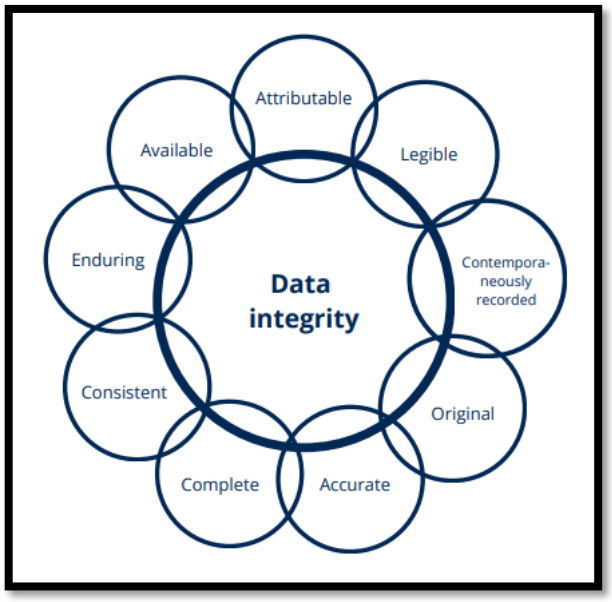


Figure 6 ALCOA+ Principles (QBD Group, 2023)

Data integrity is applicable to all records, electronic and paper. Electronic systems offer opportunities for improved compliance with DI due to potential for system integration, removal of manual execution steps, enhanced security features and improved audit trail capabilities (Charoo *et al.*, 2023). Industry 4.0, or Pharma 4.0, describes smart factories that integrate autonomous real-time monitoring and control to enable improved responsiveness and flexibility. (Alosert *et al.*, 2022) As technologies advance and digitalisation continues in the pharmaceutical industry the quantity of data generated is growing. This is relevant to the implementation of electronic records as they create another data source. Due to the potential for large quantities of data to be generated as a result, data integrity (DI) should be central to design considerations. Data integrity is of paramount importance to assure product quality.

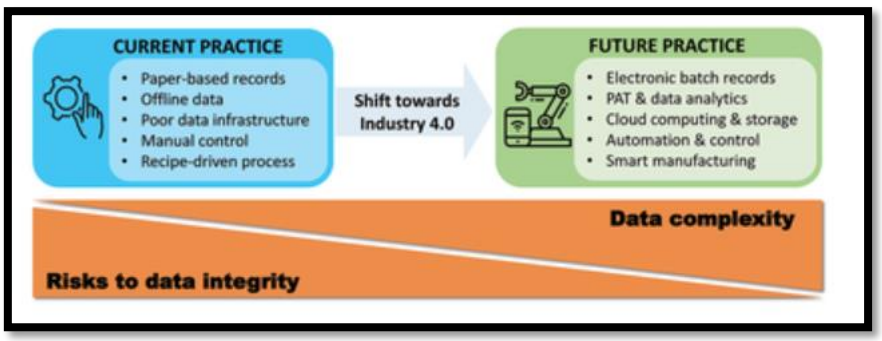


Figure 7 Data Integrity and Pharma 4.0(Alosert et al.*, 2022)*

Where electronic record implementation is considered, it is necessary to have the required IT infrastructure in place to handle the information generated throughout the data lifecycle (Figure 8). The data collected must be managed, control must be exercised to ensure data is stored, transferred and backed-up appropriately. Without a robust infrastructure in place additional risk to ongoing processing is created if a system breaks down. Systems must be designed in such a way that controls for the detection of errors, omission and inconsistencies in data are in place. (Charoo *et al.*, 2023)

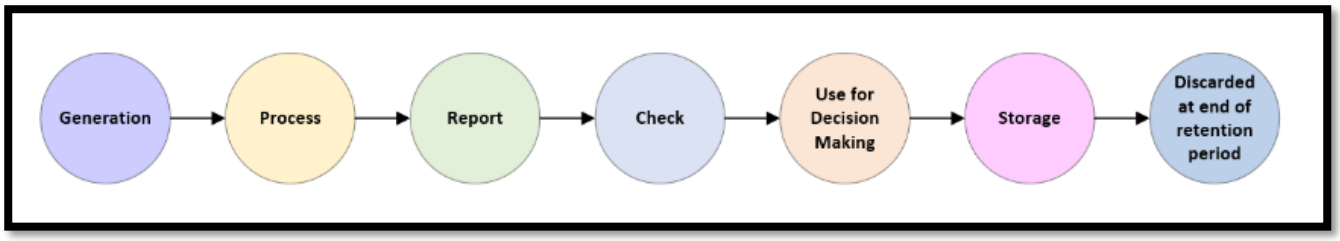


Figure 8 Data Lifecycle (Author's Own)

Electronic records are "data and information that are created, modified, archived, retrieved, and distributed by a computer system with a specific regulatory purpose" (QBD Group, 2023). Electronic records have become more prevalent in the pharmaceutical industry in recent years as technological advances have enabled the reduction of paper-based systems for many platforms, such as document management systems (DMS), inventory systems and production control systems. The use of electronic systems has many associated benefits:

1. Reduced Costs
2. Availability of Information
3. Reduced environmental impact (reduced paper consumption)
4. Ease of finding information
5. Streamline compliance activities
6. Reduced potential for human error.

However, the implementation of electronic records also requires enhanced security measures to maintain data integrity. Testing of electronic records during validation demonstrates the integrity of the data being processed by the computer system. An audit trail of electronic records is required to document timestamped history of operator entries and actions that create, modify, or delete electronic records. (FDA, 1997) Where electronic records are employed electronic

signatures are used in place of operator initials. Electronic signatures refer to "computer data compilation of any symbol or series of symbols executed, adopted, or authorised by an individual to be the legally binding equivalent of the individual's handwritten signature" (FDA, 1997). Where electronic records and signatures are employed a robust password management process must be in place to prevent inadvertent use of credentials.

2.6 Impact of Quality Risk Management and Review by Exception on eBRs

Process understanding, and quality risk management (QRM) are at the core of enabling Review by Exception (RbE) in production processes. As identified within ICH guideline Q9 (R1):

"Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle" (2023).

RbE, is defined by The International Society for Pharmaceutical Engineering (ISPE) as:

"An approach in which manufacturing and quality data are screened to present or report only critical process exceptions as required by approvers for review and disposition of intermediates and products" (Zebib, 2019).

While digitalisation, and adoption of new technologies, such as eBRs, can reduce risk in the manufacture of medicinal products they must be fit for purpose. Without adequate understanding and controls unidentified risks may be introduced. (ICH, 2023) Risks should be classified based on the probability of occurrence, of harm, and the severity of the harm (Figure 9).

		Severity				
		Negligible (1)	Marginal (2)	Moderate (3)	Critical (4)	Catastrophic (5)
Probability	Almost certain (5)	Medium (5)	High (10)	High (15)	High (20)	High (25)
	Likely (4)	Low (4)	Medium (8)	High (12)	High (16)	High (20)
	Possible (3)	Low (3)	Medium (6)	Medium (9)	High (12)	High (15)
	Unlikely (2)	Low (2)	Low (4)	Medium (6)	Medium (8)	High (10)
	Rare (1)	Low (1)	Low (2)	Low (3)	Low (4)	Medium (5)

Figure 9 Risk Evaluation Matrix (PRES, 2013)

RbE is an element of risk-based decision-making, where decisions are informed by knowledge of risks relevant to the decision and whether risks are at an acceptable level. (ICH, 2023) Where critical steps/parameters are established using QRM approach, process anomalies or inconsistencies are identified at these steps will require quality oversight. Where all parameters meet pre-defined ranges and specifications QA oversight is not required and records will progress to auto-closure. This approach significantly reduces the time taken to perform post-execution reviews on whole documents by highlighting those requiring further investigation. Failure to appropriately identify risks within a process represents a concern in the design and implementation of eBRs as issues may go unnoticed with manual review removed from the process. An appropriate QRM process should be completed during eBR implementation in each area, or per unit operation.

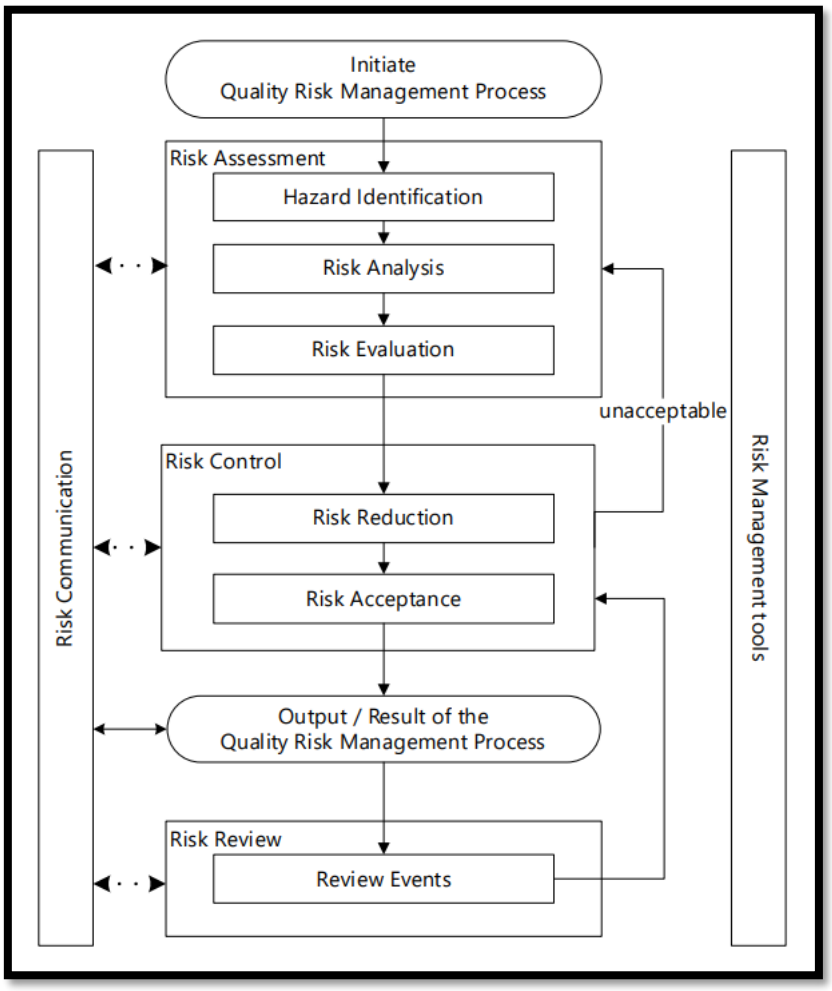


Figure 10 Example Quality Risk Management Process (ICH, 2023, p.9)

2.7 Impact of Right First Time on eBRs

A key enabler for reduced production times is "right-first-time" (RFT) execution. The use of digitalization to integrate systems and remove manual interventions increases likelihood of RFT execution. RFT targets zero defects from beginning to end of a production process. Within the pharmaceutical industry large quantities of documentation are required to comply with regulatory requirements. Paper based batch records often require the manual performance of hundreds of steps such as, data recording, in-process calculations, expiry details of solutions used, and the time and dates of activities completed. Where manual execution is performed there is potential for mistakes, missed entries or incomplete recording of information. The use of electronic BRs (eBRs) mitigates against many of these concerns as data can be recorded directly from instruments and calculations performed by the system, as well as enforcing the completion of all steps.

However, while the use of eBRs increases the potential to interface multiple equipment and instrumentation sets appropriate controls must be implemented for these systems. For example, in process results or readings from weigh scales, pH meters, conductivity meters, osmometers, refractometers, Filter integrity testers (FIT) or spectroscopy instruments (SoloVPE), now have the potential to be retrieved through automated interfaces direct to the batch record removing potential for transcription errors. Each interface must be validated to ensure validity of information retrieved. Interface validation is also required to enable integration of eBR with automation systems, e.g., DeltaV, Foxboro and inventory management systems, e.g., SAP.

Human errors contribute to a failure to deliver on the RFT principles. This is a major source of inefficiency in manufacturing processes that can be reduced, or even eliminated, through integration of eBRs. Reducing potential and likelihood of occurrence represents a key area in reducing production times. (Bona *et al.*, 2021) The creation of flexible batch records, capable of accommodating multiple products enables process standardisation and reduction of process specific elements which require ongoing management to ensure compliance with regulations. Standardisation of processes represents an element of lean thinking that can be applied to the pharmaceutical industry; however this has been performed with limited success. (Bragança and Costa, 2015)

2.8 Organisational Change and eBRs

The implementation of eBRs is an organisational strategic innovation decision to ensure the organisation remains in tune with digital transformation in the pharmaceutical, and biopharmaceutical, industry. To incite change within an organisation all relevant stake holders must be accepting of the fact that time to adapt and learn is critical to ensure that the desired change can be realised effectively (de Wit, 2020). Within a facility where paper batch records are core to operations, and indeed the previous success of a facility, such a drastic transition to eBRs may be met with resistance and scepticism. To achieve the required change de Wit proposes that there are three main organisational arenas where management need to direct their influence. (2020) These subsystems are the parts of the organisation most resistant to change:

1. The political arena – this is where new strategic directions are set. In this area it is necessary to build a coalition of supporters for this strategic change to ensure the plan is not implemented half-heartedly, opposed or silently sabotaged. In the case of eBR adoption, each site must have absolute commitment to implementation from senior management and area management. This can pose particular challenges for those in management as it is a change posed to a system through which they have progressed or excelled thus creating an identity threat when faced with a new system of which they have little to no understanding of at the outset. This can affect the ability to see new directions without prejudice and embrace changes that impinge upon these identities. (de Wit, 2020) Individuals who identify strongly with batch records are most likely to defend old processes and content in response to significant change.
2. The cultural arena – this is where cultural influence needs to be exercised, questioning of shared values, ideas and habits prevalent in the organisation that may resist changes proposed. Leaders must create a new image of a desired future state using eBRs and develop and embed a new set of beliefs and values to reach this point. Organisational functions, such as technical services, who are the owners of batch record content, and quality, who are responsible for batch release, represent areas where identity-based response could post a challenge in eBR adoption.
3. The psychological arena – both the hearts and minds of personnel impacted need to be won over to affect change successfully. This is required to encourage others to follow the direction proposed with commitment and dedication. Having gained the trust and respect of those around them leaders must continue to address the emotional needs of the organisation to mitigate concerns and navigate the change process. There are many behavioural challenges, that must be

addressed in order to successful manage the change from paper to electronic batch records. It has been hypothsised that, in order to initiate change, management of the effects of transformation on the core identities and motivations of key individuals and groups must be paramount. (Augier and Teece, 2009) In order to be able to adapt to new technologies companies must overcome resistance to this where individuals defend old directions and ways of working. This is relevant to the implementation of electronic batch records as paper batch record design, and their use, is ingrained in the thought processes of many throughout all layers of the organisation.

Change can be measured using two variables: magnitude and pace (Figure 11).

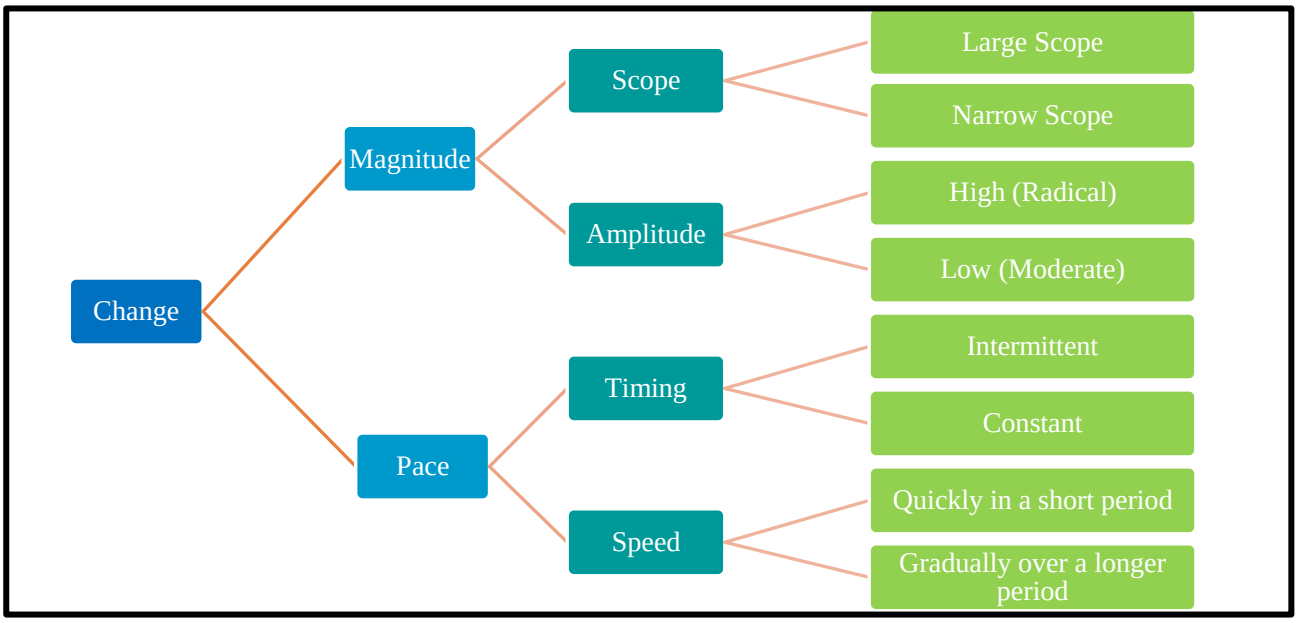


Figure 11 Types of Change(de Wit, 2020)

Both the magnitude and pace of eBR migration need to be balanced to optimise the associated benefits while mitigating against internal resistance that may be detrimental to the overall outcome. The timing of migration to eBRs should be considered, as stated by de Wit people may be more receptive to accepting radical and painful changes when they are completely necessary (2020). However, people are also at risk of shunning new ideas in a period of upheaval. (de Wit, 2020) When implementing change, sources of organisational rigidity may become evident (Figure 12).

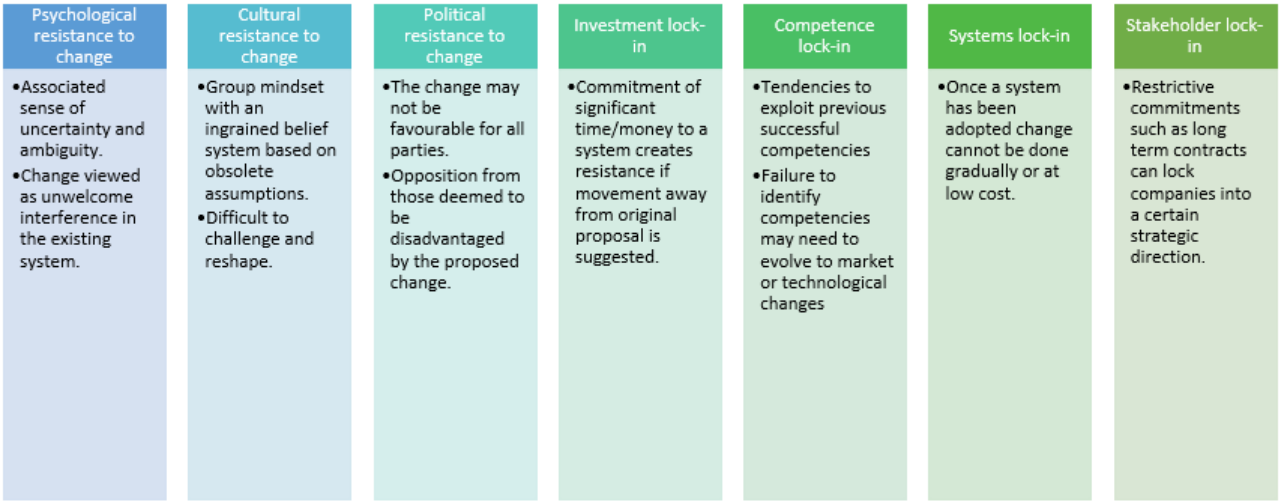


Figure 12 Sources of Organisational Rigidity (de Wit, 2020)

Identifying these sources, and developing strategies to counteract such thought processes, is required. It is important to acknowledge that the barriers to implementation may very across the organisational hierarchy as each area has unique considerations and concerns. It is necessary to seek to understand the concerns across a broad population in order to adapt the change strategy appropriately.

2.9 Knowledge Management and eBRs

The implementation of electronic batch records represents a challenge in the realm of knowledge management. As new technologies are introduced the necessary systems need to exist to be able to design, operate and initiate changes within these records. As defined by ICH Q10

"Knowledge Management (KM) is a set of enabling capabilities and associated behaviours; that supports how knowledge is acquired, analysed, stored, disseminated and applied; so that knowledge will flow, grow and evolve over time."

(Lipa, 2011)

Knowledge management is a key enabler to the introduction of electronic records and is critical to enabling a state of control. This knowledge management requirement must be understood across the organisation and is applicable to the lifecycle of these record, and all functions involved in each stage.

