Awareness, Benefits and Challenges to Digital Twin Adoption in the Irish Pharmaceutical and Biopharmaceutical Industry

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

MSc in Pharmaceutical Business & Technology

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Griffith College

Candidate Declaration

Candidate Name: Rory Shevlin

I certify that the dissertation entitled:

Awareness, Benefits and Challenges to Digital Twin Adoption in the Irish Pharmaceutical and Biopharmaceutical Industry, submitted in partial fulfilment of the requirements for the degree of MSc in Pharmaceutical Business & Technology is the result of my own work and that where reference is made to work of others, due acknowledgment is given.

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Contents

Table of Figures

List of Tables

Acronyms & Abbreviations

AI: Artificial Intelligence
ANN: Artificial Neural Network
CFD: Computational Fluid Dynamics
CHO: Chinese Hamster Ovary
CPP: Critical Process Parameters
CQA: Critical Quality Attributes
DEM: Discrete Element Method
DoE: Design of Experiments
EMA: European Medicines Agency
FDA: Food and Drug Administration
FEM: Finite Element Method
FRAME: Framework for Regulatory Advanced Manufacturing Evaluation
GDPR: General Data Protection Regulation
GMP: Good Manufacturing Practices
HMI: Human Machine Interface
ICF: Informed Consent Form
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IoT: Internet of Things
M2M: Machine to Machine
mDoE: Multiple Design of Experiments
MES: Manufacturing Execution System
ML: Machine Learning
MQTT: Message Queue Telemetry Transport
MVSA: Multivariate Statistical Analysis
NARX: Nonlinear Autoregressive with Exogenous Inputs
NIR: Near Infrared
OPC: Open Platform Communications
PAAS: Platform as a Service
PAT: Process Analytical Technology
PCA: Principal Component Analysis
pFMEA: process Failures Modes Effects & Analysis
PIL: Participant Information Leaflet
PLS: Partial Least Squares
QbD: Quality by Design
QTPP: Quality Target Product Profile
SCADA: Supervisory Control and Data Acquisition
SME: Subject Matter Expert

ABSTRACT

Awareness, Benefits and Challenges to Digital Twin Adoption in the Irish Pharmaceutical and Biopharmaceutical Industry

Rory Shevlin

In this dissertation the awareness of Digital Twin adoption in the Irish Pharmaceutical and Biopharmaceutical industry are investigated. The benefits of Digital Twins, and the technical and regulatory barriers to their adoption are studied. Research was conducted using a mixed-method approach of an online survey (n=109) and an interview that was thematically analysed (n=4). All participants currently work in the Irish Pharmaceutical or Biopharmaceutical industry. The interview process inclusion criteria required participants to have an expert level of knowledge in 'Digital 4.0' technology.

The survey identified a low awareness level of Digital Twins within the industry generally. There is a notable skew towards lower knowledge levels outside of Automation and IT roles. The interviews supported this with three of the participants describing awareness as minimal and the fourth indicating that knowledge was limited to those directly involved in implementation. The lack of engagement from operations and quality stakeholders would be essential for widespread adoption and highlights a need for broader understanding. Furthermore, there is general confusion across all roles on the definition and purpose of a Digital Twin.

The benefits of Digital Twins were considered significant by both survey and interview participants. A greater understanding of manufacturing processes and improved process yields were repeatedly identified as major potential benefits. The interview responses supported and emphasised that financial justifications from both a capital and sustaining perspective are essential. Therefore, investment should be directed strategically to obtain the greatest return.

The chief technical barriers identified in the primary research were that of data and system integration. The regulatory barriers were not widely perceived as significant from the survey population. However, respondents that did feel they were significant identified vendor model regulatory compliance and traceability of data as the main barriers. The interview responses indicated the regulatory barriers were significant and that the lack of a regulatory framework or guidance around Digital Twin validation and implementation generally, is a critical barrier to broader adoption of Digital Twins within the industry.

1.0 Introduction

1.1 Overview

Digital Twins are an innovative concept which is rapidly gaining traction in different industrial settings. One of these is that of the Irish pharmaceutical and biopharmaceutical sectors. This concept was first introduced in 2002 and can be described as a virtual replica of a physical system or process, that enables real-time data monitoring, predictive analysis and simulation. Effectively, this can reflect the performance and behaviour of the physical system and provide a myriad of insights.

To be considered a true Digital Twin, it is generally agreed that it must contain three distinct components: a physical process such as a bioreactor, a virtual model of this bioreactor such as a Finite Element Modelling (FEM) computer simulation, and the communication network of hardware and software which link the two. Ideally the virtual model should be updated in real-time and algorithmically decide whether to modify the behaviour of the physical counterpart i.e., the information should be bidirectional. If this information is unidirectional, then this model falls somewhere between a Digital Twin and a 'Digital Shadow' (Grieves, 2019).