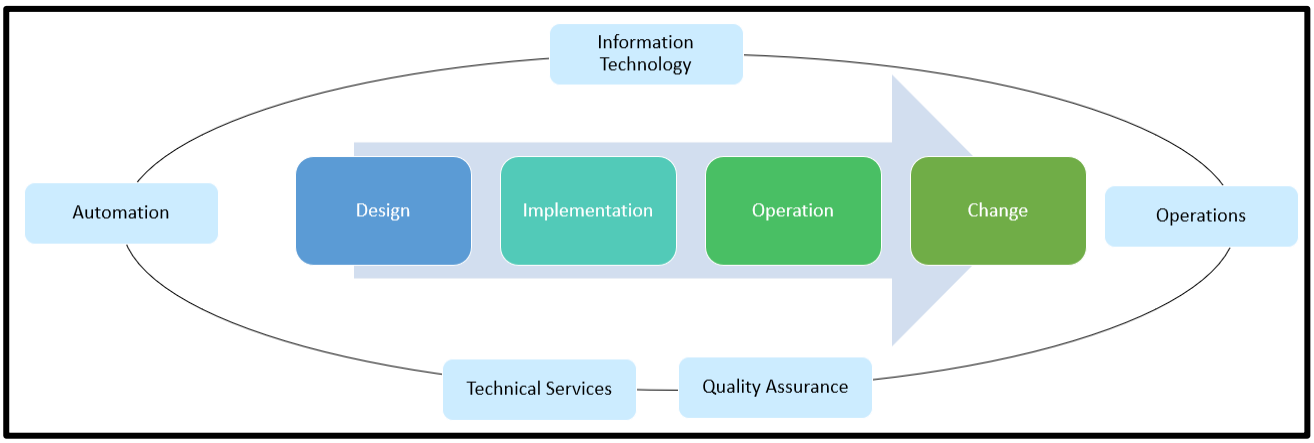


Figure 13 Knowledge Management (Author's Own)

2.10 Electronic records in Manufacturing

While the adoption of electronic records in the biopharmaceutical industry is lagging compared to other industries there are learnings and insights that can be obtained from literature associated with many different manufacturing areas. The implementation of electronic batch records represent an opportunity for organisations to merge IT strategy with business strategy. (Mantravadi and Møller, 2019) Manufacturing Execution Systems, or MES, enable the integration of planning systems (enterprise resource planning ERP) and controlling systems (automation systems, sensors) and also uses manufacturing information (equipment, resources) to support manufacturing processes. These MES enable the pharmaceutical industry to reduce production costs and also to increase compliance with regulatory requirements. (Blumenthal, 2004) In one study, eBR adoption within a company was found to have resulted in a 75% reduction in human errors during execution. (Marsh and Eyers, 2016) This same study concluded that cost, resources to implemented and the in-built obsolescence of manufacturing software systems were the main disadvantages associated with eBR implementation. (Marsh and Eyers, 2016) Cost reduction is believed to be achieved with MES implementation as a result of reduced inventories, improved manufacturing lead times, and decreased number of personnel required to handle the regulatory documents. (Adler *et al.*, 1995) Towards the end of the last millennium, Rocketdyne, a company working to provide NASA with engines for next generation space shuttles, experienced time reduction benefits associated with paperless manufacturing, removing lengthy processes associated with manual execution. (Chase, 1998) Blumenthal identified typical goals associated with MES implementation include, immediate documentation of process steps, improved data

quality for assessing processes and production, reduction of administrative work for maintaining documentation, rapid access to current data and improving process reliability. (Blumenthal, 2004)

Other studies have also cited that eBRs present challenges where companies are dynamic and require adaptive execution strategies and an ability to respond to change. (Saenz de Ugarte *et al.*, 2009) This was also demonstrated by Marsh et. al, identified that barriers to the implementation of Manufacturing Resource Planning (MRP) systems include cost of implementation, a need to reengineer business processes, the complexity and time of implementation and the need for employees to adjust to working in new systems. (2014) Blumenthal identified that systems must be flexible enough to adjust to the most versatile workflows and that customisation is necessary and wanted. (2004) This study concluded that eBR functionality is strongly influenced by parameters outlined in master batch record requirements and also identified that depending of the complexity of procedures and number of products to be manufactured, these customisation activities may take several months. In order to reduce the time associated with customisation it was proposed that reusable description elements and well-structures master batch record availability are core to reducing the effort of electronic batch record design. (Blumenthal, 2004) Additional literature identified the requirement for adaptability of MES systems, that a standard solution cannot be powerful enough to make all the conceivable modifications via parameters. (Kletti, 2007)

It was found that the expectations for the realised benefits associated with MRP adoption may have been unrealistic and seen “as a panacea for solving all the challenges experienced.” (Marsh *et al.*, 2014) Blumenthal identified the requirement to integrate all key users in the implementation process, to create an opportunity for them to get familiar with the system prior to implementation, citing that without the necessary experience and understanding of the objectives the implementation “would inevitably be doomed to failure.” (2004) This proposal of integrating end users at an early stage, when defining system requirements or identifying key functionality, indicates the importance of these end users. The users are in a unique position to also influence and make contributions during design to enhance the system. This early integration is linked to organisational change and bringing end users on the journey to implementation to ensure success. “They have to be convinced of the benefits the MES provides for them.” (Blumenthal, 2004)

The magnitude of the task to translate paper to electronic records was a topic present in the literature. Blumenthal identified this as an "intellectual challenge that should not be underestimated" and that those involved should be well trained in defining master batch records. (2004) Mantravadi and Møller identified a need for organisations to acquire better IT competencies in order to successfully implement and manage MES systems on an ongoing basis. (2019) MES has the capability to create potential new ways to display instructions to operations, the technology would allow more streamlined documents, including pictures, checklists and potentially videos. This however would require a complete design overhaul, and associated resources associated with same, in order to create and maintain these documents. (Adler *et al.*, 1995)

In spite of the belief that additional operational visibility and intelligence systems creates increased business value Mantravadi and Møller concluded that there were no direct links within academic literature where manufacturing execution systems have provided direction in the business decision-making process. (2019) However, it was demonstrated that the implementation of MES within the food and beverage industry reduced lead time and cost, improved overall quality, increased production transparency, and resulted in efficiencies gained. (Chen and Voigt, 2020)

2.11 Impact of eBR adoption in the Biopharmaceutical Industry

Within the biopharmaceutical space, each drug substance batch can comprise of more than 11 production steps each with an associated batch record. Each product has specific regulatory commitments, which may vary dependent on molecule attributes with each of these required to be assessed during production as part of the quality system to ensure compliance throughout the manufacturing process. Additionally, each upstream and downstream step will utilise media or buffer components. Each of these components will also require a batch record to ensure formulation requirements and end-point specifications which are confirmed prior to use. Where column packing and UF/DF membrane installations are required per molecule there are additional batch record requirements to ensure requirements are met prior to commencement of a campaign, further adding to batch records in the system. Each of these batch records requires significant time to develop, review, approve and store. The man hours associated with paper batch records represents a risk in batch production and release and creates difficulties as

companies target reduced batch production times. Without the implementation of eBRs companies may be at risk of becoming personnel constrained to a point where increased batch production does not result in additional batch releases, creating a requirement for more batch storage, typically large-scale low temperature freezer systems which have high costs associated with running and maintenance. Even for a moderate campaign duration the batch record numbers can be considerable.

An in-depth analysis was performed on one of the biotech manufacturing facilities where the implementation of eBRs is well progressed. Within this facility a combination of paper batch records, hybrid paper-electronic batch records and full electronic batch records are utilised. The hybrid paper-electronic batch records incorporate a large number of system steps and inventory steps required in production, significantly reducing the number of manual execution steps required. To determine the number of paper records removed with the introduction of eBRs the 2022 production schedule was used alongside the eBR system (MES) and the production order (PO) release history.

- A total of 57 batches were filled within this facility in 2022.
- The production process consists of 12 Unit Operation Steps.
- The process utilises 36 unique Media/Buffer Operations.
- Half, or 6 Unit Operation Steps, have been converted to eBR.
- Nighty seven percent, or 35 Media/Buffer operations, have been converted to eBR.

Process flow is demonstrated in Figure 14 below, where steps highlighted in green have been converted to eBR.

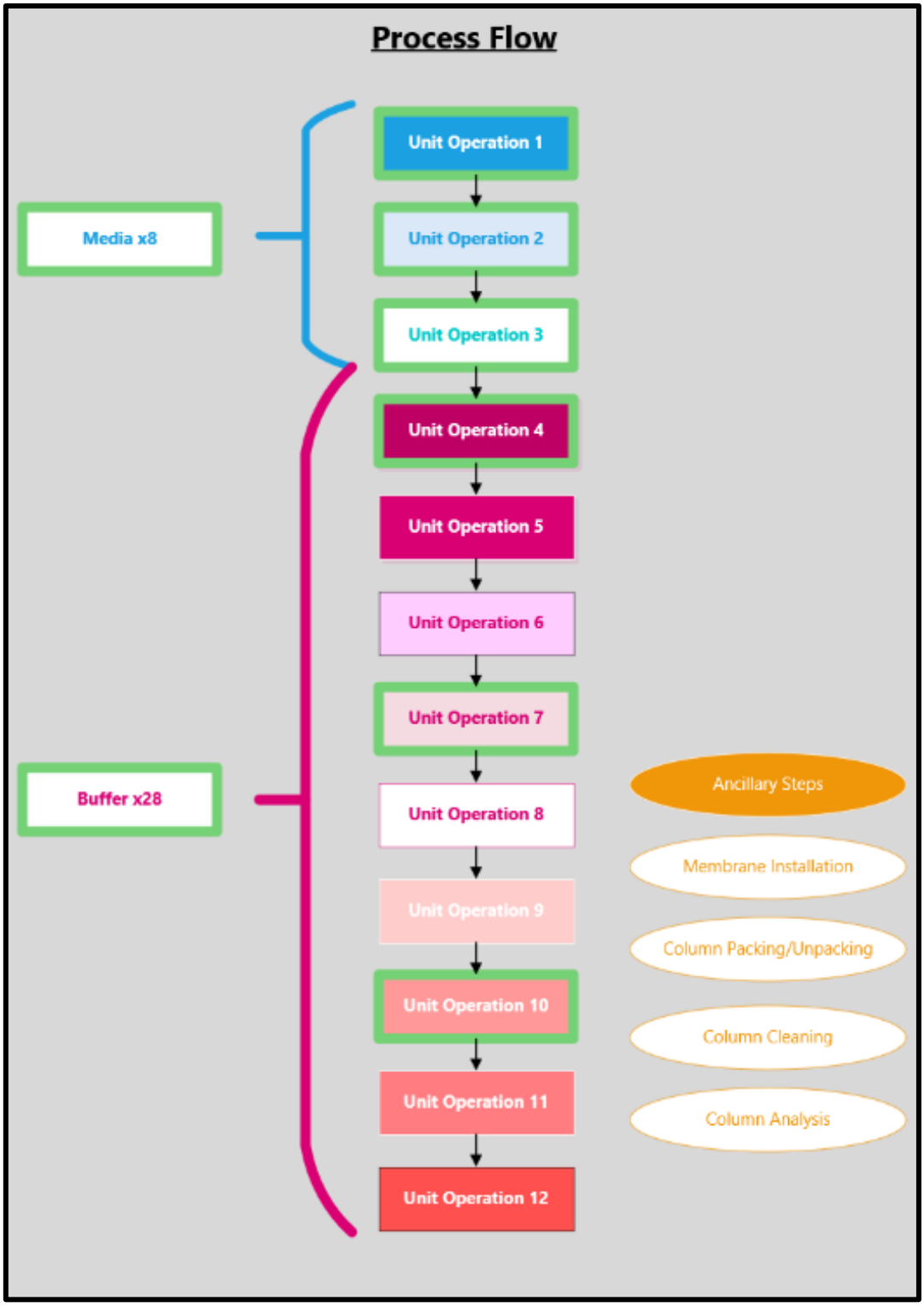


Figure 14 Process Flow (Author's Own)

Where eBRs have been implemented the paper records previously required to complete these steps have been removed. Additionally, for each paper batch record issue two issuance steps were required to be completed prior to introduction of eBRs to ensure collation has been completed and that the required labels are present with the record. For each paper record previously utilised three post execution manual review steps have also been removed. For all eBRs implemented review by exception is in place and records will close automatically if executed as per design. These manual review steps have also been eliminated as a result of eBR implementation. The quantity of paper records, manual issuance steps and manual review steps removed as a result of eBR implementation within this facility is demonstrated in Figure 15 and Figure 16, illustrating significant removal of manual steps as part of the batch record release and approval processes.

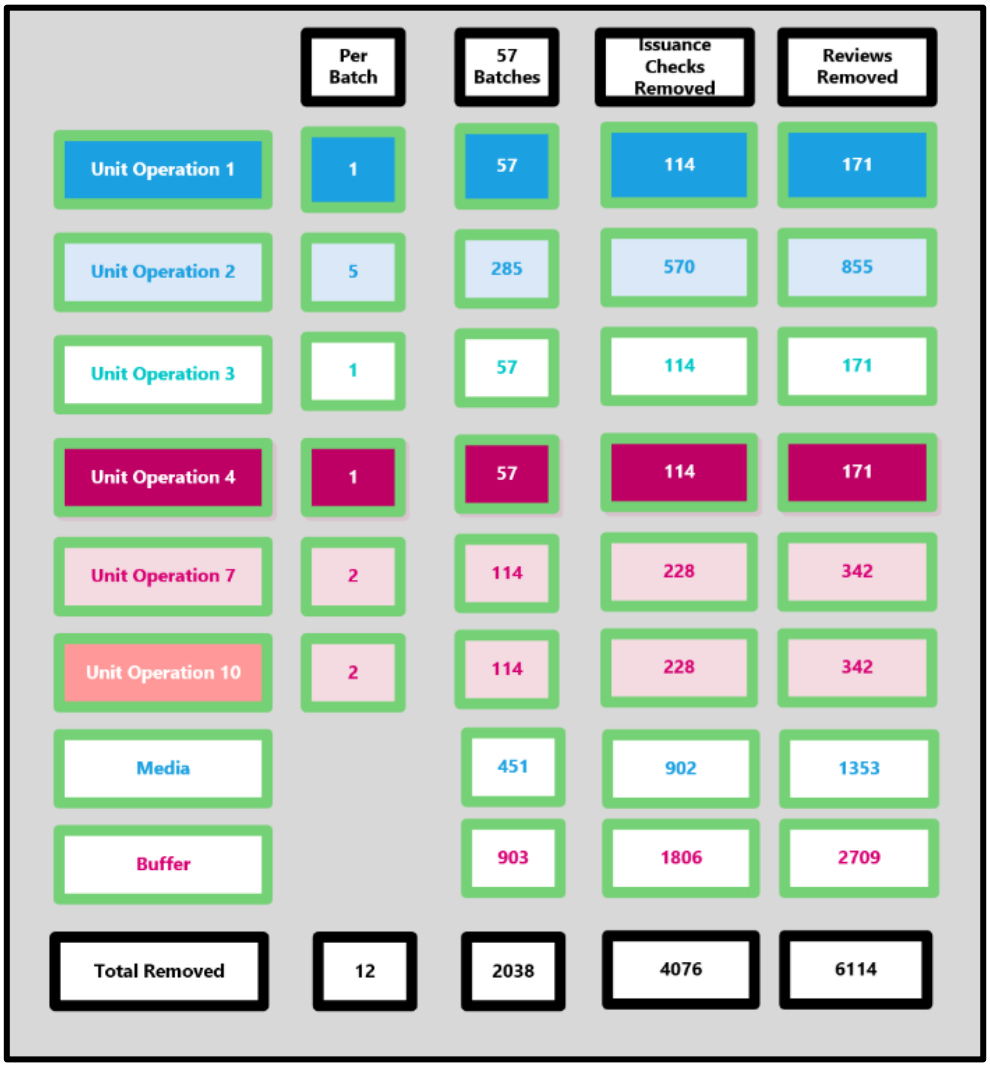


Figure 15 Reduction in Steps as a result of eBR Implementation (Author's Own)

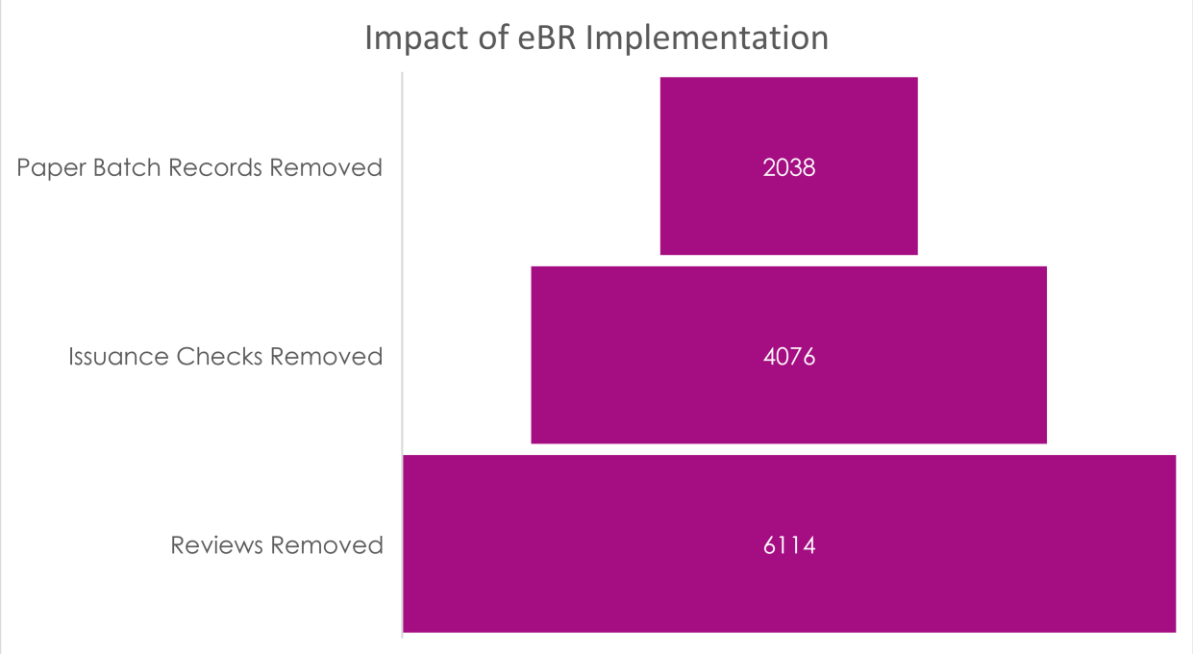


Figure 16 Impact of eBR implementation (Author's Own)

The potential to remove paper records and manual reviews from production represents an opportunity to reduce the time associated with administrative tasks and ultimately the potential risk for error at any of these points in the process.

While eBR implementation is well progressed within this facility there still remains significant benefit to further adoption at the remaining unit operation steps. The potential benefits to be realised if the building were to be one hundred percent electronic are demonstrated below. (Figure 17)

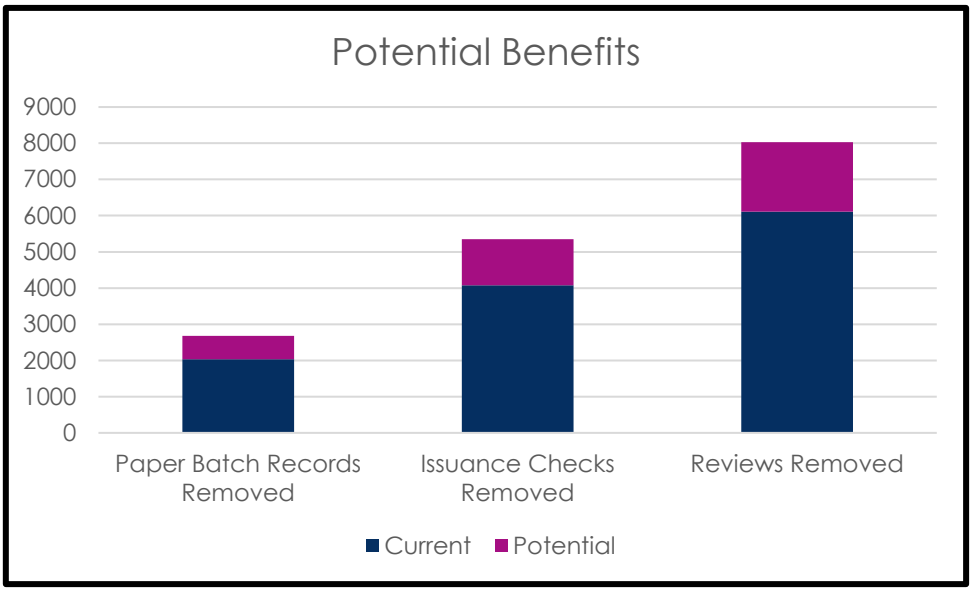


Figure 17 Potential Benefits of further eBR Implementation (Author's Own)

2.12 Further potential for eBR implementation

The analysis of barriers to implementation of eBRs, both technical and organisational, has the potential to reduce risks associated with data integrity (DI) during production, ensuring regulatory compliance and mitigating against potential audit findings enabling continued supply to market, and therefore continued supply of medicines to patients. The analysis of mindsets toward eBR adoption has the potential to identify internal resistance to change and can inform the approach taken to enable a timely introduction of eBRs. The technical challenges associated with the design of eBRs for a multiproduct facility need to be understood to reduce potential for rework in the future, which may negate initial benefits obtained from introduction of eBRs.

2.13 Proposed Conceptual Framework

The conceptual framework outlined in Figure 18 has been developed from information gathered during the literature review phase. The conceptual framework suggests that increased demands for products will drive reduced production times and process intensification. With such production demands the importance of right first time (RFT) execution increases alongside a requirement to ensure an efficient batch release process is in place. Additionally, with increasing regulatory requirements associated with data integrity there is a need to reduce manual execution activities and adopt new technologies to enable this.

The adoption of electronic records is represented within the conceptual framework as it represents an opportunity to enhance the batch release process, reduce execution errors, mitigate against errors associated with human factors and improve date integrity controls. There is a need to innovate and adopt new technologies to meet increasing regulatory requirements and to enable reduced production and batch release times.

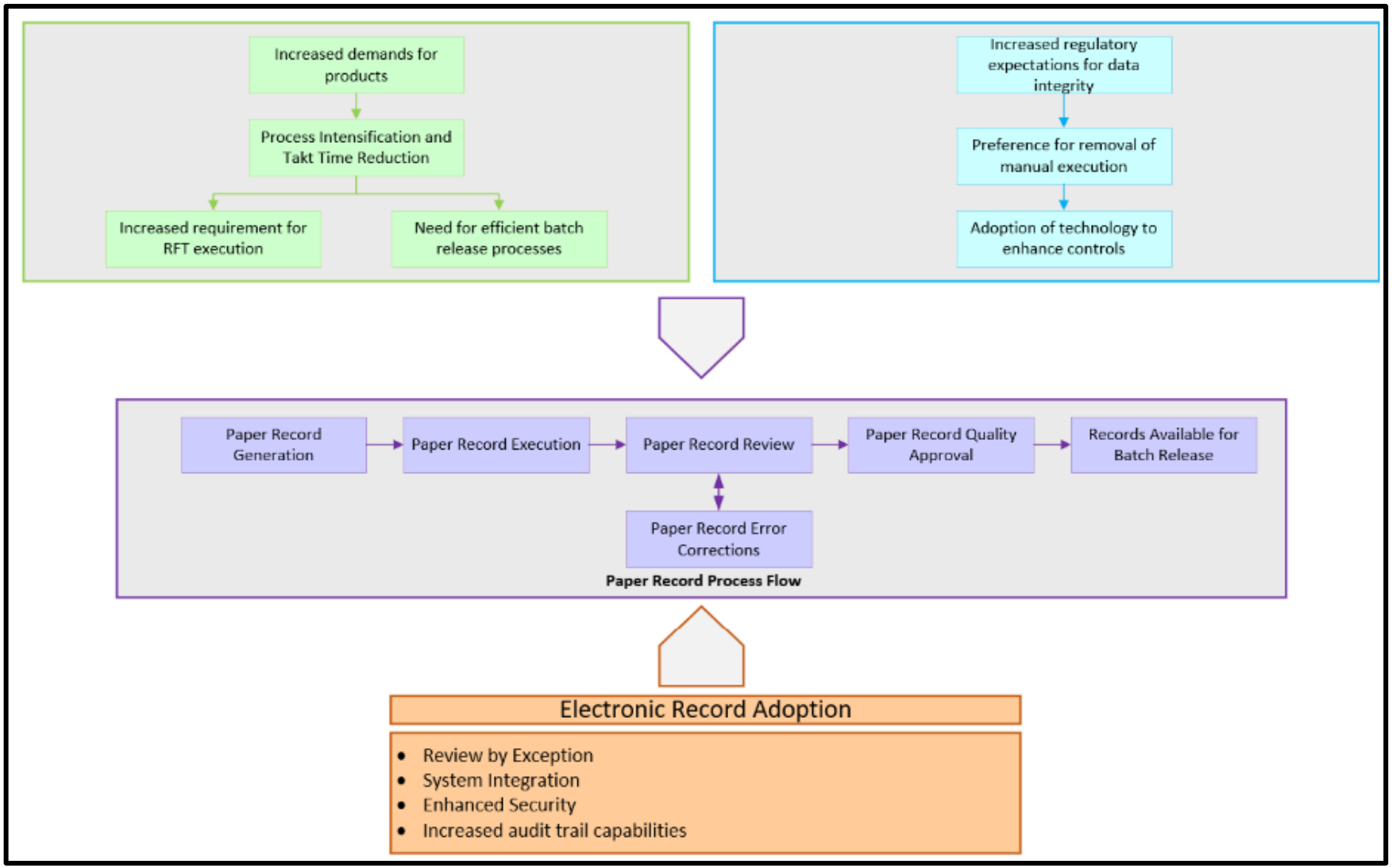


Figure 18 Conceptual Framework (Author's Own)

CHAPTER THREE

1. RESEARCH METHODOLOGY

The aim of this research is to investigate the electronic batch record design and implementation process within multi-product biopharmaceutical facilities. This chapter will outline the research paradigm, research design and research approach utilised to conduct this research.

1.1Research Paradigm and Overall Approach

There are four predominant research paradigms, post positivism, constructivism, advocacy/participatory, and pragmatic. The selection of a research paradigm will dictate how the research is conducted. The characteristics of these paradigms are indicated in Figure 19 below.