This technology has the potential to revolutionise the Irish pharmaceutical and biopharmaceutical industry in numerous ways, including optimising the yields of processing steps, reducing bottlenecks and providing simulated training. However, widespread adoption is not apparent in industry, and this is unsurprising given the many challenges from both a regulatory and technical standpoint. A detailed understanding of these is critical for companies in Ireland to stay ahead of the curve and reap the benefits of Digital Twins in the 'Industry 4.0' era.

1.2 Aims and Objectives of the Dissertation

This study aims to better understand the current awareness of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical industry. Furthermore, it investigates what the perceived benefits are, so this information can be disseminated out to industry stakeholders that may not fully appreciate the power of these tools. In order to present a complete picture to the decision makers, this study also aims to understand what the technical and regulatory barriers to Digital Twins are and to make recommendations for the regulatory agencies to engage and encourage adoption of this technology.

The objectives are as follows:

1. To evaluate the current awareness level of Digital Twin technology:
   - Among employees in the Irish Pharmaceutical and Biopharmaceutical Industry.
   - How does this awareness level differ based on employees' position and functional area within the organisation.
2. To identify the key benefits of implementing Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.
3. To investigate the technical barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the challenges in data integration, network infrastructure and technical skill base in Ireland.

4. To investigate the regulatory barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the data integrity, cybersecurity and Good Manufacturing Practices (GMP) compliance challenges with a focus on FDA and EMA regulations.
5. To make recommendations for industry and regulators to prepare for widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

The results from the data gathered in this study will be used to test the following hypotheses:

H1: The majority of employees in the Irish Pharmaceutical and Biopharmaceutical Industry have low awareness of Digital Twin technology.
H2: Awareness of Digital Twin technology is significantly higher among employees in Automation and IT roles compared to those in Process Engineering, Quality, Validation, and Operational roles.
H3: Employees who are aware of Digital Twin technology perceive it as offering significant benefits, such as improved process efficiency, enhanced product quality, and reduced operational costs.
H4: The primary technical barriers to the adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry are related to data integration, network infrastructure, and the technical skill base.
H5: Regulatory concerns, particularly related to data integrity, cybersecurity, and GMP compliance, are significant barriers to the widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.
H6: Regulatory frameworks and industry standards currently in place are insufficient to support the large-scale implementation of Digital Twin technology, necessitating new guidelines and incentives from regulatory bodies.

1.3 Research Questions

The research questions that are linked to the objectives of this study are as follows:

1. What is the level of awareness of Digital Twin Technology within the Irish Pharmaceutical and Biopharmaceutical industry?
2. How does the awareness level of Digital Twin Technology within the Irish Pharmaceutical and Biopharmaceutical industry vary based on employees' position and functional area?
3. What are the key benefits to implementing Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry?
4. What are the main technical barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry?
5. What are the main regulatory barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry?
6. What recommendations should be made to the industry and regulators to prepare for widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry?

1.4 Significance of the Research

The significance of this study is its potential to impact on future decision making in a crucial sector for the Irish economy. Ireland is a major hub for pharmaceutical and biopharmaceutical manufacturing as the third largest exporter of pharmaceuticals in the world and the largest exporter in the EU. This sector contributes 50% of the country's exports and it has built this success on being at the forefront of next-generation technologies (IPHA, 2024). If Digital Twins do become a foundational tool within the industry (as many predict), then it is crucial for Irish companies to enhance their competitiveness in global markets by adoption of these technologies. In order to do this, it is necessary to increase awareness of the technology and also have an objective assessment of what these technologies can deliver and what the challenges are, so that the significant investment required can be directed strategically in order to maximise a return for shareholders.

1.5 Access and Research Ethics Issues

The primary research methods for data collection, synthesis and interpretation conducted in this study were conducted according to ethical standards. This was in order to protect participants' confidentiality, maintain the integrity of the research process and to ensure that all data was handled responsibly and in compliance with General Data Protection Regulation (GDPR). All participants were fully informed about the purpose, methods and any possible uses of the research and any risks that may be involved. All information supplied by subjects was kept confidential and anonymised. This research is independent from any conflict of interest and in the event of a conflict of interest from a participant they were given the option to withdraw from the study. Furthermore, at any time participants could withdraw from this research for any reason. A Participation Information Leaflet (PIL) was given to each of the participants as part of the invitation letter which explained the background of the research, any risks and benefits and the confidentiality they could expect. The participants were asked to sign an Informed Consent Form (ICF). All findings will be disseminated in an appropriate manner.

1.6 Structure of Research

Chapter 1: Introduction

This chapter gives an overview and definition of Digital Twins and raises questions of the industry's awareness of these tools and what the benefits and challenges to their adoption may be. It also discusses the significance of this adoption within the Irish market and outlines the research questions and objectives that will be used to explore this further.

Chapter 2: Literature Review

This chapter gives an overview of the state-of-the-art Digital Twin technology generally. This explores different aspects of the technology and the research already conducted into them. This establishes a framework against which the findings of this study's primary research can be compared and contrasted.