Postpositivism	Constructivism
• Determination • Reductionism • Empirical observation and measurement • Theory verification	• Understanding • Multiple participant meanings • Social and historical construction • Theory generation
Advocacy/Participatory	**Pragmatism**
• Political • Empowerment issue-oriented • Collaborative • Change-oriented	• Consequences of actions • Problem-centered • Pluralistic • Real-world practice oriented

Figure 19 Research Paradigms (Creswell, 2009)

The research paradigm selected for this dissertation is a pragmatic approach. Traditional paradigms are associated with quantitative or qualitative research approaches. These traditional paradigms do not support a combined quantitative-qualitative approach due to inherent paradigmatic differences (Maarouf, 2019). A pragmatic approach embraces the plurality of methods and the results from the research questions is of importance rather than the methods employed during conduction of the research (Kaushik and Walsh, 2019). Pragmatists believe that reality is constantly evolving and that there may be single or multiple realities (Kaushik and Walsh, 2019). Employing a pragmatic approach enables a selection of methods, techniques and procedures that best satisfy the needs associated with the proposed research question.

Quantitative research is based on objectivism and positivism, while qualitative research is based on subjectivism and interpretivism (Maarouf, 2019). While quantitative researchers consider themselves independent from the research topic, qualitative research proposes that the

researcher's construction of reality can result in multiple realities. A mixed method approach employs elements of quantitative and qualitative approaches.

Secondary research, conducted through literature review, identified that while the design, implementation, and management processes of electronic records is well documented there is a lack of information on the impact of electronic records within facilities. Analysis of the impact of eBR implementation within a biopharmaceutical facility outlined in section 2.11 demonstrates the benefits realised, and potential additional benefits to be realised, through eBR adoption. As electronic records have been adopted to varying degrees of success across manufacturing areas a qualitative approach will be utilised to identify the main challenges associated with some manufacturing areas over others, an area which is not well documented within the literature.

A qualitative and quantitative approach will be used to investigate potential resistance to electronic record adoption within the organisation. A sequential approach will be taken to data gathering, whereby quantitative data will be collected, followed by qualitative data. The data collected during the quantitative data gathering stage will be used to inform subsequent qualitative approaches.

1.2Primary Research

The purpose of this research is to analyse electronic record impact and potential within biopharmaceutical facilities. Electronic records have the potential to drastically reduce the number of manual tasks and reviews completed as part of batch production activities, as well as mititgating against data integrity concerns. Therefore, understanding the barriers to implementation, both technical and organisational, has the potential to (a) reduce the time required to introduce electronic record technology, (b) reduce the risks associated with introduction of electronic record technology, (c) reduce rework associated with electronic record design within a multi-product facility, and (d) identify organisational mindsets that need to be addressed to enable seamless electronic record implementation.

The research is significant as it will demonstrate challenges in electronic record adoption within currently operational multi-product Irish biopharmaceutical facilities, information which is lacking in current literature.

The research will have the following Objectives:

O1: Identify barriers to implementation of electronic records in multi-product biopharmaceutical facilities.

O2: Identify organisational mindset towards adoption of electronic records in place of traditional paper records across organisational hierarchies.

O3: Quantify reduction of paper records where electronic records are fully implemented.

Electronic records are relevant for the entire pharmaceutical industry in Ireland, however, based on platform specifications Biopharmaceutical companies represent a subset of these companies. Additionally, while biopharmaceutical processes follow similar production process there are business specificities and intricacies associated with each companies process development that result in company specific challenges in adoption. Similarly, based on organisational structure and function alignment the challenges faced will vary by company. Individuals often seek to align their own internal cognitive map with that of their employers and as such their internal opinions and attitudes towards topics are influenced by same, as a result this presents a nuance that is company specific. (de Wit, 2020) Therefore, for the purpose of this research the sample chosen was internal at the researchers place of work. The response rate for survey distributed internally was estimated to be high based on personal connection between researcher and participants.(Petrovčič *et al.*, 2016) Information will be collected from stakeholders within the business based on their role in eBR implementation as outlined below.

(i) Responsible for the introduction of eBRs. (Senior Management/Area Management)

(ii) Subject Matter Experts (SMES) involved in the design and implementation of eBRs. (eBR Project Team)

(iii) End users of the eBRs. (Operations Personnel and Technical Operations)

(iv) Quality personnel responsible for quality systems and batch release (QA and QP)

The results from the survey and interviews will be used to test the hypotheses identified below:

H1: Significant benefit has been attained from the implementation of electronic records.

H2: There is a relationship between time using eBRs and attitudes towards them.

H3: The challenges linked to electronic record adoption in certain biopharmaceutical areas is unique and not well understood.

H4. Successful implementation of electronic records is multi-faceted and is dependent not only on technical considerations but the appetite for change within the organisation.

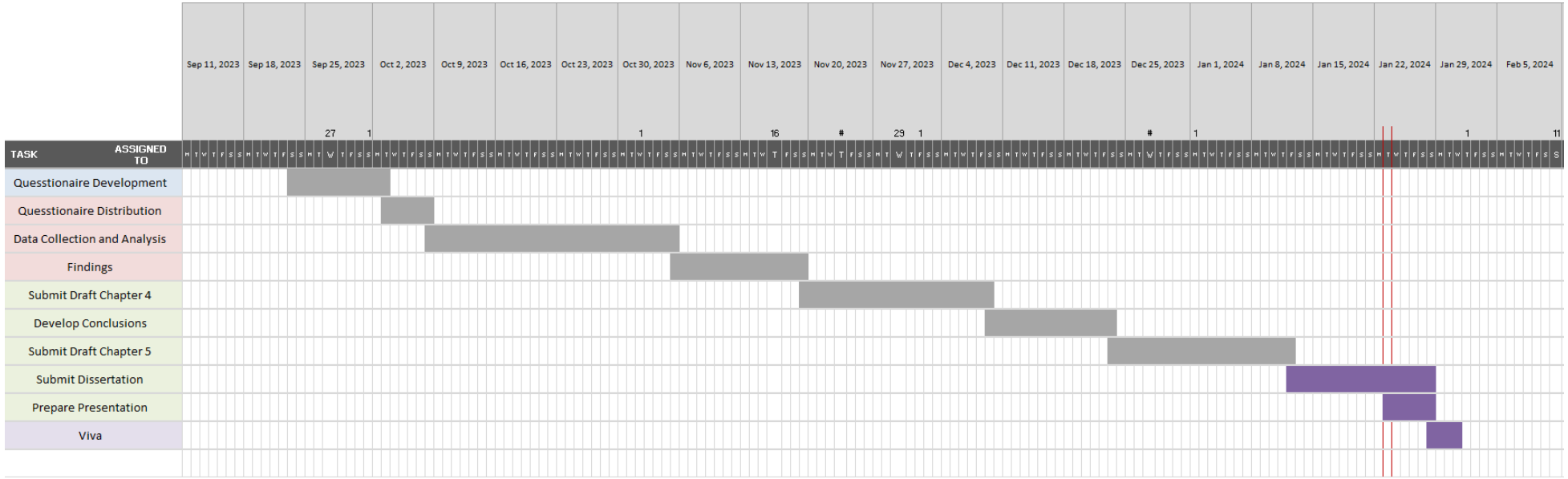
3.3 Timeline for Research

The proposed timeline for this research is indicated in Table 1 and Table 2 below.

Table 1 Timeline for Research (Table)

TASK	ASSIGNED TO	PROGRESS	START	END
Meet with Thesis Supervisor		100%	9/15/23	9/16/23
Part B Proposal Submission		100%	9/15/23	9/30/23
Ethic Forms Completion		100%	9/23/23	9/28/23
Quesstionaire Development		100%	9/23/23	10/3/23
Quesstionaire Distribution		100%	10/3/23	10/8/23
Data Collection and Analysis		100%	10/8/23	11/5/23
Findings		100%	11/5/23	11/19/23
Submit Draft Chapter 4		100%	11/19/23	12/9/23
Develop Conclusions		100%	12/9/23	12/23/23
Submit Draft Chapter 5		100%	12/23/23	1/12/24
Submit Dissertation		0%	1/12/24	1/28/24
Prepare Presentation		0%	1/23/24	1/28/24
Viva		0%	1/28/24	1/31/24

Table 2 Gantt Chart- Research Timeline



3.4 Phase 1 – Survey

A survey was used to gain an understanding of the current understanding of eBRs across organisational hierarchies and functions. The survey was also utilized to identify mindsets towards electronic record adoption throughout organisational hierarchies. The organisational groups and functions are identified below. (Table 3)

Table 3 Survey Participants - Organisational & Functional

Organisational Group	Responsibilities
Senior Management	Key stakeholders in eBR adoption
Area Management	Responsible for implementation
Supervision	Oversight of eBRs in production
Operator	End User of eBR
Technical	Technical support of eBRs
Functional Group	**Responsibilities**
Operations	End Users of eBRs
Engineering	Technical support of eBRs
Technical Services (incl. Micro)	Process Stewards & technical support of eBRs
Quality Assurance	Production Quality Oversight
Qualified Person(s)	Batch Release Oversight
IT	Responsible for eBR introduction
Automation	Owners of Automation system which interact with eBRs

The survey was conducted on Microsoft Forms and comprised of 24 questions. The questions posed to participants took a number of different forms including:

(i) Likert scale questions – participants were asked to rate their agreement/opinion on a rating scale to quantitatively assess current opinions and attitudes towards elements of the eBR process. Likert scales enable the collection of quantitative estimates of

subjective traits or thoughts, producing numerical data that can be visually represented. (South *et al.*, 2022)

(ii) Closed-ended questions were used to obtain factual information about participants experience with eBRs. Closed-ended questions provide a simpler process for respondents to represent their attitudes and encourage a higher response rate from participants. (Griffith, 1999)

(iii) Open-ended questions were used to gain additional insight into participants opinions on challenges or changes to eBR processes. Open-ended questions enabled participants to express their opinions towards eBRs in their own words without being biased to bound to closed alternatives. (Baburajan *et al.*, 2022)

An option of "Other" was provided for some questions to provide additional opportunity to participants to provide alternative insights into the question posed. An option of "N/A" was also provided to participants for a number of questions.

The survey contained an introduction to the research and purpose of the survey as it relates to this dissertation title. The overview also contained information based on relevancy of all questions to participants and directions on steps to take during completion where questions were deemed not relevant to the participant. Consent to participate in the survey was gathered in initial questions, Q1 and Q2, where participants were asked to indicate their understanding of the purposed of the survey and consent to their data being used for the purpose of this research.

Questions 3 – 5 were focused on gathering information on organisational area, function, and level of MES adoption within participants areas. Questions 6 – 12 aimed to identify time exposure to eBRs and opinions towards eBRs. These questions aimed to identify whether any change in opinions had been observed since introduction where applicable to determine whether time had a role to play in opinions towards eBRs, in support of exploring H2, that there is a relationship between time using eBRs and attitudes towards them.

In support of objective 1, A Likert scale question was used to determine ease of electronic record adoption alongside a multiple-choice question and free text question to gain insight into elements which made adoption for difficult. (Q13 – Q15) A series of Likert statements were then utilized to get an insight into agreement with a series of statements related to eBR operation and implementation. (Q16) Likert scales were also utilized to determine familiarity with eBR related

processes and agreement with statements linked with eBR delivery processes. (Q17 & Q18) Questions 16-18 were selected to investigate H1, significant benefit has been attained from the implementation of electronic records and, H3, the challenges linked to electronic record adoption in certain biopharmaceutical areas is unique and not well understood. Question 19 was used to gain further insight into attitudes towards eBR adoption and understanding of electronic records compared with paper records. Questions 20 through 22 were used to identify whether there was perceived improvement or deterioration in processes associated with batch record execution since the implementation of eBRs within survey participants. These questions were aimed at better understanding internal mindsets towards eBR implementation as identified in objective O2 of this research. Questions 19-22 were designed to facilitate an understanding of the elements that contribute to the success of eBR implementation, in support of H4. The final three questions were open text questions where participants were asked to provide any proposed (i) technical changes, (ii) changes to the eBR implementation process, or (iii) any other information they deemed relevant to survey completion. Refer to "Appendix A – Survey" for complete survey questionnaire.

3.4.1 Sample Selection

The survey was distributed via email to participants. E-mail was chosen as method of distribution due to ease of access to participants and ease of completion for participants, as all individuals involved have daily access to their email. The Microsoft Forms platform was chosen to conduct the survey based on internal use of this form within the company, and therefore familiarity of participants with the platform was expected. The Microsoft Forms platform also enabled easy export of information collected to Microsoft Excel for Analysis.

3.4.2 Data Analysis

The information collected in the surveys was analysed using Excel. The Likert-scale and closed-ended question data was analysed and represented visually using pie-charts and bar-charts. The data was represented by organisational or functional groups to demonstrate any differences and/or similarities in data collected by role played in the company.

The open-ended questions were analysed using thematic analysis (TA) to identify any trends in the information provided. TA is a method of "identifying, analysing, and reporting patterns (themes) within data." (Castleberry and Nolen, 2018)

3.5 Phase 2 – Interview

To obtain additional information from subject matter experts on the eBR implementation process a qualitative approach was used. Interviews were conducted with individuals who are currently, or have previously, been involved in an eBR implementation process. These interviews allowed further investigation of elements explored within the survey. The interviews were conducted through Microsoft Teams. The interview process consisted of 10 questions across the following areas:

(i) Role in eBR implementation
(ii) Understanding of drivers for eBR implementation
(iii) Priority of eBR implementation within the business
(iv) Challenges and benefits associated with eBR implementation
(v) Structure of eBR implementation
(vi) Behavioural and technical challenges of eBR implementation

The questions were semi-structured questions to provide structure while allowing flexibility for the interviewees to provide their own perspective and inputs. (Leavy, 2020) Semi-structured interviews have also been found to be successful in enabling reciprocity between the interviewer and interviewee. (Kallio *et al.*, 2016)

The initial question, Q1, and Question 5 looked to identify an understanding of roles and responsibilities associated with eBRs across participants. These questions were selected to identify if there was consistency in role understanding across the interview group. This question was designed to identify whether role understanding represented a barrier to eBR implementation, Objective O1.

Question Q2 asked interviewees to identify benefits associated with electronic records compared to paper records, as hypthosised in H1. This question was selected to provide additional information, and allow comparison, of data related to the benefits attributed to eBR implementation collected via survey performed.

Three questions, Q3, Q8 and, Q9, were linked to objective O1 and O2, aimed at identifying and understanding barriers to implementation of electronic records. Question 3 aimed to identify any challenges related to electronic records when compared to paper records. Question 8 focused on the technical challenges that were encountered during implementation and

understanding of these challenges while Question 9 was focused on organisation/behavioural challenges. Participants were asked whether these were issues that were expected or unexpected during implementation, how the challenges supported or prevented the introduction process, and how they could have been prevented, or could be prevented in the future (where applicable). Questions 8 and 9 also explored the response to challenges encountered during implementation, looking at the processes in place during the implementation process and whether there were learnings from these responses. These questions were selected to support investigation of hypotheses H3 and H4.

Questions 4 and 6 further explored H4 and also supported O2. Question 4 asked participants which group benefits the most from the implementation of eBRs to help in determining internal motivations for eBR adoption based on benefits realised. In Question 6 interviewees were asked to rate the priority of eBR implementation for themselves, their immediate line manager, and the overall biotech business. Question 6 was selected to look at internal attitudes to eBR implementation across hierarchies, as well as perceived importance across different management layers in the business.

Question 7 focused specifically on the eBR implementation process, and the gathering of information related to H3. It explored the interviewees understanding at the initial outset of the project and whether the process of implementation worked well. This question was selected to look at the structures utilised for eBR implementation and to explore whether there were any learnings from projects already completed.

Question 10 allowed participants to provide any additional insights or information they felt was relevant to eBR implementation process to allow for the collection of data which may not have been explicitly captured through prior questions.

The information collected in the interviews will be combined with survey results to provide insights into electronic batch record adoption within multi-product biopharmaceutical facilities.

3.5.1 Sample Selection

The interviewees were selected based on experience and were selected from a range of organisational groups to ensure a representative selection from across the business. The participants will currently be, or were previously, involved in an eBR implementation project. Participants were involved in the projects as either business representatives or eBR subject matter representatives (SMEs). The eBR SMEs are knowledgeable in the electronic batch record design and requirements whereas the business representatives can be considered process knowledgeable with limited understanding of eBRs from an IT perspective.

3.5.2 Data analysis

Thematic analysis (TA) was performed on the data collected. The information was compiled and organised into interview transcripts which were created from the interview recordings. The data collected was then disassembled to identify similarities and differences in the information collected through coding. Coding is "the process by which raw data…are gradually converted into usable data through the identification of themes, concepts, or ideas that have some connection with each other". (Austin and Sutton, 2014) The themes identified represent patterns in the codes and represent a holistic view of information being portrayed. The importance of each theme identified is related to whether it captures something important in relation to the overall research questions and is not dependent on frequency of appearance in the data, or on quantity of data contained within the theme. (Castleberry and Nolen, 2018)

3.6 Ethical Considerations

The research ethics for this dissertation were carefully considered during the ethics application process. No ethical considerations related to sensitive topics, research procedures or participation were identified. Participation in the research was voluntary and all participants were informed that they could withdraw at any stage during involvement in the research. All data collected was anonymised to protect individuals. Data was attributed to the organisational areas to inform research conclusions and identify trends within certain hierarchies. Participants were selected from within the researcher's own workplace network and contact was made via company email only. Permission from organisational leaders was obtained prior to conducting primary research. Data used to compare different production process was generalized and did not contain any confidential information. It was also used to inform the complexity of requirements but not product specific requirements. No confidential information pertaining to the organisation is disclosed within this research.

Prior to interview a Participant Information Letter (PIL) was generated and provided for each interviewee in order to give them an overview of the research content and purpose. An Informed Consent Form (ICF) was also prepared and was read and signed by participants prior to interview. Copies of the PIL and ICF are shown in Appendix C – Participant Information Letter (or Leaflet) and

Appendix D – Informed Consent Form Those completing the online survey were asked to tick two boxes at the start of the survey – one to state that they understood the research and one to give their consent for their data to be used.

All information pertinent to this research, including signed consent forms from interview participants, survey transcripts, and survey results, are stored electronically on researcher's laptop and backed-up on a cloud-based system. Files which contain any personal information of participants are stored in a separate password protected folder.

CHAPTER FOUR

4. FINDINGS AND ANALYSIS

4.1Findings and Analysis from Online Survey

4.1.1 Survey Participation

A sample size of 120 was achieved for the survey. However, all questions were not relevant to all participants, depending on the role held within the organisation, therefore the sample analysed for each element is exhibited within each section. In addition, one participant answered "No" to their understanding of the purpose of this survey, therefore this result was removed from the data collected and their results are not reflected in data analysis below.

The survey was conducted using Microsoft Forms. Survey results were exported to Microsoft Excel for analysis. The data was analysed across Organisational Groups and Functional Groups. The breakdown for organisation group participation is indicated in Figure 20 and for functional group participation in Figure 21.

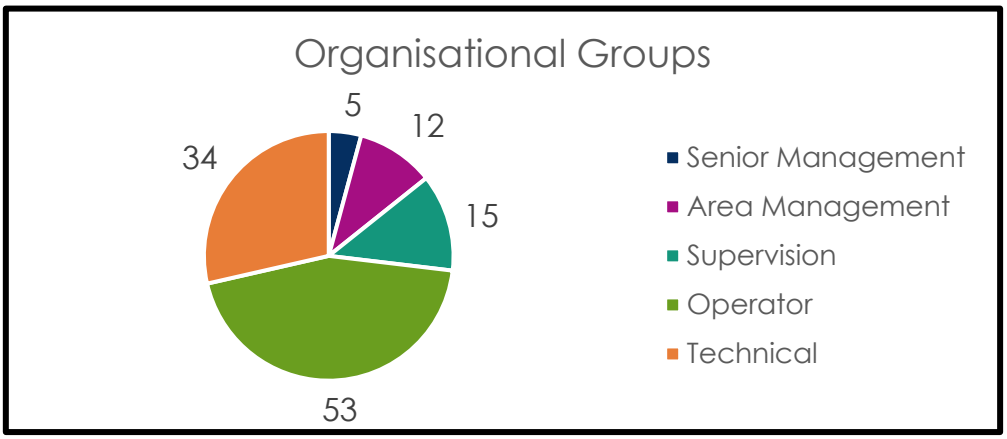


Figure 20 Oganisational Group Participation

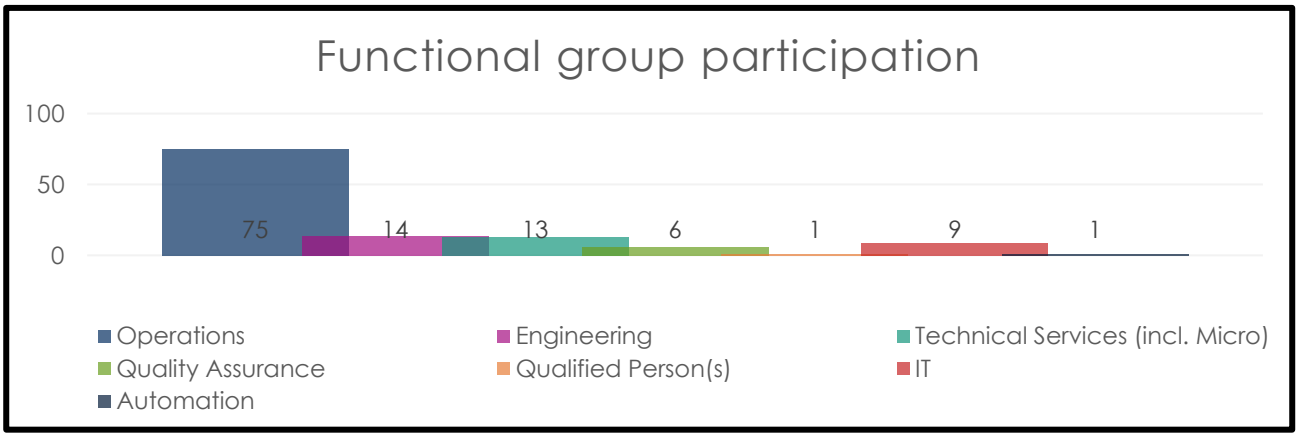


Figure 21 Functional Group Participation

Table 4 demonstrates survey participants functional groups as they relate to each organisational group.

Table 4 Organisational and Functional Group Breakdown

Organisational Group	N	Function
Senior Management	5	QA (N=1), Operations (N=3), Engineering (N=1)
Area Management	12	QA (N=1), Operations (N=4), Engineering (N=3), Technical Services (incl. Micro) (N=3), Automation (N=1)
Supervision	15	Operations (N=15)
Operator	53	Operations (N=53)
Technical	34	Engineering (N=10), IT (N=9), QP (N=1), QA (N=4), Technical Services (incl. Micro) (N=10)

Organisational groups across the organisation were well represented relative to overall size of each group. Organisational groups were also well distributed across functional groups. Automation and Qualified Person(s) were not well represented in the data collected, N=1 for both groups and data collected from these groups would require additional participation to gather meaningful data.

4.1.2 eBR Experience of Participants

The experience of the participants with eBRs is indicated in below Figure 22, with 88% of participants indicating use of eBR within their area for batch manufacturing, where eBRs have either replaced paper records, or are used alongside paper records. The experience of the survey participants is suitable for the purpose of this research as it will provide data relative to those using the electronic records as well as those who are not exposed to electronic records. This is important as it will provide details on reality of opinions throughout the groups involved in implementation as well as perceptions from those who have not been involved first-hand.