Chapter 3: Research Methodology

The purpose of this chapter is to outline how the overall study has been conducted. It discusses research paradigms and the philosophical approach used before detailing the practicalities of this work including the target population and the design of the different tools used to obtain the primary data.

Chapter 4: Findings and analysis

In this chapter the results that have been obtained through primary data collection methods are presented through data visualisation and analysis techniques in order to address the objectives of this research. Qualitative and quantitative data are analysed together in a mixed method approach.

Chapter 5: Conclusion and Recommendations

This chapter summarises the conclusions from the study and describes the implications of these. Practical recommendations are made for industry stakeholders and regulators. Recommendations are also made for future work. The limitations of the study are discussed in this chapter.

2.0 Literature Review

2.1 Research Topic

This study aims to investigate the current awareness of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical industry. It investigates the benefits of this technology and also the technical and regulatory barriers that may discourage adoption of these technologies. This literature review has been conducted to help design the primary research data collection methods. Furthermore, the findings of it will be compared and contrasted with the results of the primary research findings in section 5.0.

In section 2.2.1 an overview of the Digital Twin framework is presented alongside the continuum of models and technologies which lack the characteristics of a full developed Digital Twin. The implication of these models for pharmaceutical validation is described in section 2.2.2. Sections 2.2.3, 2.2.4 & 2.2.5 review the three major components of a Digital Twin which are the physical model, the data communication component, and the virtual component respectively.

2.2 Detailed Literature Review

2.2.1 Overview of Digital Twins

2.2.1.1 Digital Twin Framework

The framework of a 'True' Digital Twin is generally understood to consist of three components. These are the (1) physical entity consisting of hardware, soft sensors, Open Platform Communication (OPC) servers and local historians, (2) a virtual entity that is a detailed Multiphysics Multi-Scale simulation model of this physical entity and (3) a communication layer which links the physical and virtual models. This communication layer should be capable of gathering heterogeneous datatypes from different sources and relaying this to the model in near real time. This communication layer should be bi-directional and facilitate the transfer of the data back to Physical Model based on the simulation's output in order to modify the operation of the field devices. Figure 1 displays one interpretation of this framework that incorporates Cloud Storage for the communication layer and an Online Dashboard for visualisation of the Digital Twins information. Components (1), (2) and (3) will be explored in Sections 2.2, 2.3 and 2.4 respectively.

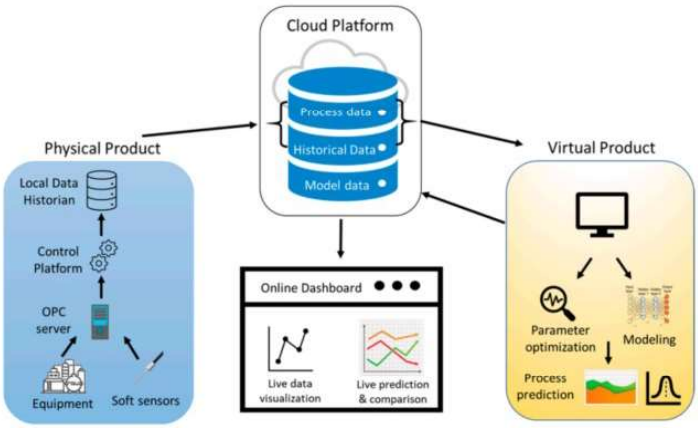

Figure 1 – Digital Twin Framework (Chen et al.*, 2020)*

2.2.1.2 Evolution of a Digital Model to a Digital Twin

There is a lack of consensus in the industry as to what can be considered a Digital Twin. At present there is no evidence of a comprehensive tool as described in Section 2.2.1.1 being used in industry at plant scale. However, there is a continuum from various levels of Digital Model to Digital Twin which is illustrated with the example of a Cell Culture Bioreactor in Figure 2.

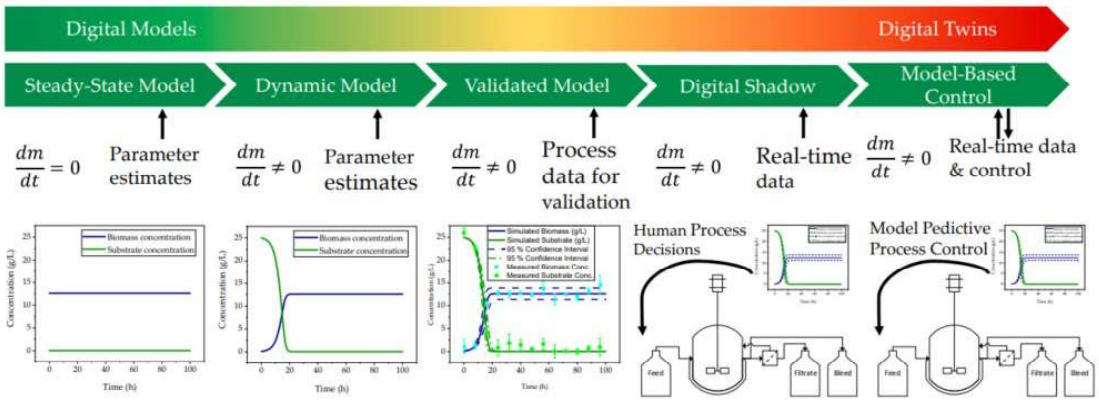

Figure 2 – Evolution of a Digital Twin for a Cell Culture Bioreactor (Helgers et al.*, 2022)*