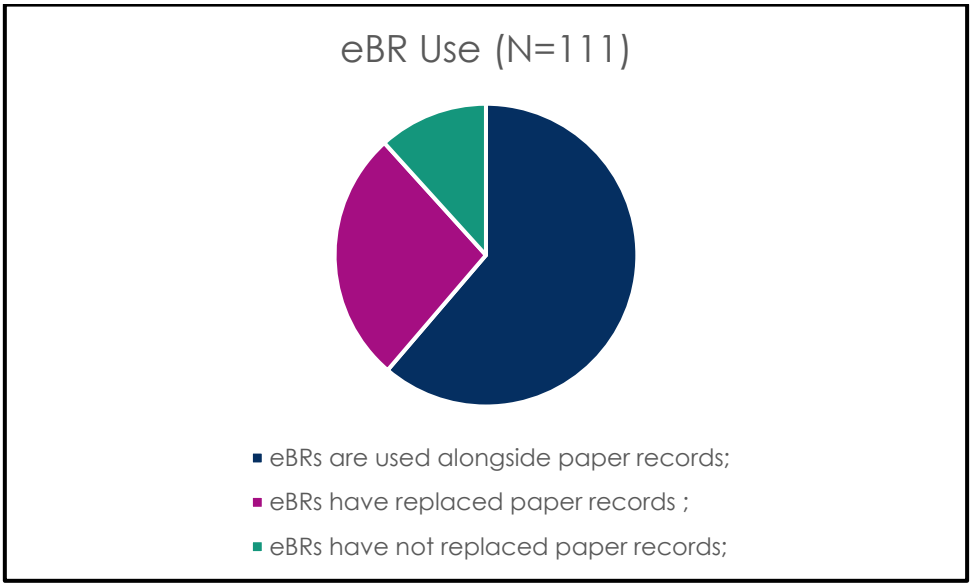


Figure 22 eBR use within Survey Participants Area

The experience of the survey participants with eBRs is demonstrated in Figure 23 below, with the majority of participants using, or exposed to, eBRs for greater than 2 years. This experience range will provide insight across a broad range of experience and supports the investigation of time impact on eBR opinions throughout the business.

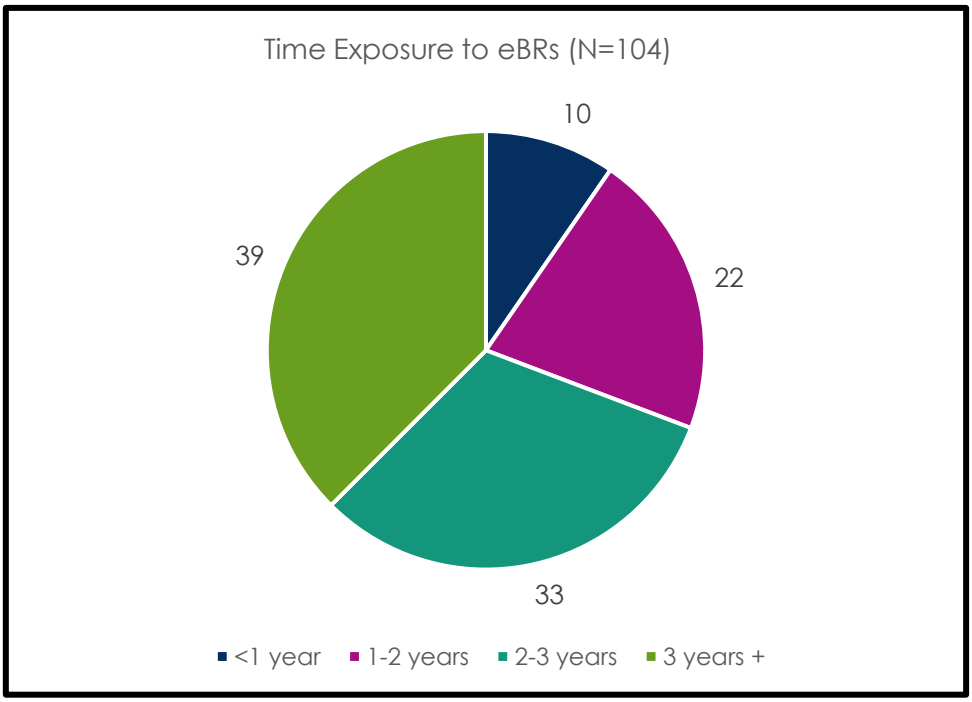


Figure 23 Time exposure to eBRs

Survey participants indicated familiarity with the eBR system (MES) with 76% of respondents having logged onto the system in the previous week. (Figure 24, Figure 25)Of the survey participants, 13% indicated they had never used the eBR environment, 69% of these participants are in management positions (Area, or Senior Management). As the primary users of electronic records are the operations function, the data collected on eBR environment use aligns with this.

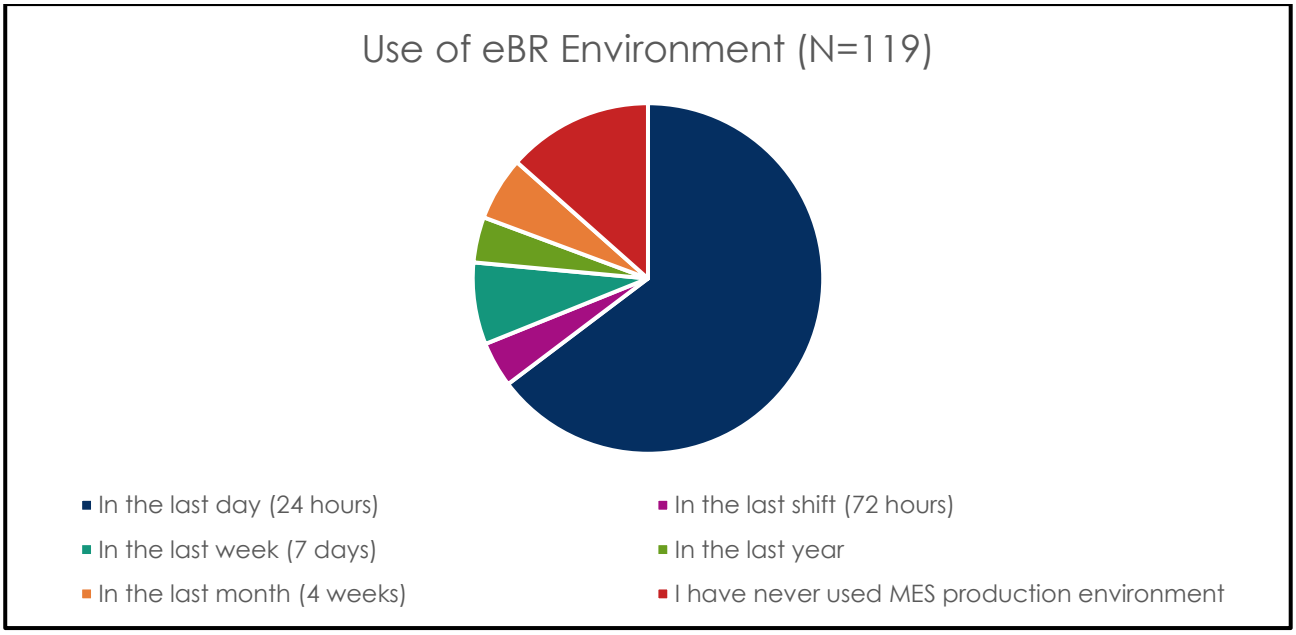


Figure 24 Use of eBR Environment

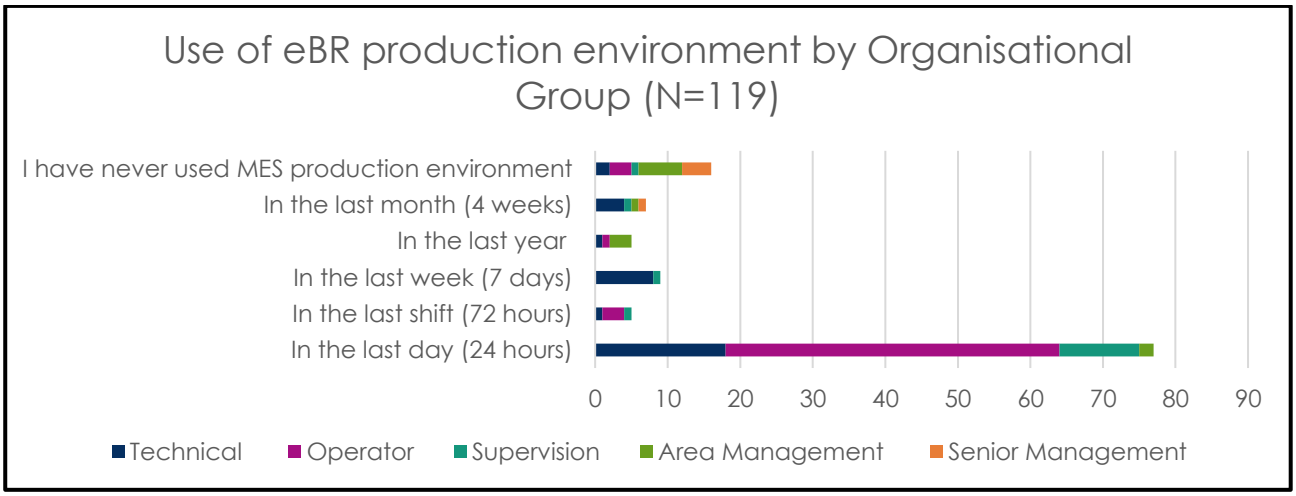


Figure 25 Use of eBR Production Environment by Organisational Group

4.1.3 Requirement for eBR Implementation

As demonstrated in Figure 26 and Figure 27, the requirement for use of eBRs within the business is well recognised and is not dependent on Organisational Group or Function in which individuals work. Neutral responses to this question were received from Technical and Operator Organisational Groups.

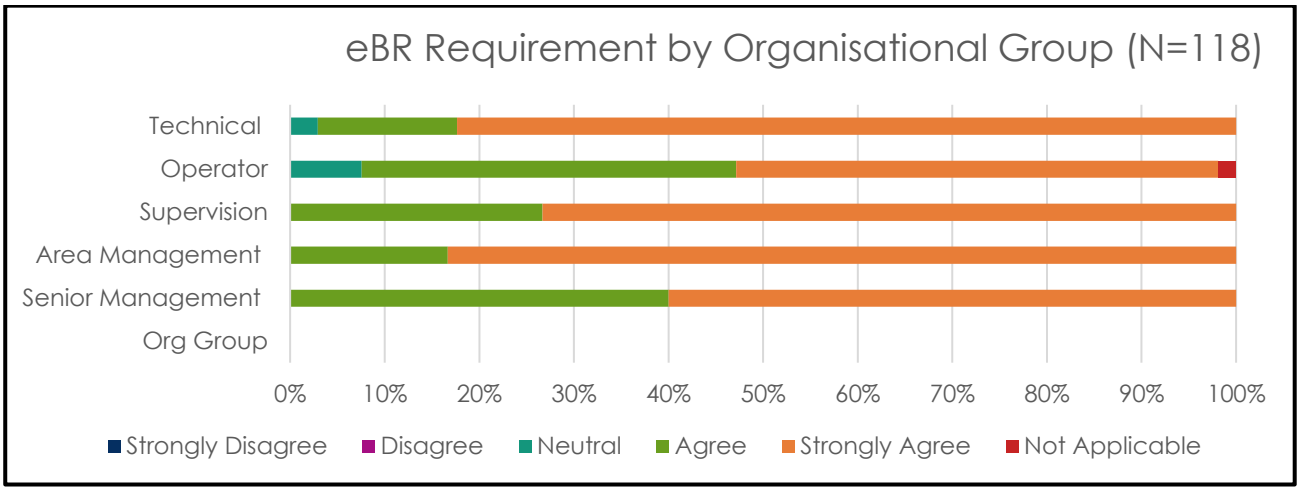


Figure 26 eBR Requirement by Organisational Group

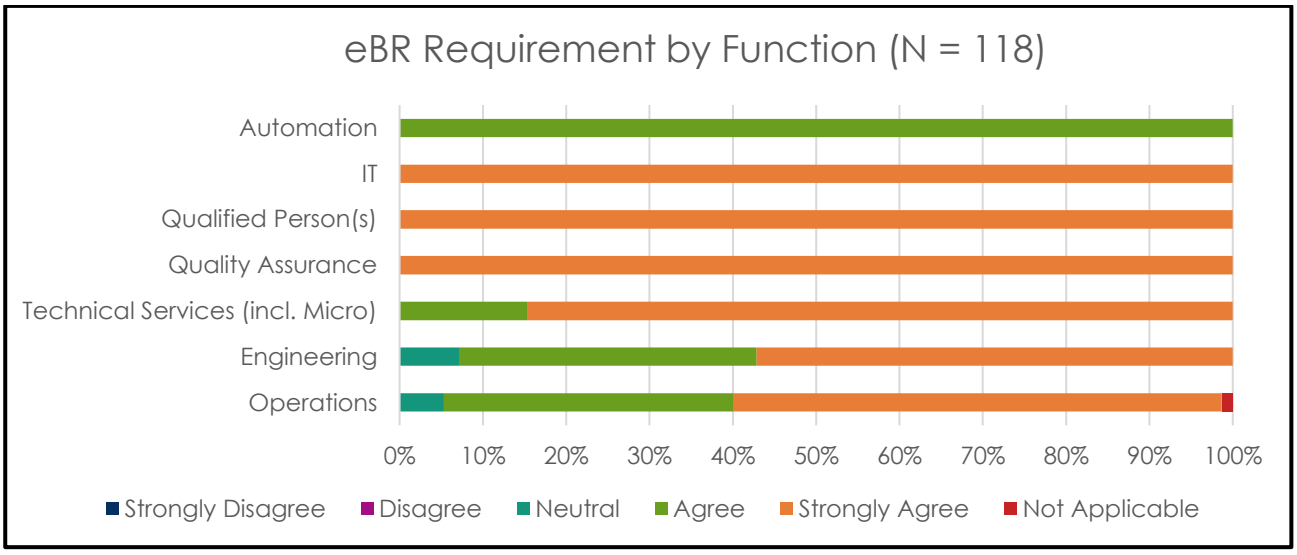


Figure 27 eBR Requirement by Functional Group

Across all functional groups it was felt that eBR adoption is necessary to enable production ramp up. The only group that indicated a negative response to this question was within the Operator pool with "Disagree" and "Strongly Disagree" both having N=1 results. These results represent <3% of overall operator numbers and <2% of overall participants who answered this question. (Figure 28)

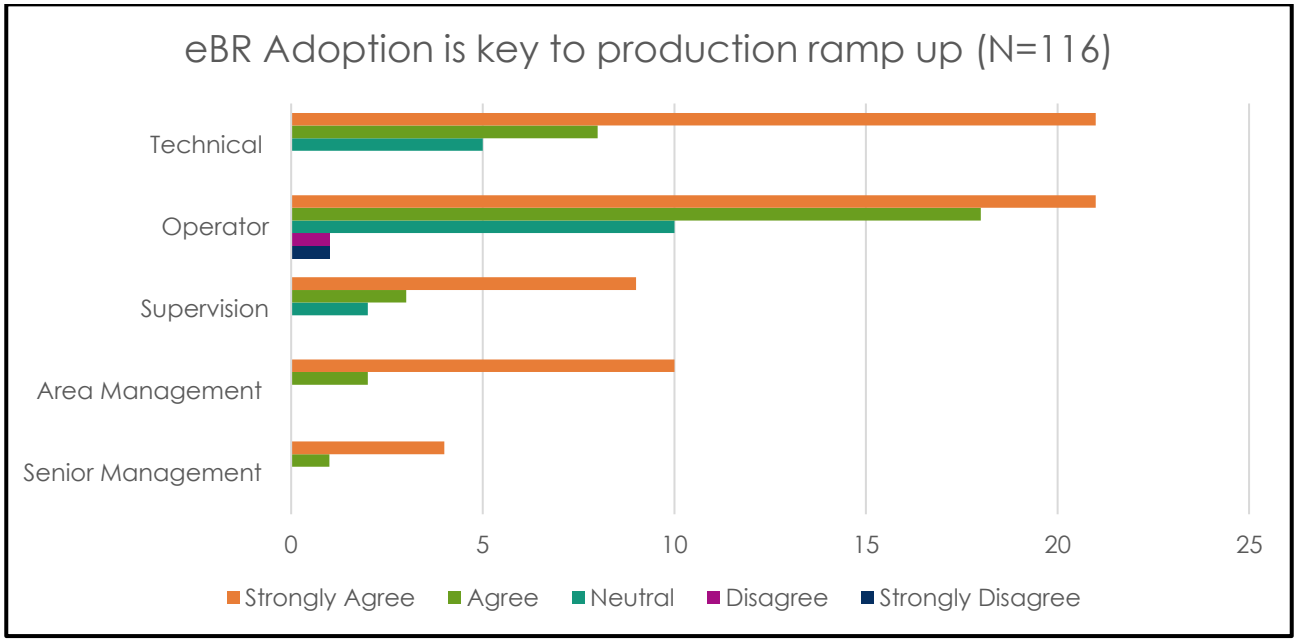


Figure 28 eBR Adoption and Production Ramp Up

In both areas where eBRs have not been adopted and in areas where eBRs have been partially or fully implemented, participants were asked to indicate the impact or potential impact of eBRs

on each participants role. In both situations the impact was deemed to be positive, however in areas where eBRs have been implemented the results were more favourable. In areas where eBRs have been implemented participants were more likely to deem the impact as "Positive", 82% vs 68%, and less likely to deem the impact as "Negative", 2% vs 8%. (Figure 29)

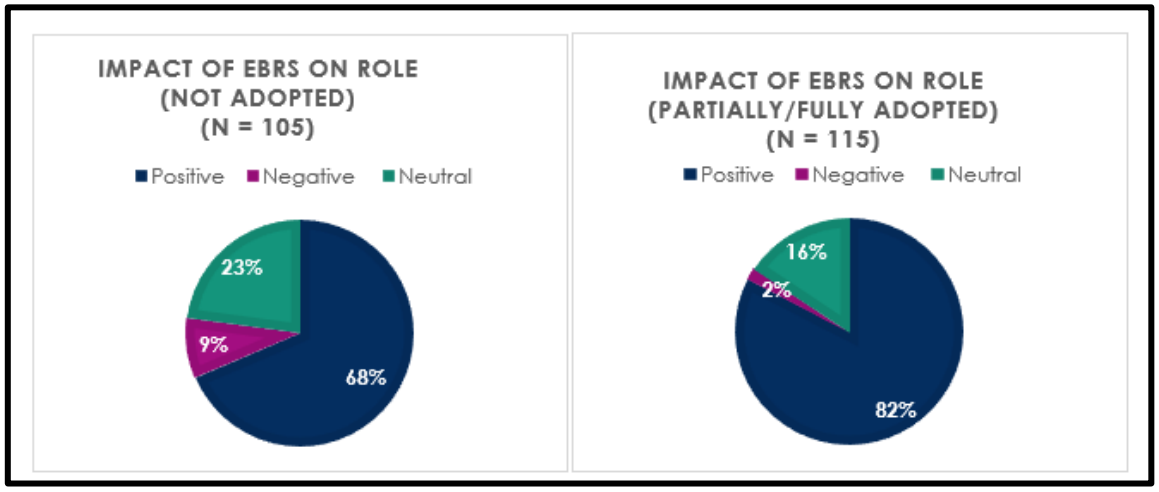


Figure 29 Impact of eBRs on Role

In areas where eBRs have been implemented participants were more likely to deem the impact as "Positive", 82% vs 68%, and less likely to deem the impact as "Negative", 2% vs 8%. These results may indicate that the true benefits of eBRs are only realised once implemented, and that there are additional benefits realised compared to perceived benefits prior to implementation. However, they may also indicate that the major benefits have already been obtained in areas where eBRs have been implemented and the same benefits may not be applicable to other areas based on process.

4.1.4 Time impact on eBR Opinion

To understand whether time played a factor in experience with eBRs, survey participants were asked to identify if their thoughts on eBRs had changed since initial adoption. Approximately half of the survey participants indicated a change in opinion since introduction of eBRs. (Figure 30)

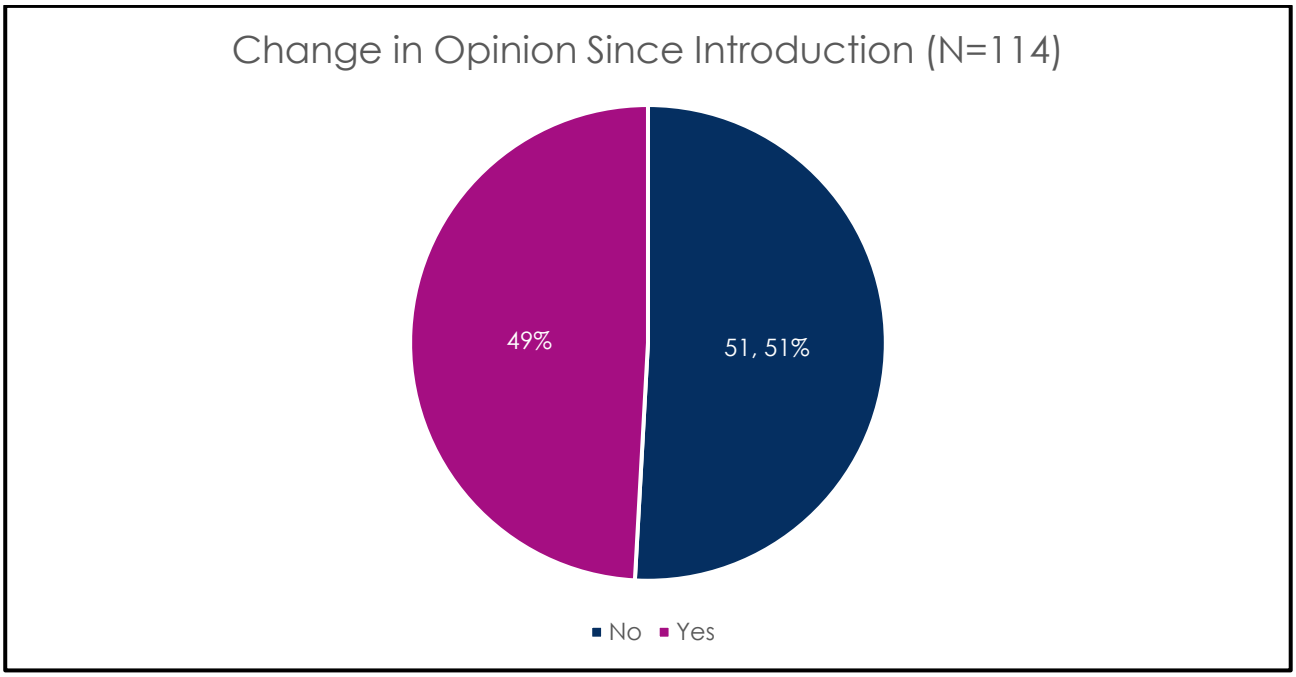


Figure 30 Change in Opinion Since Initial Adoption

Where participants indicated a change in opinion (N=56), the change was majority positive with 86% indicating same. (Figure 31)

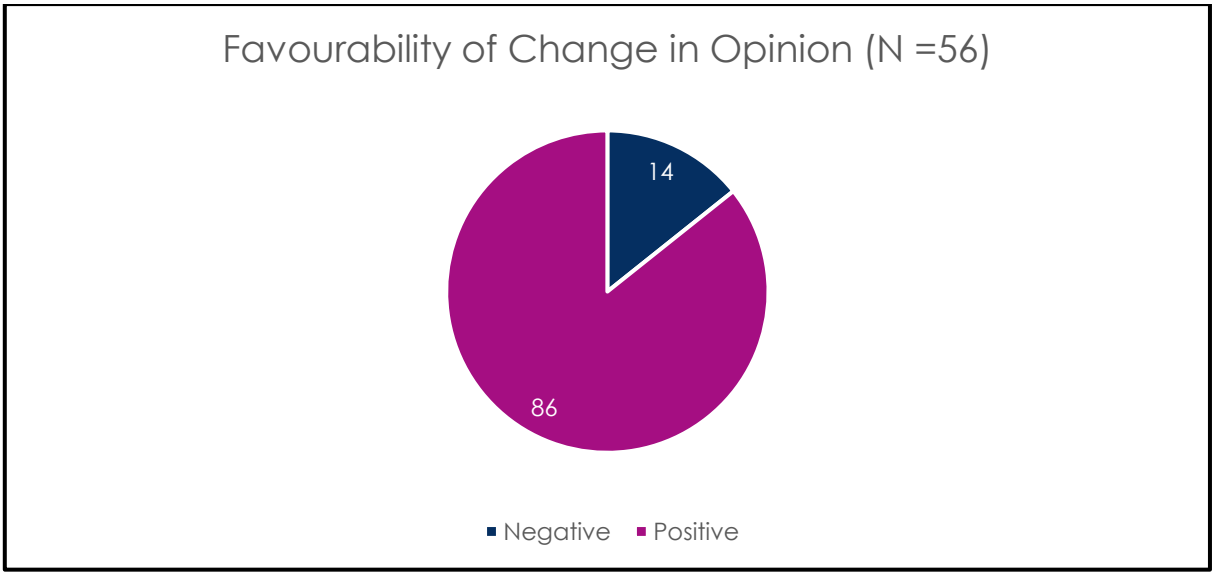


Figure 31 Favourability of Change in Opinion

Senior management were most likely to have indicated a change in opinion with 80% of those surveyed identifying a change in opinion. (Figure 32) This change in opinion may be linked to understanding of eBR benefits at a Senior Management level. Supervision and Operator groups were least likely to change their opinion following implementation. This is hypothesised to be

linked to their role as end users, and therefore their familiarity with the benefits that can be achieved with the implementation of electronic records.

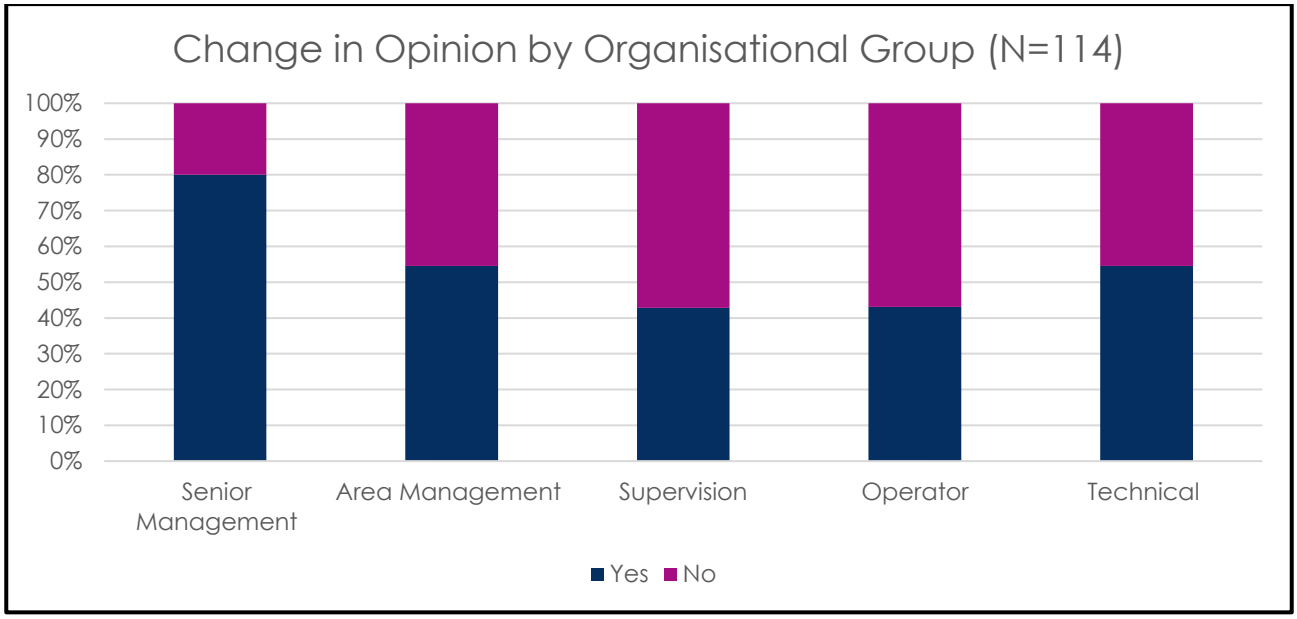


Figure 32 Change in Opinion by Organisational Group

Where a change in opinion was identified, N=48, Senior Management and Supervision were the most likely groups to indicate that this change had been positive with 100% of survey participants indicating same. (Figure 33) Area management were most likely to indicate a negative change in opinion since eBR adoption (33%).

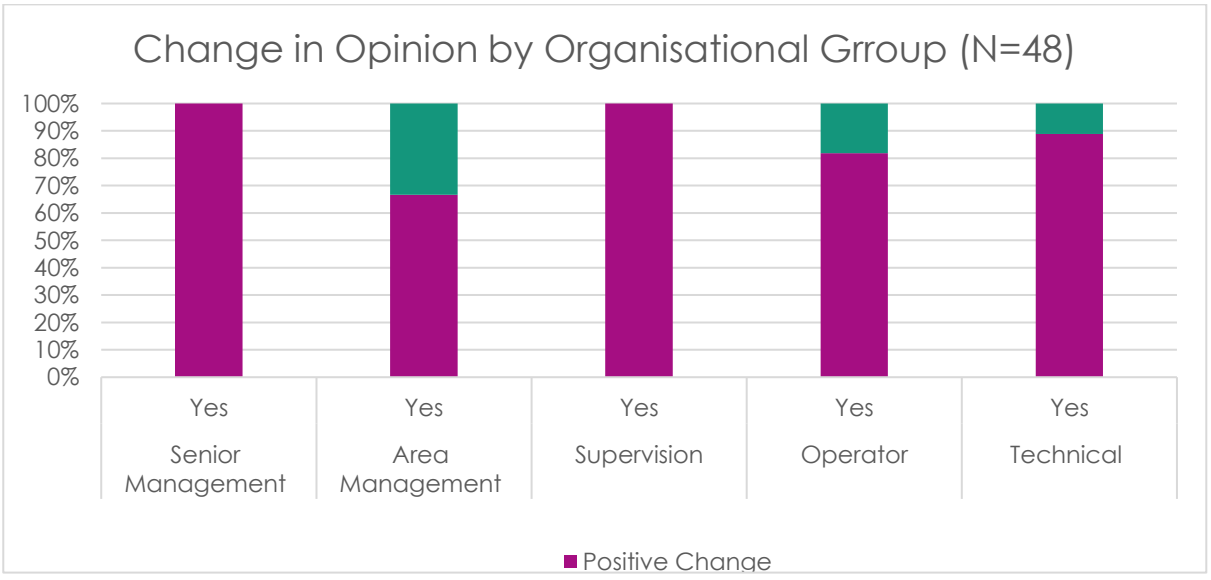


Figure 33 Change in Opinion by Organisational Group (Favourability)

In addition to results outlined above the number of positive responses was plotted against length of time using/exposed to electronic records, and a trendline applied in Microsoft Excel, to identify if there was any relationship identified. This relationship is depicted in Figure 34 below. There is a strong correlation in number of positive responses and number of years of exposure, R^2 = 0.9747, for "Positive" responses. Time does not appear to have an impact on "Neutral" or "Negative" response (R^2 = 0.2).

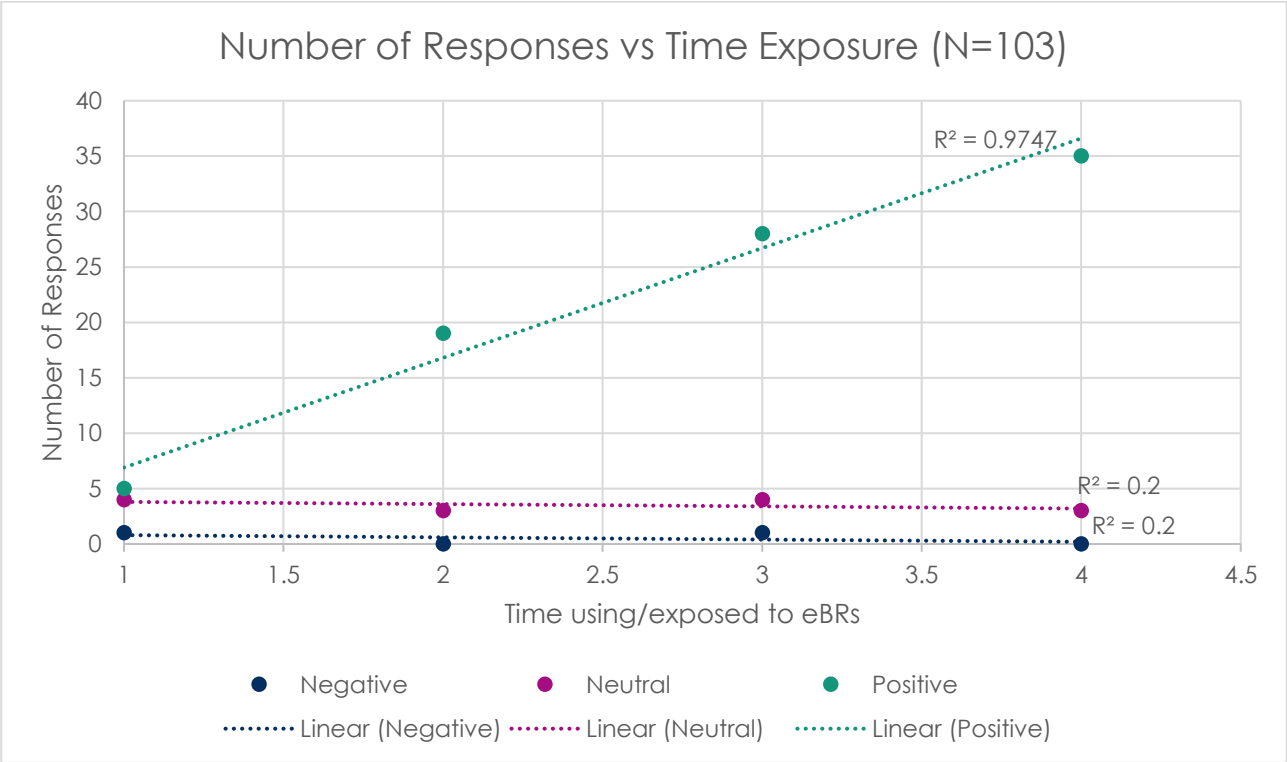


Figure 34 Number of Positive Responses vs Time Exposure

4.1.5 eBR User Understanding

A series of questions were used to identify users understanding of the eBR systems and execution of their role as it relates to eBRs. The sample size for each question is contained in Table 5.

Table 5 Sample Sizes for eBR Understanding Analysis

Role Understanding	Sample Size (N)
I understand my role in electronic record adoption	112
I have the same understanding of eBRs as I do of paper batch records	111
I have the required IT knowledge to perform my role as it relates to electronic batch records	107
I have the required process knowledge to perform my role as it relates to electronic batch records	107
I understand how the eBR interacts with other systems/equipment that are used in eBR execution	111
I understand my responsibilities as they relate to electronic record implementation and management	114
I know who to contact to answer my questions related to eBRs	114
I have the required process knowledge to make decisions related to eBR implementation	108
I understand how eBRs control quality critical parameters	114
I know how to access information within eBRs	112

Greater than 60% of participants indicated a positive response to all statements. (Figure 35)

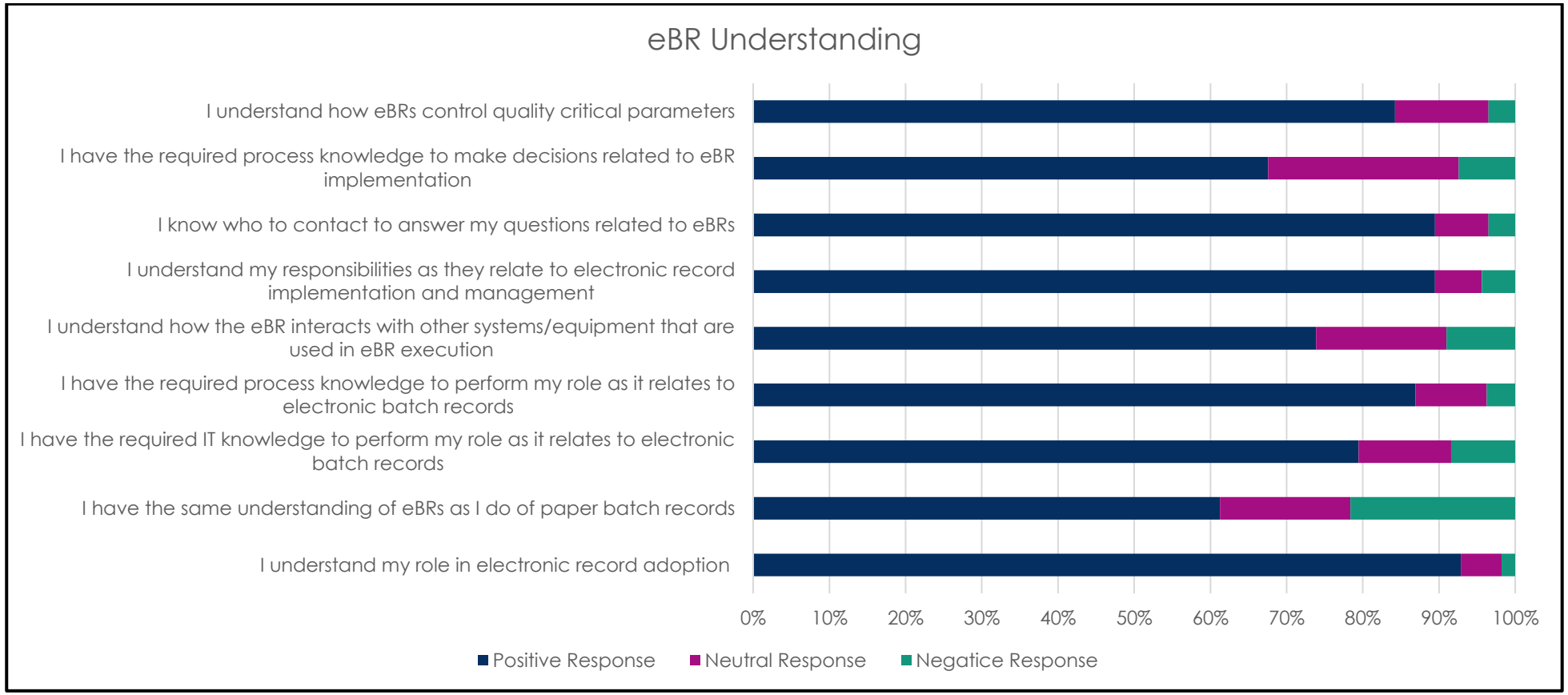


Figure 35 eBR Understanding Favourability

Participants were found to have a lesser understanding of eBRs relative to paper records in comparison to the other statements in Figure 35. These participants were more likely to be from Engineering and Operations functions. (Figure 36)

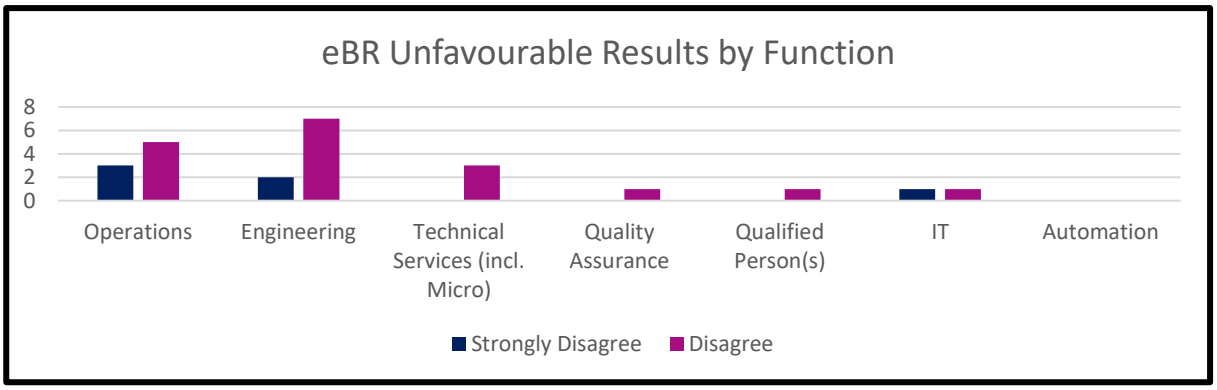


Figure 36 eBR Unfavourable Results by Function

4.1.6 Adaption to eBRs

A series of questions were used to identify the ease of adaption to the eBR system. These results are depicted in Figure 37 and Figure 38 below.

Note: Senior and Area management were not represented here as they are not users of the system.

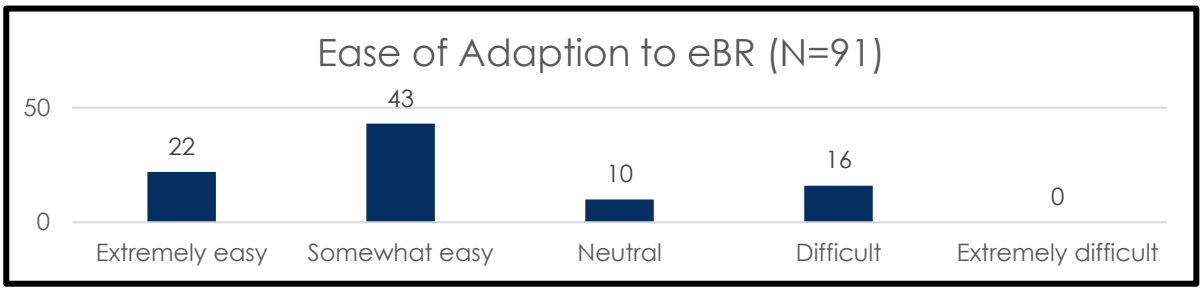


Figure 37 Ease of Adaption to eBR

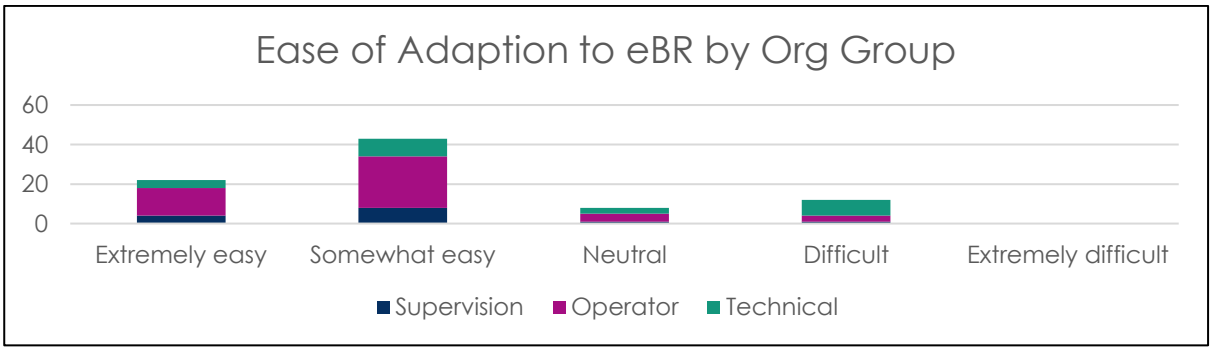


Figure 38 Ease of Adaption to eBR by Org Group

The majority of those surveyed, >71%, rated the ease of adaption to eBRs as "Extremely Easy" or "Somewhat Easy". The Technical organisational group were most likely to rate the adoption of eBRs as "Difficult". No organisational group identified the adaption to eBRs as "Extremely Difficult."

As indicated in Figure 39 and Figure 40, challenges in adapting to the new system were most frequently attributed to not understanding how the eBR functioned in comparison to a paper record.

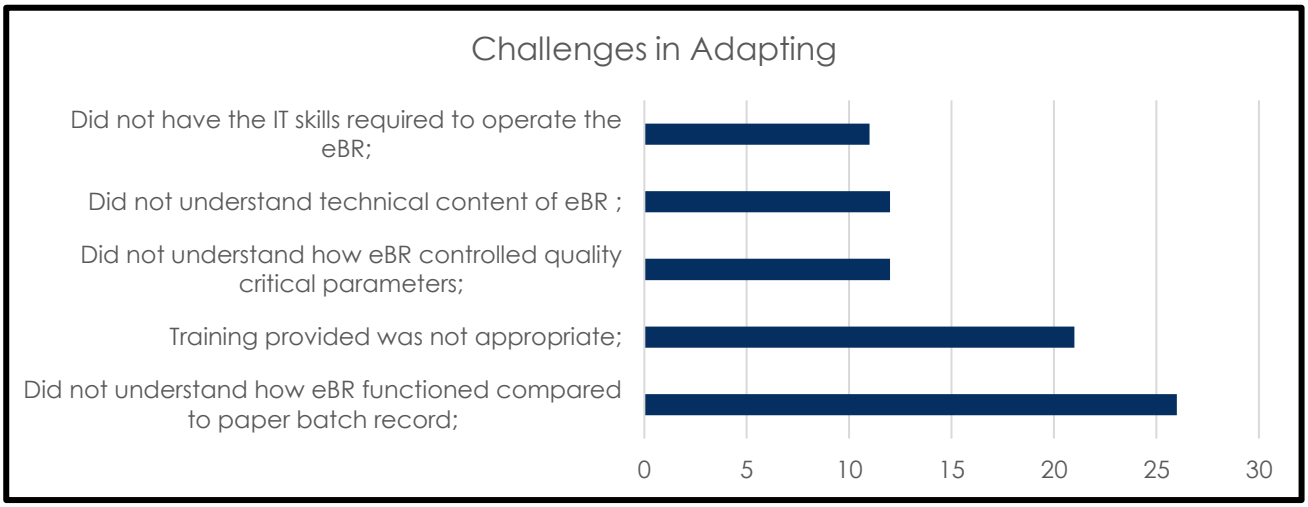


Figure 39 Challenges in eBR Adaption

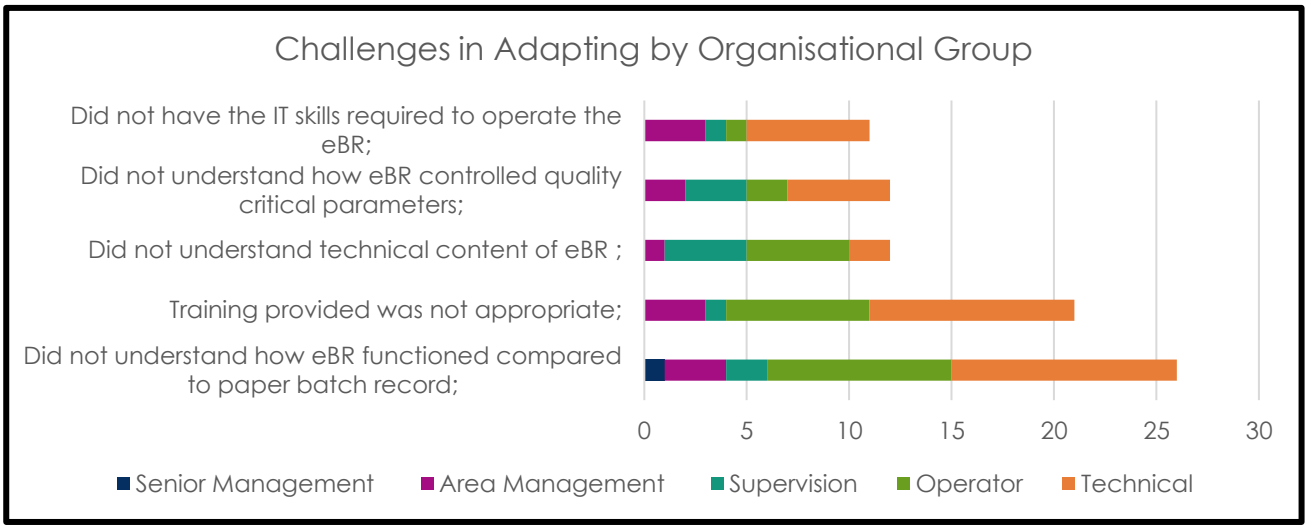


Figure 40 Challenges in eBR Adaption by Organisational Group

An open-ended question was also posed to participants to outline any additional areas, or to further expand on option selected, which made adaptation to eBR use **more difficult**. Participants provided greater insight into how understanding eBR functionality compared to paper has impacted adoption. Through the adoption of eBRs there have been difficulties in the translation of the following elements:

- **How the control strategy was met using electronic records compared to paper records**. Where is the check performed and what systems are being used? While these requirements have not changed in the transition to electronic records the results indicate an uncertainty in understanding around this process.
- **How to navigate a manufacturing review report and what the system step information means**. The manufacturing review document contains all executed steps as well as all system steps performed, the meaning behind these system steps is not well understood within technical and management functions, without intimate knowledge of IT processes this can make navigation more challenging.
- **How to navigate a manufacturing review report in response to an event or when reviewing retrospectively**. This is especially true in audit scenarios when presenting an eBR compared to a paper record. There is more technical knowledge required to explain the metadata and IT system controls that was not needed when using paper

records. In response to an event, without the relevant knowledge deciphering the true cause, impact, or which system failed, can be more challenging.