2.2.2 The Validated Model

A pre-requisite for the implementation of a Digital Twin in the highly regulated Pharmaceutical/Biopharmaceutical industry is that the model must be validated quantitatively. Models are normally developed during the process development stage and include complex phenomena such as feed-back inhibitions and mass-transfer calculations. Models can be Mechanistic, Data-Driven or a Hybrid of the two (Portela *et al.*, 2020). Where Mechanistic models generally have a higher computation complexity than a purely data driven model, they often better represent the process. However, they are rarely adaptive and compatible with self-improvement through automated parameter refinement and for this reason Hybrid models are often seen as a good trade-off (Chen *et al.*, 2020).

A Digital Model should be able to accurately represent the fundamental processes of a unit operation such as cell growth, product formation and substrate consumption but it lacks real-time data integration. The major limitation of using a Digital model alone is that it is purely predictive and relies on historical data and theoretical or empirical calculation. It will not take account of dynamic changes in the unit's environment that may introduce error. A workflow of this model validation using a Quality by Design (QbD) approach is displayed in Figure 3 and relies heavily on process understanding (Helgers et al., 2022). This reliance on process understanding for model validation is also central to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance.

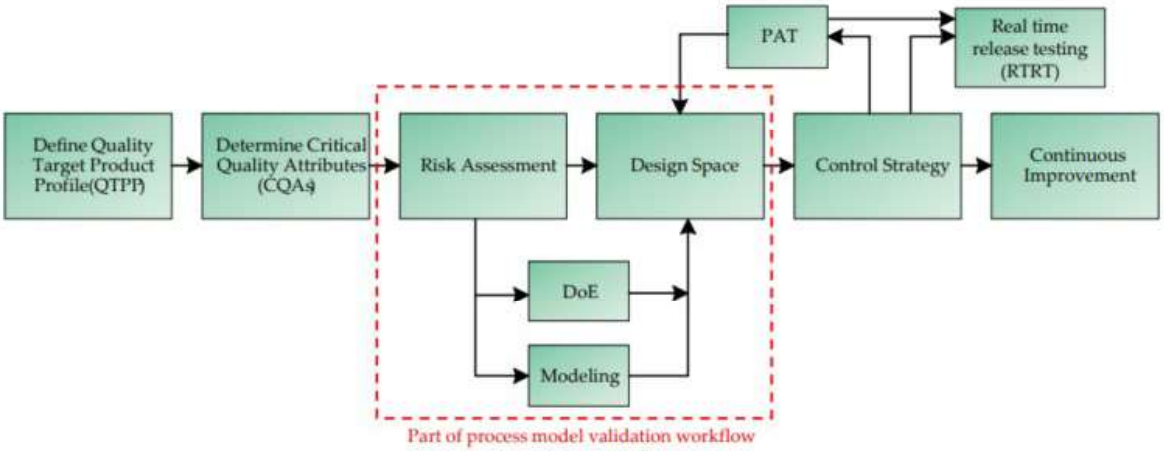

Figure 3 – Model Validation using a QbD approach (Helgers et al.*, 2022)*

The importance of both the ICH Q9(R1) 'Quality Risk Management' and ICH Q10 'Pharmaceutical Quality System' can be observed in the model validation in terms of their requirements for Risk Assessments and process performance monitoring respectively (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2008; 2023). The regulatory guidance most relevant to validation of the model is ICH Q8(R2) 'Pharmaceutical Development' which defines the Quality Target Product Profile (QTPP) and identifies Critical Quality Attributes (CQAs) and how the Critical Process Parameters (CPPs) impact on these. This in-depth process understanding is key to establishing the design space, which is the combination of input variables and process parameters that are required for a controlled process (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2009).

2.2.2.1 The Digital Shadow

The digital shadow is a more advanced representation which can integrate real-time data from the unit's instrumentation. This allows it to correct for errors - dependent on the sampling rate. Furthermore, if the model is designed to be adaptive it can update its model parameters to align better with the physical counterpart. However, the defining characteristic is that the data is not bidirectional. It will identify performance deviations and should predict cell culture performance, but it will not autonomously perform operations on the physical model. This design is often preferable in industry as it is easier to introduce for a validated process (Ding *et al.*, 2023).

2.2.2.2 The Digital Twin

The digital twin builds upon the operation of the digital shadow by implementing closed-loop control onto the physical model in order to optimise the performance of the unit operation. However, as described by (Udugama *et al.* (2021) closed-loop control without any human interaction may currently be impossible in many industrial fermentation operations as some steps are still carried out by operator intervention. Therefore, this author asserts that an effective Human Machine Interface (HMI) is key to provide the interpretations of the digital twin to the operator and engineer and allow experienced personnel to decide on whether to implement the Digital Twin recommendations based on experience and knowledge of the underlying assumptions of the model. However, Cimino et al. (2019) purport that it is possible to move towards fully autonomous control by leveraging off of existing Manufacturing Execution Systems (MES) that have rules written into them which should take decision making away from operators.

One study developed an open-source digital-twin framework for cell culture. The model was that of a metabolic pathway for Chinese Hamster Ovary (CHO) cells. The T25 flask (Figure 5) was monitored using Near Infrared (NIR) spectroscopy which was validated experimentally to be able to measure cell density of the inoculum (Figure 4). A Kalman filter was used to reduce signal noise during sampling as these can fluctuate and the digital model was validated to be able to predict cell density, glucose and lactic acid concentrations.

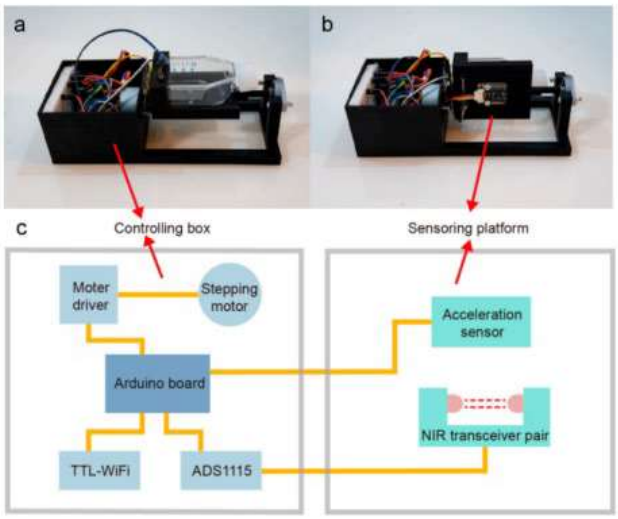

Figure 5 – NIR spectroscopy Experimental Setup (Zhao et al., 2023)

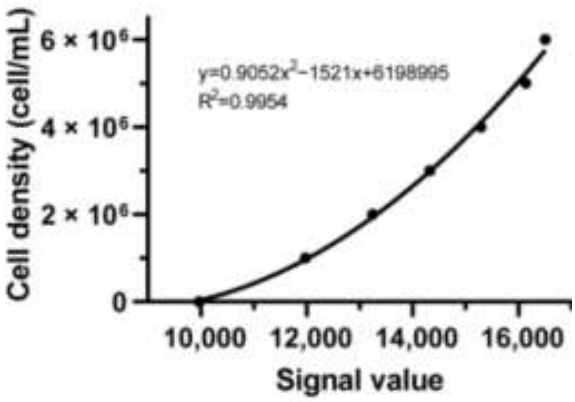

Figure 4– NIR spectroscopy measurement validation (Zhao et al., 2023)

A 72-hour cell culture experiment was carried out to evaluate the effects of fluctuations in environmental conditions and substrate concentrations on the cell growth of the inoculum. Interestingly, at a high sample rate the Digital Twin and Digital Shadow offered similar performance in terms of being able to predict cell density as the accumulated error was effectively nullified every 15 minutes and the adaptive benefit of the Digital Twin with respect to automatic update of the kinetic parameter was not realised. At lower sampling rates however this is not the case where the ability of the Digital Twin to predict culture performance 'self-improved' whereas the Digital Shadow did not (Figure 6). Zobel-Roos *et al.* (2019) raise the question whether in future regulatory bodies will consider filings acceptable without a Digital Twin model of a process given that QbD and Process Analytical Technology (PAT) approaches have been required by regulators since 2004.

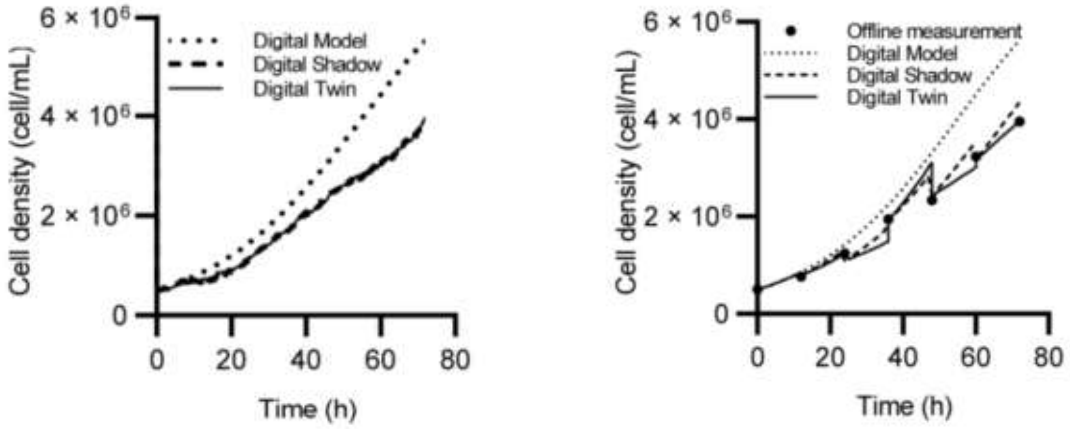

Figure 6 – Cell Density over Time at Higher (Left) and Lower (Right) sampling rates (Zhao et al., 2023)

2.2.3 Physical Model Component of a Digital Twin

2.2.3.1 Critical Process Parameters

CPPs of the relevant processing step are those which must be controlled with acceptable operating ranges in order to ensure the stability, quality and efficacy of drug production. Determination of these is a lengthy process which is guided by regulatory frameworks including the ICH Q8(R2) Pharmaceutical Development guideline (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2009).