- **What structure of documents/systems sit behind the eBR and how do they impact**. While personnel were familiar with the flow of information to paper batch records and the relevant reference documentation, this is not the case when it comes to electronic batch records and their relevant design and source documentation.
- **The impossibility of designing an eBR that can accommodate all scenarios.** However, which scenarios were incorporated was not understood by supporting teams, posing additional challenges when responding to issues for the first time.

The use of electronic batch records requires some IT knowledge to be able to navigate the system and perform specific tasks. Overall, the survey demonstrated that overall IT knowledge is not prohibitive to use of eBRs within biotech manufacturing with >79% favourability. (Figure 41)

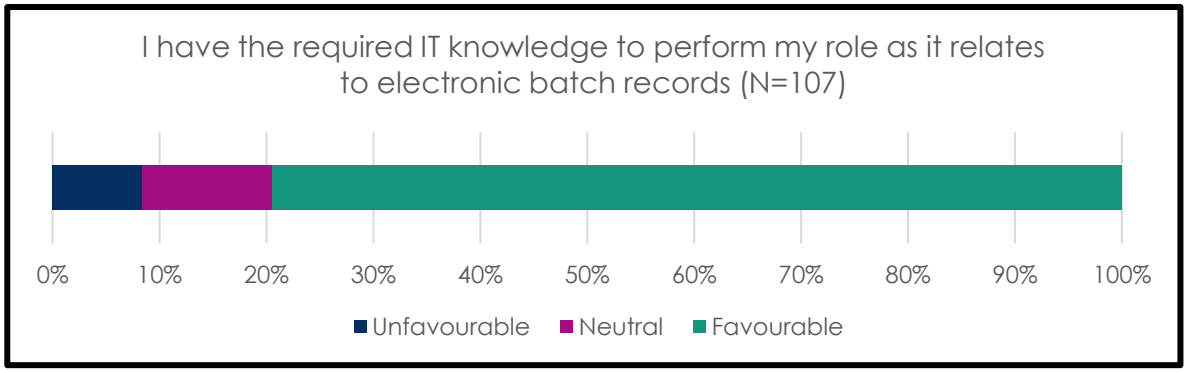


Figure 41 IT Knowledge Favourability

The unfavourable results were most likely to be represented by the Technical Org Group (N = 4) and most likely to come from the Engineering function (N=4). Area management were also more likely to rate their IT knowledge as unfavourable or neutral (N=7) than positively (N=1). (Figure 42)

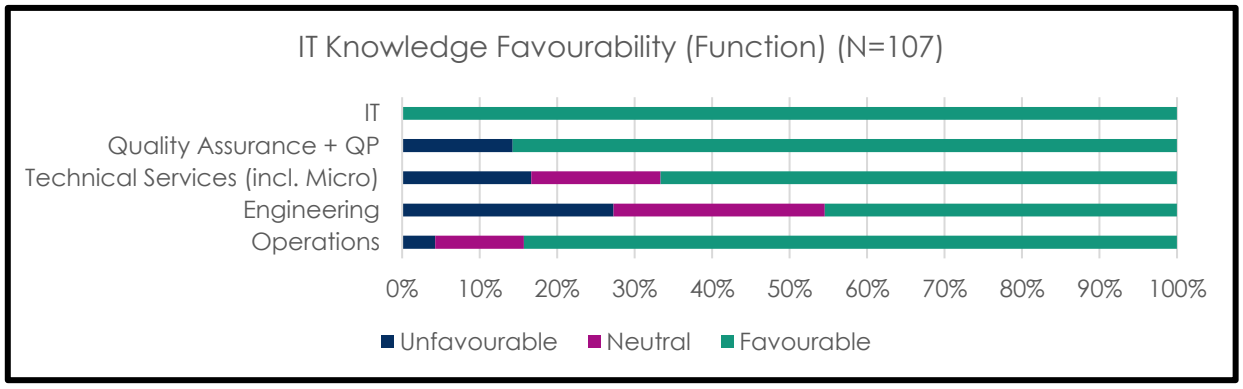


Figure 42 IT Knowledge Favourability (Function)

4.1.7 Open Ended Survey Questions

A series of three open ended questions were posed to participants to gather any additional information pertaining to eBR implementation that may be relevant to this research. Supplementary useful information was sought by asking these extra freeform questions and their answers provided important insights. The information was collected and analysed to identify themes within the answers. Participants were asked:

- Are there any technical changes you would make to the current eBR?
- Are there any changes you would make to the current eBR implementation process?
- Is there anything else you would like to include pertaining to eBR implementation and adoption?

Throughout the answers provided "speed" was a common denominator across all organisational groups. Speed was mentioned in the following contexts:

- Speed of implementation is not sufficient.
- Speed of IT system and current software being used to run eBRs is too slow. Performance issues linked to other systems integrated with eBR was also identified.
- Speed of enabling updates to eBRs is too slow.

Senior and area management were most likely to mention speed of implementation as a concern. Operators and supervision were most likely to mention the speed of the current operating system as a significant challenge. All organisational groups were equally likely to declare the speed of updates to the eBRs once implemented as inadequate.

Resources and resourcing constraints were commonly mentioned throughout the answers collected. Resourcing was referenced at the following points in eBR implementation:

- Operations resources are not utilised to best effect during design and project implementation.
- IT resources are not sufficient to support implementation and ongoing management of recipes already in use in production.
- Resourcing structure does not facilitate decision making.
- Resources are not dedicated only to eBR implementation.

Knowledge and training were also common themes throughout the answers provided. These areas were reflected as they relate to the following areas:

- Lack of knowledge of how the eBR is built and hierarchy of controls, training not provided around this.
- Lack of knowledge on how the eBR interacts with other systems, training is not provided on this.
- Training is not performed on real life examples or test systems, there is no hands-on interactions before use in production.
- Technical support is outsourced from production process teams and training handover between these groups is insufficient.
- Training time is not sufficient to adapt to eBR.
- Support during roll out of new eBRs is not sufficient to handover to production.
- Lack of tools to support ongoing understanding and use of eBRs.
- eBRs have removed the visibility of the whole process compared to paper batch records.

4.2Findings and Analysis from Interviews

A series of 11 interviews were conducted as part of this research. These interviews were conducted with representatives from Technical and Area Management organisational groups. Representatives were selected based on their involved in current or previous projects to implement electronic records within an area. Project representatives include both eBR subject matter experts (SMEs) and production representatives from the business Table 6.

Table 6 Interview Participants

#	Interviewee Organisational Group	Interviewee Function	Project Involvement
1	Technical	TSMS	Business
2	Technical	TSMS	Business
3	Area Management	Operations + TSMS	Business
4	Area Management	Operations	Business
5	Area Management	Operations	eBR SME
6	Technical	IT	eBR SME
7	Technical	QA	eBR SME
8	Technical	IT	eBR SME
9	Technical	TSMS	eBR SME
10	Technical	TSMS	Business
11	Technical	Engineering	Business

The interviewee findings can be separated into the following themes:

4.2.1 Benefits of eBR Implementation

Interviewees were consistent in their response to the benefits associated with eBR implementation. “Going back to paper feels like going back in time.” (Interviewee 9) The

theme of compliance, associated with elements such as "Right-first-time", GDP ensured through execution and Human Error reduction was the most prevalent through all the interviews. "Can't go off and do things out of sequence or in an inconsistent manner. Ensure compliance from start to finish." (Interviewee 6) "They have hard stops if there are issues you can't just drive on. Less human error." (Interviewee 11) "Anything with electronic is more reliable once validated correctly and right first time." (Interviewee 7) "Right first time on the floor." (Interviewee 4)

Another related theme emerging from the interviews includes; System integration and auto-reads. The removal of manual transcriptions and direct interactions between eBR and supporting systems (automation/instrumentation) reduce the potential for error at these steps. "Checking everything at the point in time when it needs to be checked….take away all that opportunity for error." (Interviewee 5) The benefits associated with data integrity were also consistently mentioned by interviewees. "More controlled environment for executing a process…remove an awful lot of paper errors that are unavoidable." (Interviewee 9) "Much tidier package, data integrity, more robust" (Interviewee 10)

The benefits attributed to the removal of manual post-execution reviews was the second most prevalent theme. The RBE approach has removed a significant number manual reviews and this benefit has been echoed by interviewees. "Auto-closure once it runs as intended." (Interviewee 10) "Streamlines post execution reviews….closes without the requirement for…post approval saving time and resources." (Interviewee 1) "Ability to close automatically without exceptions…currently….review and supporting comments is a huge workload." (Interviewee 3)

Removal of manual printing and administrative tasks. This reduces the overall resource demand related to batch record release and record reconciliation. "There's a benefit from point of view of eliminating paper and the resources to go with that…removes printing requirement." (Interviewee 1) "Takes a huge amount of admin work out." (Interviewee 3) As the eBRs designed are flexible across all molecules there is associated work removed during campaign start up. "eBR have generic tickets so don't have to update every campaign, just reviewed and approved once." (Interviewee 5)

Interviewee 4 identified "operator confidence in the system" as a benefit as a result of eBR implementation, this was also indicated by other interviewees. "Once designed correctly they (operators) know that there'll be nothing coming back to them…new operators, less confusing….guide them through the process." (Interviewee 8)

Within the interview process it was also highlighted by Interviewee 1, Interviewee 2 and, Interviewee 9 that the availability of records digitally aids in the access to information and prevents having to physically locate a batch record to obtain information.

4.2.2 Challenges of eBR Implementation

The technical challenges associated with the introduction of a new system was also a prevalent theme throughout the interviews. With the introduction of new systems there is a steep learning curve associated with system operation and controls. There are limitations with the IT system being used increasing the complexity of eBR design as well as system reliability. "Limitations of IT system…drives complexity when you have different molecules and variables as these get very large and have to be contained throughout the different hierarchies." (Interviewee 5) "The robustness of eBR system, performance of MES, issues in Building A and Building B this morning, no reason why any of it happens. When things go wrong it's like finding a needle in a haystack." (Interviewee 5)

The challenges associated with the decision to create generic eBRs, i.e., recipes which are flexible to accommodate all molecules in the facility, were identified by interviewees. These challenges are associated with scope determination, technical complexity, and testing restrictions. "Trying to build a single recipe and this recipe being OK for your 6 molecule and different flavours of molecules…hard to configure that in." (Interviewee 5) "Delivering common eBRs across two trains, separate systems that do talk to each other at certain times and share common functionality." (Interviewee 6) "Not having a simulation system is a technical challenge. Neither Ops or IT can use it before it goes lives…. Reviewing code is very static for IT" (Interviewee 5)

This complexity also has implications related to knowledge management and training. "Generic part/complexity is impacting, impacting on change, to change recipe now is harder based on this…take a lot of time to figure out how to do it and all the potential consequences across all the different variations for all the molecules" (Interviewee 5) "Not possible to map

out all the difference scenarios so have to have an understanding of how to investigate and troubleshoot eBRs but training takes a lot of time and isn't established yet." (Interviewee 9)

In turn, this complexity has consequences in the ongoing change management and troubleshooting of issues as they occur. "If recipe was smaller and less complex IT would get their heads around easier to support it…relies on information being fed and people understanding all the areas it needs to be fed into." (Interviewee 5) "There's a steep learning curve and then traying to train end uses who haven't been involved in the designed and setup of it is fairly challenging." (Interviewee 9)

The complexity of the recipe increases the number of steps being completed by the electronic system. The speed of this system was highlighted during interviews as a limitation that often drives frustration during system operations, "eBR system being "really slow", expectations, understanding the capabilities of the system." (Interviewee 5)

4.2.3 Mindset and Team Dynamics around eBR Implementation

A similar theme presented by interviewees is the theme of mindset change to enable eBR implementation. This change is a fundamental shift in both change from paper to electronic but also content and how batch record content and structure is determined and finalised for use in production. "We have taught people for years that the ticket tells you everything and you sign it…big change in mindset needed to bring people on that journey." (Interviewee 4) eBRs present "a different way of working", as reflected throughout the interviews. The transition to a new system after a long period, greater than 10 years, of using the paper records requires a fundamental change to how people work. As eBRs are being adopted incrementally operations are frequently working with both paper and electronic records, creating a constant comparison between both record types. "It's a different mindset and it's hard, and genuinely hard for people, have to think about it, not using any of your own experience." (Interviewee 5)

This challenge is not isolated to end users and production only but one that impacts the whole business. "Reluctance to make decisions and reluctance to change….from the whole business…it's easier to just replicate…than try to improve." (Interviewee 5) A potential lack of direction of what is trying to be achieved was exhibited by interviewees. "It's a new way of working for everyone…another challenge we have, different mindset needed for

everyone…. everyone comes with different opinions and different approaches and trying to marry all of them together is difficult." (Interviewee 6)

Some apprehension to the addition of eBRs was posed by interviewees. "People feel there are more things being tracked. Might not want the system…delicate." (Interviewee 9) "Need to see engagement from outside, from supervisors and operators, needs to be one of the operator goals. In other places people wanted to help." (Interviewee 8) "People tend to step away from it rather than dig deep and step into it." (Interviewee 5)

From the interviews it is evident that there was a disconnect between the business representatives understanding of the eBR implementation process vs the eBR SMEs understanding of what was expected and required. Through the interviews there was a trend of referring to "the business" and "IT" as two distinct groups with different needs and requirements rather than seeing them as one entity. They are intrinsically linked with throughout eBR implementation and creating a one team unity is important to prevent an "us and them" mentality. "Relationships need to be built within the group" (Interviewee 1) "Things got heated when there was push back. Should have been parked, both sides come back with proposal and have an adult conversation." (Interviewee 11) "Think that could have been a smoother process if communicated, created resistance on process team side." (Interviewee 10) "We don't fully understand their challenges, but they don't understand ours." (Interviewee 3)

Through the interviews differences in opinions between IT and the business SMEs were highlighted as a pinch point in implementation process. A "reluctance to build in options" into the eBR was identified often requiring extended conversations that were not value adding. "Everything is worth challenging to get an understanding…. not right to take one person's view as gospel but need a fine line between it." (Interviewee 1) Addition of more capabilities adds to the complexity of the recipe and increases the time associated with the project, where requirements are not understood up front the time and budget allocated will not be sufficient to add extra elements and will impact overall project delivery. Of those interviewed five were considered eBR SMEs. Of these SMEs three mentioned impacts to the implementation as it relates to monetary cost of extended project durations. "Time and money" (Interviewee 6) "Delays to project go live and cost." (Interviewee 5) "Budget impact"

(Interviewee 9) Monetary impact was not mentioned by any of the Business representatives, where cost was depicted in terms of quality impact as a result of not updating recipe accordingly. “Awful lot of pressure on just getting it done as opposed to getting it done right” (Interviewee 2) “eBR SMEs think we are asking for more but it’s just what is needed.” (Interviewee 3) “I felt it was clunky and there was always “our perspective” vs “IT perspective” and how we wanted something to run didn’t marry up with what system designed.” (Interviewee 10) “Stressing that it needs to be done but no understanding that technical format/content is not there to actually get it over the line” (Interviewee 2)

As mentioned by interviewee 3, there were “changes from assumptions which led to a source of friction”, these were “decisions made before business were even involved”. The full scope of the recipe required should be determined by the eBR team in tandem with the business to avoid these clashes during implementation as they impact relationships in the project team. “eBR SMES have one expectation on where they need to go in their sprints and business has a different thing. Business haven’t worked through what they want, doing it on the fly.” (Interviewee 3) As mentioned by Interviewee 1 “Technical people there for technical support and should be trusted to do that.” These decisions should be agreed across all impacted areas. Interviewees from the business side and eBR side did not expect this to happen at commencement of the project. “I was fairly frustrated….an awful lot of emotion and stress as a lot of conflicting interests at the time.” (Interviewee 2) Dichotomy of right and wrong in decision making processes. “I feel I was always arguing about creep in scope, extra and extra and extra was the narrative but two sides of the same coin depending on what side you sit on.” (Interviewee 3)

Interviewees identified that the roles and responsibilities associated within individual groups during eBR implementation were not clearly understood. “I don’t think roles and responsibilities were communicated up front.” (Interviewee 10) There was a sense that priorities were sometimes misaligned with role of the function in the project. “Tech team should have been focused on tech items” (Interviewee 2) “Lean is fine to an extent but if a technical person is giving a hard “No” on something a lot of time wasted then.” (Interviewee 11)

The impact of not having clearly understood responsibilities was identified by interviewees. Unrealistic expectations "puts people off future projects with the same groups…, given someone had experience it would be useful for them to do more." (Interviewee 11)

4.2.4 Unrealistic Expectations for eBRs

Without a clear understanding of what is trying to be achieved through the implementation of eBRs a false expectation of the end product will continue to persist. This expectation has led to a prevalent mindset that the transition to eBRs is not beneficial, but disadvantageous to production. "Feedback you get is not constructive it's criticism…straight criticism and not productive. Can't respond a whole lot can just tell someone just doesn't want it." (Interviewee 9) "Everyone is using the systems, need everyone to have that expectation that they need to get into it and learn it. Because not everyone has experience and hasn't been through it, we need to find a way to educate people who are going to be involved." (Interviewee 5) "Undermines the confidence of the end user in the overall process." (Interviewee 4)

Interviewees identified that a gap may exist between global and site missions for the adoption of eBRs. "Disagreement through global project vs site. Global mission is very clear, site not so much." (Interviewee 3)

Through the interviewees the theme of the role of eBRs and how they fit into the total control strategy was raised. Interviewees identified a previous tendency to rely on paper batch record to play multiple roles, in excess of regulatory expectations and requirements. Interviewees identified a need to evolve this thought process and the potential to use the eBR implementation as an opportunity to remove excess content. "Understanding how eBR sits in the overall group of systems and what role it is there to play. Understand what it should and shouldn't control, previous reliance on using the paper batch record to have everything. Need to challenge ourselves on content in eBR and potentially using other systems we have available to us." (Interviewee 3) "Get paper tickers sorted first. Be stricter about our paper tickets, can't just be a home for stuff that falls down in other systems." (Interviewee 5)

Interviewees proposed that while the eBR implementation would enable a refinement of batch record content a greater education of personnel on regulatory batch record requirements and structure of controls needs to take place first such is the change internally. “Batch record is more than ticket. Just a learning curve. Need to know what we can use as part of that whole package because it was always just Paper ticket before.” (Interviewee 10) A need to understand necessary elements compared to desirable attributes was presented by interviewees. “What do we want from this system vs what are other systems doing…. what do you do up front versus what do you do after, huge trade-offs there.” (Interviewee 3)

The initial expectations were also a topic identified through interviews. “Considering all the work and configuration that goes into it….the issues are really such a small number of these, always going to have teething issues at the start...Complex beast of a delivery” (Interviewee 7) “Teething issues are interpreted as design deficiencies….expectation that things will go perfectly is too high, see it with paper tickets as well but causes more frustration as eBRs are a massive change in practice, reluctance to it.” (Interviewee 9)

The lack of flexibility associated with electronic records, when compared with paper records, was also a theme through interviews. As eBRs execute to a predefined recipe, and it is not feasible to build in every potential scenario, the ability to respond and document unexpected events or deviations from this path poses a challenge. This finding is also consistent with survey results. “Explain why we can’t change certain things or why we can.” (Interviewee 4)

As eBRs are being incrementally adopted throughout the biotech business this mindset not only impacts eBRs implemented but also proposed projects. “Colours opinions of wider groups….only hearing negative things…builds biases in people who aren’t fully aware of the situation who then resist that change when it comes to them.” (Interviewee 9) “Even people who do support the system are all negative about it. People don’t see the benefits.” (Interviewee 9) “Easier to go back to paper system is perception.” (Interviewee 4)

Given the negative connotations associated with eBR implementation this can impact those working on the initiative to implement. “Fighting an uphill battle to champion things, eventually going to move on, can’t force people to like it but if they won’t meet you halfway you aren’t going to make the effort yourself.” (Interviewee 9) “Subset of us who really care

about it and would love to be involved and would sign up to it in a heartbeat, very small people who actually want to care." (Interviewee 3)

4.2.5 Prioritisation of eBR implementation within the business

The need for eBR prioritisation was well recognised across all interviewees to enable faster adoption. However, it was also felt that while eBRs are a stated priority they are over deprioritised in the face of peaks in workload and therefore actions regarding eBRs are not consistent with the messaging surrounding them. While it is believed that they are high priorities it was evident through the interviews that it is a "balancing act" and there are "a lot of other high priorities". (Interviewee 2) It was recognised that there has been an evolution in eBRs as a priority for the business. "In recent years there has been a big move towards implementation…as benefits have been seen…. it's been recognised that there is high benefit" (Interviewee 1)

However, access to leadership to enable this represented as an improvement area by interviewees. "Not getting the time with senior management to make decisions…. how much are eBRs a feature? Never. As a wider business group how do we say it's a priority, we don't even talk about it?" (Interviewee 3) "It is important but not as important as it should be…. falls down in their priorities from time to time and then delays roll out." (Interviewee 6)

Interviewees provided insight into the challenge in understanding the difficulties associated with eBR implementation that are not always seen to those outside of direct impact groups. "Does get underestimated how hard that job is to do…groups of individuals across different areas with fundamental differences in what they see eBRs bring." (Interviewee 5) "Looking in from the outside I wondered how it was taking so long to implement. Appreciate now being immersed in it." (Interviewee 7)

The challenge of eBR implementation in an operational plant was clear through interviews. This represents an added complexity to the implementation process. "Manager wants batches being produced so not prioritized over production, top 10" (Interviewee 11) "Not a priority because it's not affecting current batches out the door on a given day, batch in the system is always a higher priority, eBR implementation never trumps this." (Interviewee 6) "It's all people really, biggest challenge is trying to deliver on a plant that is trying to get product out the door." (Interviewee 5) "Very conflicting…. hard to prioritise it over the day to day." (Interviewee 3)

A misalignment between stated priorities and how it manifests in reality at a leadership level is believed to have challenged buy in across the whole business. “My managers involvement is minimal.” (Interviewee 7) “I have never seen plant leadership anywhere need the process…. probably seen as a metric rather than fully bought into it.” (Interviewee 4) “I think it is in the Top 5 in theory, but not in practice/reality.” (Interviewee 5) This lack of ability to get buy in across the business impacts the implementation process as the importance is not known or understood across all layers of the organisation. “Quite low…very little buy in. Compared to other places I worked very little engagement from process teams until it comes in and then it’s too late for engagement.” (Interviewee 8) We aren’t getting attendance; people don’t understand the importance of it.” (interviewee 5) “It’s a known priority but sometimes doesn’t feel like a high priority…You see it in terms of resources.” (Interviewee 9) “Talks a good show but still not that high on the list.” (Interviewee 4)