It involves mapping out the process flow and identifying each unit operation and the relationship between the different process variables such as temperature and pressure and how they relate to the CQAs of the final product. Risk assessment techniques such as process Failure Modes Effects & Analysis (pFMEA) are used to identify which of these variables may affect the CQAs and the Design of Experiments (DoE) method is used to investigate the effects of these variables by manipulating them. Historical data analysis and regression analysis identifies correlations between process parameters and quality issues. Kuchemüller *et al.* (2020) presented a case study where a model-assisted DoE (mDoE) was paired with a digital model of a monoclonal antibody CHO cell culture for medium optimisation. The authors used the model for their initial inputs of different media compositions with widely distributed boundary values. Based on the results, the input range was then narrowed and these were assessed experimentally and found to have good agreement with the Kinetic Model. The experimental results were also used to refine the model in a Hybrid type approach. The conclusion of the authors is that an mDoE approach can be used to significantly shorten process development timelines (in this case a 75% reduction in the number of experiments from 16 to 4). As shown in Figure 7, the experimental and simulated results agreed that within the defined boundary conditions the optimal media feed composition to maximise yield and product quality was to the maximise initial glucose and minimise initial glutamine concentration.

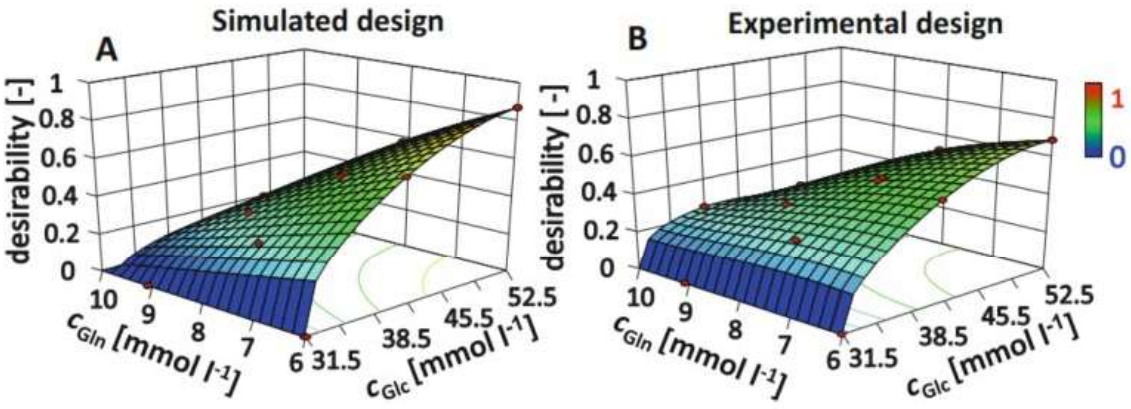

Figure 7 – Simulated and Experimental mDoE for the effect of Glucose and Glutamine concentrations on cell culture (Kuchemüller et al.*, 2020)*

The challenges of accurate and real-time data acquisition from these sensors for integration within a Digital Twin are like those seen when transferring the data to a SCADA (Supervisory Control and Data Acquisition) system such as signal degradation and sensor drift. However, there are specific challenges to Digital Twins which a SCADA system can use localised controller nodes to mitigate against. Furthermore, data transmission latency and loss can impede real-time monitoring and decision making. Two techniques which can be employed to reduce these effects are: (1) utilising high-speed optical fibre cables for wired connections and then replacing traditional broadband connections with advanced wireless technologies such as 5G to ensure high transmission rates and quality and (2) using data compression to lower the data burden will alleviate transmission latency. Machine Learning algorithms that detect and transmit only the changes occurring in the system avoids redundant data transmission when there are no updates. As the number of sensors monitored grows it becomes increasing complex to manage, process and store the data which can pose scalability issues requires a sophisticated data management strategy (Mashaly, 2021).

2.2.3.2 Critical Quality Attributes and Process Analytical Technology

The advent of PAT in the pharmaceutical and biopharmaceutical industry is of critical importance to the feasibility of Digital Twin models as the timely collection of CQA data is crucial for real time refinement. PAT tools have become well established in the pharmaceutical and biopharmaceutical industry for uses such as measuring tablet content uniformity, blend uniformity of a mixing process and also the particle size of crystals to facilitate real time release testing (Yu et al., 2007; Goodwin et al., 2018; Sierra-Vega et al., 2019).