The impact of the lack of visibility and discussion about eBRs was presented by interviewees. Engagement with eBR is required not just from those involved in the project implementation but also the wider business. “Communication is key from both sides…..eBR team can be stronger and want to include the business more and then the business need to pull more and really engage with it.” (Interviewee 5) “How are people going to care if we never talk or hear about it? How many people feel it’s something to do with them?” (Interviewee 3) This lack of visibility may be impacting engagement with eBRs across the business as it is not seen as a priority. “People need to engage…if people can see the benefits and not the challenges it will go a massive way.” (Interviewee 9) The role of the production business in the eBR implementation was clear through interviews. A need to understand and own this implementation was demonstrated by interviewees. “Only way it’ll be successful is if we take more of a stake in the ownership of it. I’ve become a believer.” (Interviewee 3) “TLs need to drive it and push it back reps to get involved” (Interviewee 8) “Reacting to MES coming in rather than preparing for it.” (Interviewee 9) “Biggest thing is engagement, it has to come from above, doesn’t seem to come naturally…. not overly concerned until it comes around to their molecule” (Interviewee 8) Previous project experience would indicate that the more engagement the better the project engagement from the business the better the product delivered. “Very strong people on process side, tough and challenging to get through

bits of it, lots and lots of meetings….better to have engaged process team challenging us." (Interviewee 8)

4.2.6 Knowledge Management/Training in use of eBRs

Knowledge management/training was also identified as a key challenge throughout the interviews. The time and effort required to upskill in the eBR design and IT system behind this design is significant and results in a reliance on a small number of key personnel. The lack of understanding also prohibits or significantly increases the time associated with eBR implementation where business input is required. This can also result in rework being required where the implications of a decision are not understood at the time and are coded into the design. "When I first did it…like someone speaking a different language, haven't a notion" (Interviewee 9) "Double Dutch to me…big leap. Zero-to-One Hundred very quickly" (Interviewee 10) "Lot of it comes back to education and general knowledge of the systems. MES has been running in other areas already, in that building but not part of your day-to-day life if you aren't in it" (Interviewee 9) "Continuous learnings amongst everyone, once you got over one thing onto the next thing." (Interviewee 2) The impact of project structure on knowledge management and training was depicted by interviewees. "Even to bring someone into the project mid project is a challenge….they have missed a lot of detail from the start, hard to swap people interchangeably." (Interviewee 9)

Training of all groups was a theme throughout the interview process. "Management need to understand what is going on to understand what is needed." (Interviewee 2) From a management perspective there needs to be appropriate training and understanding of what role they are playing. "Being in governance making decisions was new for me…no forethought…I hadn't thought about it anymore than anyone else." (Interviewee 3) "wasn't clear expectations on what I was doing in my role, could have been hands off." (Interviewee 3) "TLs have their process knowledge and say have knowledge on paper tickets, understand it and happy to talk about it, come to look at an MES issue they are totally out of their depth, they don't have any idea and that's a hard place for them to be in, a hard place to be in management and supervision." (Interviewee 5) Challenges at a leadership level to adapt to eBRs and support implementation were hypothesised by interviewees: "people struggle with the eBR system, once you start to ask questions a little bit it gets very complex and turns people off really quickly." (Interviewee 5)

The lack of a hands-on training process was highlighted by interviewees. "Training as a group is a big thing…go hands on with people, have time to engage and talk through it, show benefits and iron out any potential issues." (Interviewee 9) "On the job learning, made it very challenging." (Interviewee 10) Being unable to run orders on a demo or simulation system was identified as a hinderance in the learning process for eBR implementation. "Can't run order easily outside of production……. not having a simulation environment has made go lives really difficult and has impacted the next project as a result." (Interviewee 5) It was hypothesised by interviewees that demo runs were viewed as a risk due to the potential for associated delays if any issues were to be identified during these runs. "See demo as a risk as find issues that have to be changed and updated." (Interviewee 9) "Ideally should test before Go Live but massive time lag." (Interviewee 8) The impact of not having a demo system was not initially understood, as indicated by Interviewee 5 "We didn't realise it was as big a thing…we thought for operators that it would be OK."

The impact of knowledge management on frontline operations was also represented in the interviews. "Because it runs seamlessly in the background people really start to lose knowledge of the process and how MES controls it." (Interviewee 5) "Trying to bring in a new process and explain it to people as well." (Interviewee 8) This knowledge gap is also impactful to technical support teams responding to issues in production. An additional technical challenge introduced with eBRs is the removal of flexibility as a result of operating within the constraints of a pre-defined recipe. "More difficult to navigate when there is an issue. Can't do inserts, harder to loop back. When it goes down the BCP process isn't well defined. Lack of flexibility." (Interviewee 11) "When exceptions do happen, because of knowledge management, it's hard….to show you have everything covered and then prove after the fact." (Interviewee 5) The process of moving responsibility from the implementation project team to the online technical process teams is made more challenging as a result. "Handover…process teams struggle, they don't know it." (Interviewee 5) "If we got calls, we weren't sure what to do as we hadn't run through it ourselves." (Interviewee 11) "Haven't upskilled technical functions to support it. People not invested in it." (Interviewee 4)

While the benefits associated with in built system interactions and integrations are clear it was also noted by interviewees that this removes visibility on what is happening within the eBR to operations personnel using the system. This has the potential to reduce process

understanding and understanding of how the eBR is controlling activities and should not be dismissed as the technical knowledge of frontline workers is critical to production. The performance of many steps by the system was also noted to contribute to the time taken for the eBR to execute during production. System speed was identified as a main point of concern for operations in the survey results and thus there is also frustration associated with enabling the eBR to complete these activities. The chosen software speed is a limitation and cannot be simply resolved, it should be considered which steps are critical and provide benefit by eBR performance compared to those that drive time without significant associated benefits. "The computer is doing it faster than what they would do and with less errors (advantage) but then the operators are standing waiting for it like watching the kettle boil." (Interviewee 5)

This challenge with knowledge management and training is also equally applicable to the IT team. "There's a big learning gap on the IT side to get our heads around the eBR system and how to work with it." (Interviewee 5) "The IT structure doesn't support knowledge management and transfer of the recipe over either." (Interviewee 5)

4.2.7 Resourcing during eBR implementation

The importance of resourcing, and potential consequences of not resourcing correctly, was mentioned throughout the interviews. Resources are critical to ensuring that the correct decisions are made at the beginning of the design process around scenarios to be enabled, these are key to the success of the project and timely delivery. "People think they aren't strong enough, changing really key foundations, difficult job regardless." (Interviewee 5) It was stated by interviewees that where design errors are introduced and not detected these may persist indefinitely if the record executes as intended. This highlights the importance of ensuring that personnel involved in eBR delivery have the requisite knowledge and experience to make decisions. "They must have an in-depth knowledge of the process and the area itself. It's key that they are knowledgeable in the area" (Interviewee 1) "Risk to the business, if it's not designed correctly you are never going to know in some cases and that's a big thing to realise…this is why it does need the strongest people and why we need everyone engaged" (Interviewee 5) "Expectation that our TSMS reps were assumed to be SMEs and they were not." (Interviewee 4) "Right people on projects, we have done different things on different projects." (Interviewee 5) "I was only business SME, I very quickly became the bottle neck…awful lot of decisions and calls and reviews have to be done by the person with the

business knowledge" (Interviewee 9) "Don't get the right people, right time, right supports." (Interviewee 6) "There were definitely times where expectations of the knowledge of the technical people were higher than realistically possible. Wanted people to know everything and make decisions there and now in the room." (Interviewee 11) "Down to inexperience or people working on their own without having all the knowledge." (Interviewee 7)

Resourcing was identified as an area where challenges were present during previous projects, specifically the dedication of resources to the project. The correct resources are also critical, a number of interviewees identified challenges with projects where the chosen business representative was not intimately familiar with the process or the area creating additional draw on others during the implementation. As stated by Interviewee 2 "there was a lot of workloads put on people…a significant demand…. compressing a lot of activities and also coinciding with other activities across areas." Management identified that the previous mechanism for resourcing the projects may not be sustainable into the future. We have tried "to approach it with as minimal an impact as possible to the business" can't continue, need to "invest heavily" with time and resources from business end. (Interviewee 3) "When we outsource to dedicated…product owners and keep away from the core business, then when we go live the people supporting the day to day don't know it." (Interviewee 5) "There's not an understanding the higher up you go up in the organisation the complexity of (i) the existing paper tickers and (ii) the complexity of eBR and decisions that need to be made to delivery a quality eBR." (Interviewee 6)

The impact of the technical complexity of trying to achieve the intended design was depicted by interviewees. "It's not that we have the wrong people on the design, the multi-product nature increase risks...no one person who could cover all molecules…more engagement of molecule representatives but can't have everyone on requirement or design as never get signed off" (Interviewee 8) "To get to the bottom of the issues need people who know it inside out…don't normally get that representation on the project." (Interviewee 5)

As eBRs are introduced area by area across the business there is high turnover of representatives from the business in the project teams, this was identified as a challenge during interviews. "Some consistency of people…always putting in new people…different people joining and making decisions makes it clunky" (Interviewee 3) This also hinders the

knowledge management process. The consistency within the teams has frequently relied on the IT eBR SMEs. “eBR SMES have to re-educate people the whole time” (Interviewee 3) Some interviewees identified benefits which may be achieved by reducing the amount of turnover within the teams, both from a technical and management perspective. “Small core group of people would get you further from overall strategic design perspective.” (Interviewee 3) “want everyone to be informed but at the same time too big and clunky. Core group decide and present strategy” (Interviewee 3) “Rotating members from management sometimes can create a perfect storm.” (Interviewee 5) “Need to put people into the project…who can survive a length of time in there. Not rotating in and out. In it from start to finish to get the benefit.” (Interviewee 4)

Ensuring the correct technical viewpoints are represented are critical to eBR implementation success, however, equally important is the representation of the end users, operators, in the final design. Through interviews it was identified that engaging with the end users, operators, was not performed consistently in eBR implementation projects. “Lack of user experience during initial roll out means there’s a lot of apathy towards the process.” (Interviewee 4) Not have operator representation on the project poses a risk to implementation. “I’m not on the floor, I don’t have that experience which is something we are conscious of but not sure how we are going to manage it.” (Interviewee 7) “Experienced operator should catch an awful lot.” (Interviewee 8) “We can also get things wrong as not real people on floor we are engaging.” (Interviewee 5) “Project team doesn’t have enough representation from the business…. someone who understands the implications on the floor.” (Interviewee 4) “End users, operations, need to be involved in designing the recipe.” (Interviewee 1) While operations are key to overall project outcome operators need to engage with the process and be bought into the process. A failure to have the operator pool engage with the process previously was demonstrated by interviewees. “More operator engagement, need to engage more throughout design lifecycle.” (Interviewee 8) “Supervisors need to engage…people won’t step in and take it on.” (Interviewee 5) “Very little operator engagement in Building B… Invited to training workshops and don’t come” (Interviewee 8)

The eBR team acknowledged through the interview process that the correct resource ask from the business must be in place for the project. “We used to ask for 2 hours a week from process teams, but it was 10-20 hours in reality.” (Interviewee 5) Without prioritisation of

eBRs within the business leadership groups the right resourcing to enable implantation will remain a challenge. “I don’t’ work with them every day though so I don’t know if people are the strongest people that are being given. Can’t really fight it, don’t have a choice. Need TLs (Team Leads) to provide the right people.” (Interviewee 5) Choosing the right person doesn’t seem to be the priority, “Systematic, there’s a problem in the group let’s offload them.” (Interviewee 4) Incorrect resources may also have implications for the decision-making process. “Management were needed for decision making.” (Interviewee 1)

The eBR implementation structure and approach to eBR implementation was acknowledged to have evolved over time during execution of several projects. The overall project methodology was identified by interviewees to be a potential challenge during execution. “Bit loose and a bit wishy washy in sort of project management or scheduling because we follow agile practices our requirements are always a bit loose…. if we are not forceful enough at the start it leads to slippage.” (Interviewee 6) This methodology is not widely utilised and was hypothesised to impact engagement with the process. “Project manager can talk a lot about agile methodology…. doesn’t engage very well, people don’t turn up as not getting anything out of it.” (Interviewee 5)

The implementation of eBRs is not a straightforward process and this was reflected in the terms used to describe the process by interviewees:

“Challenging” (Interviewee 1, 8)

“Exhausting” (Interviewee 2)

“What it took to get there was too much” (Interviewee 3)

“Stressful” (Interviewee 11)

There were several contributing elements to this identified by interviewees, these are outlined in subheadings below.

4.2.7.1 eBR Design Scope Determination

The design scope for eBR implementation was prevalent theme throughout interviews. “Recipes are always more complicated that people think going in…. the assessment of what is needed is always underbaked” (Interviewee 3) “I don’t think the project team realise what they need to implement…. not sure if they are scoping right first day.”

(Interviewee 4) It is evident that difficulties in this process have contributed to the challenges of eBR implementation. At present the eBR implementation process starts with the creation of an eBR implementation team in an area. This project commences on the assumption that paper records are aligned across molecules, however once commenced interviewees have identified that this assumption is false. "Paper tickets don't tell us the true story…. like the paper tickets were built in different countries" (Interviewee 8) "We see a lot of inconsistencies in paper tickets, trying to translate that into a consistent eBR is a challenge." (Interviewee 6) "Errors in batch records when it comes to try align from eBR side into a common set of steps, was it an error or a genuine decision, generally not very clear." (Interviewee 9) "We start always thinking that the paper tickets are perfect, that's the perception and that we just to convert to eBR but the reality is they are not perfect and that's not baked into the structure, not a straight translation." (Interviewee 5) "Spend so much time looking at paper batch records couldn't follow what was similar or dissimilar, or what was even the right one. Should know this before we go anywhere need eBR." (Interviewee 2) The lack of a predefined blueprint paper record to input into the eBR design process results in the eBR implementation project team being tasked with determining the history and decision related to each misalignment identified. "Paper ticket might not be translatable to functionality of what is happening on the floor. Paper tickets aren't perfect either." (Interviewee 2)

The suitability of current eBR implementation project responsibilities was questioned by a number of interviewees. "Compromise less on design if you know what you want. We don't invest enough up front." (Interviewee 3) "The narrative before we start is that it's the same process, until you look into it it's not known…underestimated the time and effort involved because of those differences" (Interviewee 6) Interviewees identified that eBR implementation should commence only when the business is in a position to translate its requirements such that it does not compromise eBR implementation. "Haven't done enough upfront work as a business…do it during allocated eBR time." (Interviewee 3) Interviewees identified a potential need to have pre work completed ahead of a gate review to determine appropriateness to proceed with eBR implementation. "Earlier assessment work needs to be done…easy to miss stuff…longer lead in process with the right people in the room to assess the tickets." (Interviewee 8) "More up-front planning

to get you thinking about it beforehand, cross functional input as well. Get everyone's ideas down and get a lot out of it." (Interviewee 10) There were some "genuine technical challenges" but "how many of them could have been avoided if we did the up-front investment?". (Interviewee 3) "Standardise ahead of eBRs coming in, standardise paper tickets/business processes." (Interviewee 6) "If our paper tickets were lean, if they were standardised across all molecules we would be in a different place." (Interviewee 5)

The challenge associated with implementing eBRs across multiple biopharmaceutical facilities and products on the same site was proposed by interviewees. "Biggest challenge that things aren't standardized. There's a perception out there that it's the same process in each building and there's no difference but in reality, they are all different. Fundamentally doing the same thing but they are not the same in terms of the real detail in them." (Interviewee 6). A generic recipe is one that can handle all molecules under production within the facility without updates required. "The biggest one (challenge) I've seen is trying to align multiple processes to fall into that golden ticket methodology. Hard when you have mature processes with different iterations." (Interviewee 9)

4.2.7.2 Approach to Decision-Making with eBRs

The decision-making approach was frequently mentioned throughout the interview feedback. The feedback was related to topics such as, engagement with eBR decisions, the decision-making process and, the documentation of decisions made and precedent for future projects.

Understanding the implications associated with eBR implementation decisions is paramount to project success. The timeliness of these decisions is also critical as while they do not imminently impact production, they can have significant impact to project timelines for project execution. A failure to engage with these decisions was hypothesised to be down to a number of factors, including mindset, lack of understanding, lack of clearly defined responsibilities in the decision-making process. "Decisions impact so many groups at the end of the day…generally we are not good at making decisions at all levels." (Interviewee 6) The delayed consequence of these decisions was proposed as rationale for some of this challenge with engagement. "Engagement can fall off for a period of time

and then it peaks at the end." (Interviewee 7) "If we need a decision, it's not going to be on the floor tomorrow or even for a number of months in reality, not urgent urgent. Urgent to our group but not to anyone else because in reality it's months away from going live." (Interviewee 6) "Boils down to team lead engagements…. depends on who's representing the process team, depends who pushes it, who is communicating clearly." (Interviewee 8) A failure to get the required engagement prevented decisions being made, increasing timelines, and driving frustrations internally within the eBR implementation team. "Nothing very timely around eBR implementation!" (Interviewee 8) "Time to make decisions, level of frustration…get people into a room to make a decision." (Interviewee 4) Need right people there for make decisions, didn't have right people at meetings to enable decision to be made. Added to time pressure on decisions. (Interviewee 1) "People need to attend the meetings. Takes ages to get a decision because it takes ages to get engagement." (Interviewee 5)

The challenge with making timely decisions throughout the eBR project was prevalent throughout the interviews. As you go up in the organisation, they "don't understand how difficult it is to get decisions made as we go through, need people to influence the decisions and drive them so we can make them quicker." (Interviewee 6) The need to make the right decision in a timely manner is evident. "The cost of the decision if they are rushed and it comes out after configuration, not fully understood and comes to quality review to ensure compliance, it takes an awful lot of time and effort leading to more delays" (Interviewee 9)

Throughout the interviews the structures in place to enable decision-making was questioned. "Escalation of decisions to governance, this doesn't work…there are a couple of meetings not working for us." (Interviewee 5) "Difficult to get people in a room or on a call where all groups are represented. People are busy rightly or wrongly." (Interviewee 6) "Get everyone into the room from the start but know what you want to change, clear statement that people know right off the bat." (Interviewee 9) While the urgency of decisions was echoed throughout the interviews there was also a sense that the correct time should be given to each decision, given the potential implications of decisions made during the eBR implementation process. "From an MES side and project side they are looking for decisions to be made very quickly and they don't have same understanding of

potential impact or work/networking required to get a decision made. Might seem like very simple questions but the networking and impacts and going around the houses it takes a lot of time." (Interviewee 9)

The roles in the decision-making process were also unclear, as represented by the interviewees. The responsibilities of each group in the process were not consistent across those interviewed. "eBR team make an assumption that the Ops TL knows the ticket in detail, not sure that is the reality." (Interviewee 5) "I would have assumed the project team would have enough experience to make the decision and they would have informed us bar the few bigger issues." (Interviewee 4) A related issue identified through the interview process is the lack of a clear owner in the decision-making process. "Not clear on who owns the decision, generally because they impact so many roles there often isn't one clear ultimate decision maker." (Interviewee 6)

A need to be able to clearly communicate the issue at hand and required decision to be made was emphasised by participants. "Pre conversations aren't happening….it hits people cold….they feel expected to respond there and then and not practical." (Interviewee 5) "Sheer importance of some of the decision making wasn't evident to me and other people, management from an end user environment we didn't understand the importance of making decisions quickly…coming at decisions cold, no context." (Interviewee 4)

The time required to make decisions is also dependent on the knowledge and experience of those required to make the decision. Where the decision makers are not well versed in eBRs this will impede their ability to make decisions. "Need to invest time…. people aren't used to not understanding things." (Interviewee 5)

The need to document decisions made during eBR projects is necessary to ensure consistency in approach to implementation and to prevent repeat conversations. This was identified by participants as something that is not well defined or executed during eBR implementation. "Strategically if we make the call is that the precedence for all, not just agree for single recipe. Where there's commonality it should feed forward. Different flavours everywhere. What is the right way? Why can't you do it the same?" (Interviewee 3) "Finding yourself reacting to and spending time reacting to decisions and comments

that were already sorted and agreed upon previously…. find yourself defending decisions as a group which were communicated, no issues at the time but now people want to change it back." (Interviewee 9) "Rework for some decisions was needed…slowed down the project." (Interviewee 5)

Positive examples of decision making were also outlined through the interviewees. These included times where issues were clearly presented, with relevant background work completed and risk assessments and it was clear what decision was to be made and by whom – propose development of a framework for decision making during eBR implementation. Define problem statement, origins of content, areas of impact and potential consequences, proposed solution/action. Does add to time required to make decisions but prevents wrong decisions or rework at a later stage as a result (Interviewee 1)

4.2.8 Strategy beyond Implementation

The need to have a strategy for eBR management once implemented was also identified by interviewees. Business processes have evolved and been fine tuned to support the paper batch record process, whether this process can maintain the correct level of support with eBRs was raised through interview process. "Has to be some MES support long term…fundamental shift" (Interviewee 4) "Business are not sure who to escalate to and it ends up coming back to project teams, definitely better way to do that and give it the time you want to." (Interviewee 9)

This strategy should consider resourcing of ongoing updates. "Even when we escalate I don't think resources are there to address it." (Interviewee 4) "Updates are challenging as well, a lot of validation to do…. which means changes can take a long time." (Interviewee 5)

The thoughts on eBR ownership once implemented was well aligned across interviewees, whereby technical services who were the owners of the paper batch records retain this responsibility as they are translated to electronic records. It was noted by interviewees that there is an additional layer added to this responsibility and the requisite training needs to be completed to allow technical services to understand eBRs to the same degree as with prior paper records. Where the correct knowledge and training are not in place then additional IT

ownership of these records would be necessary to ensure that the right knowledge level is present. “An “eBR system literate” TSMS rep would be the goal. Someone who understands the system and understands the process more than an IT person would.” (Interviewee 6) The long-term structure for eBR support and ownership needs to evolve to support the recipes in place.

4.3 Overall Summary of findings

This research had three main objectives, (O1) to identify the barriers to implementation of electronic records in multi-product bipharmaceutical facilities, (O2) identify organisational minset towards adoption of electronic records in place of traditional paper records across organisational hierarchies, and, (O3) quantify reduction of paper records where electronic records are fully implemented. The data collected in the survey and interviews is assessed with these objectives in mind and against the following research hypotheses proposed:

H1: Significant benefit has been attained from the implementation of electronic records.

H2: There is a relationship between time using eBRs and attitudes towards them.

H3: The challenges linked to electronic record adoption in certain biopharmaceutical areas is unique and not well understood.

H4. Successful implementation of electronic records is multi-faceted and is dependent not only on technical considerations but the appetite for change within the organisation.

The compliance benefits depicted in the survey and interviews are well correlated with the significant reduction in manual tasks, controlled right first-time execution and removal of manual reviews represented across both data sets. The ongoing requirement for continued eBR implementation was acknowledged by survey participants. The substantial reduction in manual activities removed within the facility where eBRs are well progressed is also outlined in this research. These results support H1, that significant benefit has been attained from the implementation of electronic records.

The survey data indicated that people were more likely to change their opinion of eBR impact from negative to positive following implementation of electronic records. This is indicated in the survey results and within interview content, as outlined in both the survey and interviews. This change is less prevalent in operations groups such as supervision and operators, indicating a better understanding of electronic records within these groups compared to others. In both the survey and interviews it was identified that the initial “Go-Live” process, when the recipes were first run, was a pinch point. The ability to seamlessly transition to electronic records was not

possible in most cases. The survey data indicated a strong correlation between the number of "Positive" responses and time using/exposed to electronic records. The survey data indicated there was no impact to number of "Neutral" or "Negative" responses based on time using/exposed to electronic records. This data relates to Hypothesis 2, with time impacting number of "Positive" responses, with no impact to "Neutral" or "Negative" responses.

Throughout the survey, the ongoing management of eBRs was identified as a challenge to the business. The need to identify and define the processes for ongoing management is required. Area management were the most likely group to indicate a change in opinion from "Positive" to "Negative" on introduction of electronic records. Area management are responsible for the teams responsible for the ongoing management of records and their updates, and this data finding is potentially linked to challenges identified with these processes.

Technical functions were identified as those most likely to deem adaption to eBRs as "Difficult" within the survey data. Throughout the interview process with a number of technical representatives these challenges were echoed. The challenges were related to a number of areas, initial understanding of how to translate paper content to electronic records, the IT requirements for electronic record design, the structure of documents that support electronic records, initial training provided for electronic records, and the skills required to troubleshoot and resolve issues with eBRs once implemented. These challenges are supported by interview findings related to to the knowledge management difficulties and hurdles which must be overcome with the training processes.

Throughout both the survey results and the interview data collected thoughts related to operational involvement in the implementation process are clear. Both data sets indicated that operational knowledge was not being utilised to the best of its ability and was preventing a more accurate and better to use product in production.

The capability of resources to deliver eBRs was reinforced through the survey data collected, however through the interview and survey results the ability to dedicate these resources to project implementation represents a hurdle. Ensuring the right resource approach is taken is paramount to the success of the eBR process. The complexity of the eBR design being attempted, the design of a generic eBR across all molecules, was well represented through survey and interview results. This additional layer of complexity to the eBR design process and increases the

risk associated with implementation as errors may not be identified for a large period of time until this molecule is back in production. Throughout interviews the preparation on the business side prior to the initiation of the eBR project was identified as an area for improvement. The lack of standardisation of paper batch record across molecules was evident through the interview process. The eBR project is set to design against a blueprint from the paper record, where multiple versions and layouts are in circulation this represents a barrier to eBR design and increases risks associated with implementation. There is a need to balance the time required to ensure the correct decision is made with the time urgency associated with it. The implementation of eBRs is a complex, multi-faceted process that can be difficult to define and understand, supporting H3.

Engagement with eBRs and prioritisation of eBR implementation represent a priority within the data collected. While the importance of implementation is acknowledged the meaningful action and commitment to this implementation poses challenges. The adoption of eBRs represents a significant change, the organisational approach to change management is critical to the success of the implementation. Without expectations to adapt and support the change there will be opposition to change and a reluctance to embrace this new technology. The successful implementation of electronic records is indeed multi-faceted and is dependent not only on technical considerations but the appetite for change within the organisation, as hypothesised in H4.

The information and data collected via the survey and interviews has fulfilled the three research objectives, and four hypotheses, proposed at the outset of this dissertation.

CHAPTER FIVE

5 CONCLUSIONS AND RECOMMENDATIONS

5.1Overview

The aim of this research was to investigate the factors impacting the design and implementation of electronic batch records within multi-product biopharmaceutical facilities. This research aimed to quantify the paper record reduction associated with electronic record adoption, achieved through the analysis of production schedules within one biopharmaceutical facility within the site studied. Other aims of this research were to gain a greater understanding of eBR benefits, and the technical challenges associated with their implementation. This research aimed to identify organisational factors impacting eBR implementation. The research objectives were investigated using a mixed-methods approach. This mixed methods approach comprised an online survey distributed to participants (N=119) and semi-structured interviews were also conducted over Teams (N=11). Survey participants provided an industry perspective on electronic records implemented. Interview participants provided meaningful insight into the eBR implementation process conducted at this biopharmaceutical site. The use of both a survey and interview provided a comprehensive understanding of the eBR design and implementation process throughout the lifecycle of eBR implementation.

5.2Recommendations

As eBRs have been implemented across different business areas, changes and modifications to the process have been made in efforts to improve this process. However, the data collected indicates an inconsistency in an overall appreciation of eBR requirements and a lack of understanding of eBR project intent. While those closest to eBR implementation are well versed in these requirements there doesn't seem to be a general understanding of what eBR implementation is there to achieve outside of these groups. Determining a well-defined mission statement for what eBRs are, and are not, that can be disseminated to all personnel, may benefit future projects.

Through the interview process, a reluctance to get involved in eBR projects was evident. A change in attitudes towards eBRs is necessary to enable the continued implementation across the business. As eBRs are a new phenomenon to many within the business, individuals are not as skilled in supporting this area as other projects or issues ongoing. The championing of this initiative by senior, and area, management is critical to enabling this.

It is not possible to infinitely test a new eBR prior to implementation, however distinct measures of acceptable risk need to be defined. As decisions related to eBR design and scope impact flexibility of the recipe once live the business need to understand the requirements. A defined approach to decision-making and testing thereof during the eBR implementation process may yield some benefits. This approach should include a mechanism for documenting the assessment, including risks and benefits, along with the agreed result to ensure consistency for future projects. The lack of a defined test system has had implications to previous projects, a commitment to the implementation of an interactive test environment may improve the success of initial implementation to areas. The resource requirements for the creation of this system also needs to be considered with respect to potential impacts to eBR project implementation and/or implementation of process improvements/required changes on live recipes. A trade-off in resource allocation may be necessary to enable the introduction of this system.

The time required to perform additional training to improve overall understanding of eBRs and knowledge of system operation is at odds with the desire to implement eBR solutions faster. A redesign of the training process would require additional resources conflicting with the resource constraints also heavily referenced in responses. This must be considered and addressed as without a fundamental change to approach it will not be possible to achieve both desired elements. The consequences of continuing without additional training, and the potential impact of this on internal mindsets to eBRs, is not trivial. Similarly, the implications of a slower eBR implementation include a continued flow of paper records and manual tasks along with reduced realisation of compliance benefits associated with eBRs, which have the potential to impact overall productivity along with reduce capabilities to release batches efficiently. This was an important finding in the surveys.

Software limitations and an aging system are contributing to performance issues however any changes to the software in use also represents challenges to validation and an ability to continue

the further roll out of eBRs across the business. A long-term strategy for the maintenance of this software system is necessary. This is required to ensure required system upgrades or improvements are baked into the production schedule to allow adequate time to complete same. The resourcing approach for system maintenance should also be defined, where the same pool of resources are implicated the consequences of this on eBR implementation projects and/or online system changes should be defined and agreed.

The resourcing approach to eBR implementation has evolved since initial project adoption and both survey and interview results emphasised this. A defined resourcing plan, with known roles and responsibilities is necessary to enable resources to be used optimally. Business commitment to the implementation project process is critical to the outcome, without the necessary buy in from all organisational groups the success of the projects is at risk. There is a need for greater understanding of eBRs at management level and a greater need to support area management to make decisions related to eBR implementation. There is also a need for greater GMP and production understanding for IT personnel involved in the eBR process. All project individuals need to understand the potential implications of an incorrect design input from a production standpoint. Equally, the benefits of eBRs need to be understood at an operator level, the increase in time of certain activities during execution have a profound impact on the reduction of time post-execution but are often only seen from impact to the person using the record.

The current eBR implementation starts with an assumption that the current paper batch record design can be translated into an electronic record. Throughout all projects completed to date there have been inconsistencies observed with the paper records that results in additional time to resolve. While many of these inconsistencies across batch records are non-impactful, they each require resources to investigate rationale behind any differences to enable a decision to be made. While these impacts are felt by the eBR project team these are not issues as a consequence of the eBR project itself. Batch record standardisation should be an expectation prior to the commencement of any eBR project, and commitment of IT resources, such that a blueprint of the required design is enabled. While this would require an additional pre-project phase requiring resources it would enable streamlining of the eBR design and implementation process itself. This additional workload also has the potential to impact overall timelines for delivery and overall resources required to support. Again, a trade-off decision may be required to optimise the

implementation process, and experience for those involved, versus continuing with the same approach and potentially having unintended consequences as a result of inadequate design or operational challenges within production.

This assumption is linked to another, whereby it is assumed the current paper batch record content is all required. It is evident through the data collected that paper records have evolved to contain information outside of regulatory requirements or expectations. This increases overall complexity of the eBR recipe design. This is an issue as a result of designing an electronic record to replace a paper record currently in use. These assumptions are ingrained from operators right through to senior management. There is a need to challenge current batch record designs prior to ever attempting a translation to electronic records.

Throughout the interview process, it became evident that there is misalignment of business and IT understanding of the responsibilities of the eBR project. A shared ownership of project delivery would enable a more positive outcome for all involved. Clear roles and responsibilities across the project groups may alleviate some of the tensions between these groups, however constant measurement of adherence to these roles and responsibilities is necessary to ensure suitability of those defined. Improved education of both groups on the requirements of each other may also provide some benefit.

The resources required to migrate from paper to electronic records are significant. Prioritisation of this workload for these resources is critical to overall project success. The eBR implementation process will commence nine to twelve months prior to go-live in production. As a result, it may be interpreted as not having any immediate benefit, allowing resources to be traded for more urgent or pressing items. To enable an overall successful outcome the priority of eBR implementation needs to be clear at a senior management and are management level. The requirement for resources needs to be clearly understood and defined for each project based on complexity. Where trade-offs are required the impact to overall delivery must be understood and accepted as a business delay to eBR implementation rather than an issue with the eBR implementation project itself. A clear understanding of where eBR sits in the business priorities may provide a benefit to area management required to make trade-offs to support the business.

The digitisation of batch records is a complex issue with many contributing elements. The issues facing the digitisation of batch records are both technical and organisational in nature. In

order to address these issues, the underlying cognitive maps of those within the organisation must first be addressed. With clear prioritisation and structures in place the implementation process may present fewer practical challenges during execution. The technical complexity of the eBR designs is primarily linked to the multi-product generic design. The benefits attributed to a generic design are significant and in order to realise this additional time to technically scope, design and implement complex designs may be appropriate. A support structure that can continue to support these recipes as time elapses ensures a robust system that can address issues in a timely and efficient manner.

5.3Limitations of Research

The limitations associated with this research performed include:

- The dataset is reflective of a single company within the biopharmaceutical industry in Ireland. This was chosen based on the fact that many challenges associated with eBR implementation are company specific and therefore the findings of the research are not generic. The desired sample size was obtained internally to provide significant insight into eBRs within this facility. However, the gathering of information across other companies in Ireland would have provided a deeper insight into eBR implementation across biopharmaceutical companies.
- Not all functions were equally represented within the survey results, most notably automation and qualified persons. The impact of eBRs on these groups is therefore not well understood, however the required participation across organisational groups was obtained, and well distributed, and therefore can be considered appropriate for intended research.

5.4Contributions of Research

- A deficit of research into eBR implementation and design within operational biopharmaceutical facilities was identified, this research addresses this gap and is therefore of benefit.
- Additionally, the organisational impact of transitioning from paper to electronic batch records is a topic that is difficult to obtain information on within the current literature,

this research provides an insight into additional factors which may impact eBR implementation and as such is beneficial.

- Through the analysis of information collected via surveys and interviews a series of recommendations for the ongoing implementation of eBRs were made to increase likelihood of success for future projects.
    - Creation of a well-defined mission statement for eBR implementation.
    - A "Top-down" effort to champion implementation of electronic records within the business.
    - Defined tool/process for decision making throughout eBR implementation.
    - Defined roles and responsibilities for implementation team.
    - Defined training structure to increase knowledge and understanding of electronic records across the business.
    - Clear alignment on eBR prioritisation across management hierarchies.
- The findings from this research represent a case study on electronic batch record implementation within a biopharmaceutical facility in Ireland which may be beneficial to other companies within the industry embarking on electronic record adoption.
- While the results depicted in this dissertation relate to a biopharmaceutical facility in Ireland the results are relevant to the pharmaceutical industry as a whole both within Ireland and abroad.

This research has provided practical insight into eBR implementation within the biopharmaceutical industry, a topic difficult to obtain information on within the current available literature.

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APPENDICES

APPENDIX A – COPY OF SURVEY

Dissertation Survey

I would like to invite you to take part in a short survey which will help me in my dissertation project investigating electronic records and the process of their design and implementation within a multi-product biopharmaceutical facility.

The purpose of this survey is to explore understanding of electronic records within a biopharmaceutical company and motivations for electronic adoption across organisational hierarchies. The survey also aims to identify some of the technical and organisational challenges that are faced in the implementation of electronic records.

You have been chosen based on your experience with and knowledge of electronic records within the organisation. The information you can provide will be hugely beneficial for my research.

Thank you in advance.

NOTE: All questions may not be relevant depending on role. Please answer questions relevant to your role, where questions are not applicable please leave blank.

* This form will record your name, please fill your name.

1. I confirm that I understand the purpose of this survey

- ◯ Yes
- ◯ No

2. I consent to my data being used for the purpose of this research

- ◯ Yes
- ◯ No

3. Which organisational group are you currently a part of?

- ◯ Senior Management
- ◯ Area Management
- ◯ Supervision
- ◯ Operator
- ◯ Technical

4. Which function are you currently a part of?

- ◯ Operations
- ◯ Engineering
- ◯ Technical Services (incl. Micro)
- ◯ Quality Assurance
- ◯ Qualified Person(s)
- ◯ IT
- ◯ Automation

5. Select which statement(s) align(s) with the level of MES adoption for batch manufacturing within your area

- [ ] eBRs have replaced paper records
- [ ] eBRs are used alongside paper records
- [ ] eBRs have not replaced paper records

6. In areas where eBRs have NOT yet been adopted, what impact do you perceive eBRs to have on your role

- ○ Positive
- ○ Negative
- ○ Neutral

7. In areas where eBRs have been partially/fully adopted, what impact do you perceive eBRs to have had on your role

- ○ Positive
- ○ Negative
- ○ Neutral

8. In areas where eBRs are partially/fully adopted please indicate length of time using/exposed to eBRs

- ◯ <1 year
- ◯ 1-2 years
- ◯ 2-3 years
- ◯ 3 years +
- ◯ N/A

9. Have your thoughts on eBRs changed since initial adoption?

- ◯ Yes
- ◯ No

10. If "yes" answered to Q9 above has the change been

- ◯ Positive
- ◯ Negative

11. Please add detail on areas which have impacted your opinion of eBRs

12. When was the last time you opened the MES production environment

- ◯ In the last day (24 hours)
- ◯ In the last shift (72 hours)
- ◯ In the last week (7 days)
- ◯ In the last month (4 weeks)
- ◯ In the last year
- ◯ I have never used MES production environment

13. How easy was it for you to adapt to electronic records compared to paper records?

- ◯ Extremely easy
- ◯ Somewhat easy
- ◯ Neutral
- ◯ Difficult
- ◯ Extremely difficult
- ◯ N/A

14. Based on your answer to Q13 above please identify the areas which made adaption to electronic records more difficult (Select all that apply)

- ☐ Did not understand technical content of eBR
- ☐ Did not understand how eBR functioned compared to paper batch record
- ☐ Did not have the IT skills required to operate the eBR
- ☐ Did not understand how eBR controlled quality critical parameters
- ☐ Training provided was not appropriate
- ☐ Other

15. Where "Other" has been selected to Q14 above please provide details below

16. Rate agreement with following statements related to eBR operation and implementation

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	N/A
I believe eBR implementation is useful	○	○	○	○	○	○
I know how to use eBRs	○	○	○	○	○	○
The eBRs are reliable	○	○	○	○	○	○
I am/my team are skilled in the use of eBRs	○	○	○	○	○	○
I had/my team had the right time to prepare for eBR implementation	○	○	○	○	○	○
I had/my team had the right level of training prior to the implementation of eBRs	○	○	○	○	○	○
The right support was available to me/my team during implementation of eBRs	○	○	○	○	○	○

17. Rate familiarity with the following

	Very familiar	Familiar	Somewhat familiar	Unfamiliar	Very unfamiliar
The eBR implementation process	○	○	○	○	○
The eBR update process	○	○	○	○	○
How eBRs interact with other equipment/systems	○	○	○	○	○
The eBR review process	○	○	○	○	○

18. Rate agreement with the following statements related to eBR implementation

	Strongly Agree	Agree	Neutral	Disagree	Strongly disagree
The right knowledge is available to implement eBRs	○	○	○	○	○
The right resources are available to implement eBRs	○	○	○	○	○
The right platform is being used for eBR implementation	○	○	○	○	○
The right IT structure is in place to deliver eBRs	○	○	○	○	○
The right business structure is in place to deliver eBRs	○	○	○	○	○
The right people are involved in eBR delivery	○	○	○	○	○
The eBR delivery timelines are achievable	○	○	○	○	○

19. Rate agreement with the following statements

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not Applicable
I believe electronic records are required	○	○	○	○	○	○
I understand my role in electronic record adoption	○	○	○	○	○	○
I have the same understanding of eBRs as I do of paper batch records	○	○	○	○	○	○
I have the required IT knowledge to perform my role as it relates to electronic batch records	○	○	○	○	○	○
I have the required process knowledge to perform my role as it relates to electronic batch records	○	○	○	○	○	○
I understand how the eBR interacts with other systems/equipment that are used in eBR execution	○	○	○	○	○	○
I understand my responsibilities as they relate to electronic record implementation and management	○	○	○	○	○	○
I know who to contact to answer my questions related to eBRs	○	○	○	○	○	○
I have the required process knowledge to make decisions related to eBR implementation	○	○	○	○	○	○
I understand how eBRs control quality critical parameters	○	○	○	○	○	○
I know how to access information within eBRs	○	○	○	○	○	○

20. Since eBR introduction rank difficulty of the following processes compared to paper records

	Much Easier	Easier	No change	More Difficult	Much More Difficult
Batch Execution	○	○	○	○	○
Batch Record Review	○	○	○	○	○
Batch Release	○	○	○	○	○
Update to BR content	○	○	○	○	○
Access required information for changes/observations within eBRs	○	○	○	○	○

21. Rate agreement with the following statements

	Strongly Agree	Agree	Neutral	Disagree	Strongly disagree
eBRs improve the overall quality/compliance of production batch records	○	○	○	○	○
eBRs reduce errors during execution compared to paper batch records	○	○	○	○	○
eBR adoption is key to production ramp up	○	○	○	○	○
eBR adoption will reduce batch release timelines	○	○	○	○	○
eBRs enhance data integrity controls during execution	○	○	○	○	○
eBRs have reduced manual tasks related to batch records	○	○	○	○	○

22. Are there any technical changes you would make to the current eBR

23. Are there any changes you would make to the current eBR implementation process?

24. Is there anything else you would like to include pertaining to eBR implementation and adoption?

APPENDIX B – INTERVIEW QUESTIONS

Interview questionnaire

Date:

Participant Name: _____

Organisational Area: _____

Function: _____

ICF Completed _____

1. What do you understand to be your role in eBR implementation?
2. What are the main benefits you see with eBRs compared to paper records?
3. What are the main challenges you see with eBRs compared to paper records?
4. Who do you think benefits the most from implementation of eBRs?
5. Who do you consider the owner of eBRs implemented in your area?
6. When you think about electronic batch records
    - 6.1 Where do they sit in your priorities?
    - 6.2 Where do you perceive them to fit in your managers priorities?
    - 6.3 Where do you perceive them to fit in overall business priorities?
7. When you think of the approach to electronic batch record implementation:
    - 7.1 Did you understand the drivers to implement electronic batch records?
    - 7.2 Did the structure of this implementation work well?
        - 7.2.1 If not
            - 7.2.1.1 Why not?
            - 7.2.1.2 What were the consequences of this structure?
            - 7.2.1.3 What could have been done differently to result in a more positive experience?
        - 7.2.2 If yes
            - 7.2.2.1 What were the key elements that made this work well?

8. When you think of electronic batch record projects completed:
    8.1 What behaviors presented obstacles or barriers?
    8.2 Did you know in advance that these would be barriers?
    8.3 How did these behaviors support/prevent the introduction of electronic records?
    8.4 What are the advantages of these behaviors?
    8.5 What are the disadvantages of these behaviors?
    8.6 What could have been done to remove these obstacles/barriers for future projects?
9. When you think of electronic batch record projects completed:
    9.1 What technical challenges presented obstacles or barriers?
    9.2 Did you know in advance that these would be barriers?
    9.3 How did these challenges support/prevent the introduction of electronic records?
    9.4 What could have prevented these technical challenges prior to commencement of the project?
    9.5 What could have been/can be done to remove these obstacles/barriers for future projects?
    9.6 Were these challenges resolved in a timely manner?
        9.6.1 If not
            9.6.1.1 Why not?
            9.6.1.2 What were the consequences of these issues not being resolved in a timely manner?
            9.6.1.3 What could have been done differently to resolve these challenges in a timely manner?
        9.6.2 If yes
            9.6.2.1 What enabled this?
            9.6.2.2 Are there any learning opportunities from this?
10. Any other information you would like to share related to eBR implementation?

APPENDIX C – PARTICIPANT INFORMATION LETTER (OR LEAFLET)

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Participant Information Letter

Electronic records and the process of their design and implementation within a multi-product biopharmaceutical facility

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 Jean O'Driscoll and I am conducting a dissertation research project into electronic records and the process of their design and implementation within a multi-product biopharmaceutical facility. The purpose of this survey is to explore understanding of electronic records within a biopharmaceutical company and motivations for electronic adoption across organisational hierarchies. The survey also aims to identify some of the technical and organisational challenges that are faced in the implementation of electronic records. This research project is being carried out with Griffith College Dublin and Innopharma as partial fulfilment of the requirements associated with MSc. Pharmaceutical Business and Technology.

WHAT WOULD TAKING PART INVOLVE?

Taking part would require your participation in a survey/interview about electronic records and the process of their design and implementation within a multi-product biopharmaceutical facility. The survey can be completed in your own time and online. The survey will take no more than 20 minutes to complete. Interviews will be conducted in person or over a Microsoft Teams meeting and will take no more than 45 minutes to complete.

WHY HAVE YOU BEEN INVITED TO TAKE PART?

You have been identified to take part based on your experience with and knowledge of electronic records within the organisation. The information you can provide will be hugely beneficial for my research.

DO YOU HAVE TO TAKE PART?

Participation in the research is completely voluntary and you are entitled to withdraw from the research at any time. If you wish to withdraw from the research please confirm same via email atodriscoll_jean_elizabeth@lilly.com

WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF TAKING PART?

The risks associated with participation are nominal, all information will be anonymised and stored in a password protected file. Any information pertaining to a particular organisation will not be disclosed without prior permission. I hope that you find participation in this survey beneficial and interesting.

WILL TAKING PART BE CONFIDENTIAL?

All information provided through the survey will be handled in the strictest confidence. Survey results will be retained for the duration of research. The results will be fully anonymised and will not result in the participant being identifiable. Data collection will be handled in line with GDPR and the national data protection laws in place. Consent forms will be collected, and retained, as part of the research process. Information pertaining to confidential company data will not be disclosed as part of this research.

HOW WILL INFORMATION YOU PROVIDE BE STORED AND PROTECTED?

Signed consent forms and original audio recordings will be retained in a password-protected file. The files will also be backed-up in an external cloud-based storage system until such time as the research project is completed and MSc. award has been conferred. A transcript of interviews in which all identifying information has been removed will be retained for a further 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 will be utilised for completion of this research dissertation only. This research dissertation will be made accessible in Griffith College Dublin's library on completion.

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

If you have any further questions, then please feel free to contact me.

Jean O'Driscoll – Researcher

odriscoll_jean_elizabeth@lilly.com

Thank you for taking the time to read this information leaflet.

APPENDIX D – INFORMED CONSENT FORM

GRIFFITH COLLEGE

Consent to take part in research

Electronic records and the process of their design and implementation within multi-product biopharmaceutical facilities

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 [*insert participant name*] 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 completing a survey relevant to electronic batch records and their adoption/use in a multiproduct biopharmaceutical facility.
- 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 the dissertation above for which this survey is being completed as part of.
- I understand that I will adhere to all of the codes of conduct and employee confidentiality for Eli Lilly Kinsale 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 in in a password-protected file. The files will also be backed-up in an external cloud-based storage system until such time as the research project is completed and MSc. award has been conferred. A transcript of interviews in which all identifying information has been removed will be

GRIFFITH COLLEGE

retained for a further two years after this. Under freedom of information legislation you are entitled to access the information you have provided at any time.

- I understand that a transcript of my interview in which all identifying information has been removed will be retained for two years from the date of the exam board.
- 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

Jean O'Driscoll

MSc Pharmaceutical Business & Technology

Griffith College Dublin

086-414-1707

odriscoll_jean_elizabeth@lilly.com

Signature of participant

[Full Name – Printed]

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