One research area of significant interest is that of spectroscopic techniques including Ultraviolet, Raman and NIR. While Raman Spectroscopy has been used for real time monitoring of a powder blending process, it has characteristically longer acquisition times than NIR and therefore, is less suitable for the needs of a Digital Twin due to previously discussed concepts including data latency and model adaptability. This difference is due to NIR spectroscopy requiring minimal to no sample preparation whereas Raman can require careful preparation to avoid fluorescence interference and to ensure proper focusing of the laser. NIR spectra also uses broad absorption bands which makes them simpler to process (Román-Ospino et al., 2016).

Uhl et al. (2023) reported on the successful validation and integration of a Digital Twin with PAT for a Liquid-Liquid extraction operation for the clarification of plasmid DNA in an E. Coli lysis process using a plug flow reaction (Figure 8).

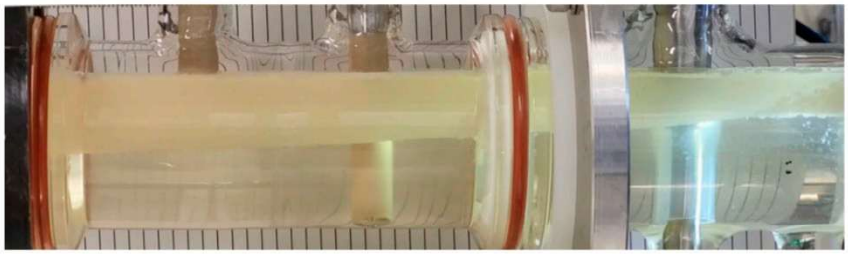

Figure 8 – Plug Flow Reactor of Liquid-Liquid extraction operation (Uhl et al.*, 2023)*

The PAT tool used in this case was that of a high-resolution macro-capable camera which could take images of the droplet 'swarm' (Figure 9) of the separating flow and analyse these using specialised software. This real-time data was then fed back into the digital model which was re-simulated at time intervals of 30 seconds, the computation took 10 seconds and the predicted period was for the next 2500 seconds. Therefore, this camera tool is adequately sophisticated to allow a bidirectional Digital Twin of this process step.

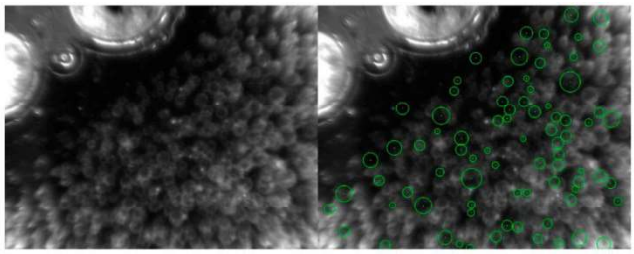

Figure 9 – Droplet Swarm of High Resolution Camera (Uhl et al.*, 2023)*

Crucially, PAT tools have the advantage of allowing local modelling of CQAs at the process level which reduces the data transmission and processing overhead that would be required if the same analysis were performed within the digital model component of the Digital Twin.

2.2.3.3 Data Heterogeneity within the Physical Model

The requirement to obtain data from different sources of the physical model for use in a comprehensive Digital Twin can be challenging as the data is likely to come from heterogeneous sources which have various formats and structures. This data must be passed to the digital model in such a way that it is cohesive and usable. The challenges presented include the dissimilar nature of the different data streams, interoperability issues between systems and also synchronising data that has been collected at different frequencies.

There are a number of Machine to Machine (M2M) interfaces that are used to facilitate data exchange to the communication layer. The two most common are OPC Unified Architecture (UA) and Message Queue Telemetry Transport (MQTT) which are discussed in detail below. All digitalisation strategies have their own advantages and drawbacks to be taken into account however, often, the M2M selected can be based on what is most compatible or vendor recommended for the current physical equipment available (Gargalo et al., 2020).

A significant benefit of OPC UA is its interoperability and flexibility between different systems due its platform independence and standardised communication protocol. This platform independence means that devices, software and systems from different manufacturers such as Windows and Linux can communication effectively. It also provides security features such as data encryption and authentication to give secure data transfer. This facilitates the pharmaceutical industries requirements for data integrity (Perzylo *et al.*, 2019).

Furthermore, OPC UA offers scalability for small and large systems. This means it can grow to handle increasing volumes of data and communications which gives some guarantee that it will be future proof for an evolving pharmaceutical site. OPC UA can also support high-frequency data sampling and continuous archiving to a suitable historian. This facilitates detailed monitoring and real time process control which is crucial for the implementation of an accurate Digital Shadow or Digital Twin.

The most significant disadvantage of using OPC UA is the complexity of implementation. It requires significant expertise and the need for specialised training can delay the implementation process and increase operational costs. Also, the initial setup costs for OPC UA infrastructure including the necessary hardware, software and licensing are high. This financial investment might be unfeasible for lab and pilot scale projects with limited budgets. Finally, while OPC UA is designed for interoperability, it may be challenging to integrate it with existing legacy systems. To ensure robust communication across different platforms often requires custom solutions which adds to complexity, cost and delays (Saif *et al.*, 2023).

Compared to OPC UA, MQTT is known for its simplicity. This reduces the complexity and initial setup time which translates into lower costs, as the implementation and maintenance expenses for MQTT are generally lower. This often makes MQTT more accessible for smaller scale projects. Additionally, MQTT is highly efficient in bandwidth usage. This means it is ideal for transmitting data over unreliable and less sophisticated networks (Singh Ahuja and Kashkari, 2021). The reduced delay time of transmitting the same data payload when using MQTT compared to OPC UA was demonstrated by one study for a range of scenarios from 10 to 1000 clients as shown in Figure 10 (Silveira Rocha et al., 2018).

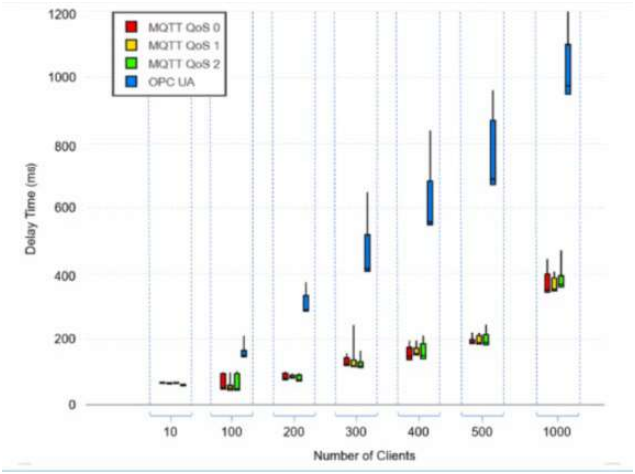

Figure 10 – Delay Time of a data payload for MQTT vs OPC depending on Number of Clients (Silveira Rocha et al., 2018)

However, a significant drawback is the limited security of MQTT. It does not contain the level of built-in encryption and authentication features as standard offered by OPC UA (it would have to rely on a message broker using 'Transport Layer Security' to do this as it is 'Publish-Subscribe' communication type), which may be seen as less secure by a regulator. Furthermore, MQTT does not provide the equal interoperability as OPC UA which makes it less suitable for complex integration scenarios where diverse systems need to communicate seamlessly. Furthermore, OPC UA is designed with industrial automation in mind with special features such as event handling, alarms and conditions that MQTT is not built for (Kant *et al.*, 2021).

The M2M interfaces are often employed to pass data to a local data historian prior to data transfer to the data communication layer. The requirements will vary based on the specific requirements of the Digital Twin but they normally include features such as data compression and aggregation and the ability to support a number of datatypes. The data integrity of this historian is crucial during network disruptions or hardware failures. It should be scalable to support evolving process requirements.

2.2.4 Data Communication Component of a Digital Twin

2.2.4.1 Commercial IoT Platforms and Cloud Services

There are a number of Internet Of Things (IoT) Platforms as a Service (PAAS) which have been developed in order to support Digital Twin implementation. These can offer tools such as data visualisation, management and analysis as well as supporting distributed computing and device management. These include Predix (General Electric), Mindsphere (Siemens), SEEQ, TrendMiner and TIBCO Cloud and they allow data to be integrated into major cloud service providers such as major cloud service providers like Amazon Web Services, Microsoft Azure, Google Cloud, and IBM Watson (Chen *et al.*, 2020).

Cloud computing is critical in the realisation of comprehensive real-time Digital Twins. These services provide vast computation capability and storage which is essential for running high-fidelity simulations and also for the analysis and storage of simulations. They allow integration from various sources with the digital twins such as Enterprise and Training systems. They can also allow remote access to the simulation data for collaboration with remote experts to accelerate innovation. This of course must meet the data integrity requirements of the regulatory bodies concerned however, Industrial PAAS platforms often have a greater focus on device connectivity and cybersecurity which can address these concerns most relevant to the pharmaceutical and biopharmaceutical industries (Leukert et al., 2016). Finally, these resources are easily scalable and often much more cost effective than conventional storage solutions. Many also offer data redundancy options (Mylrea *et al.*, 2021).

2.2.5 Virtual Component of a Digital Twin

2.2.5.1 Mechanistic vs Data Driven vs Hybrid

Mechanistic Models:

Mechanistic Digital Twin models are based on the fundamental laws governing a process which may include physical, chemical and biological. Mathematical equations derived from these laws are used to simulate and predict the behaviour of that system. These models may also use Computational Fluid Dynamics (CFD) techniques such as the FEM or the Discrete Element Method (DEM) for complex Multiphysics simulations.

The advantage of these models is that they rely on underlying process knowledge which makes them more acceptable to regulatory bodies. They are particularly useful for scenario analysis as they can predict outcomes based on manipulation of input variables using these underlying principles. However, developing these models is complex and time consuming and requires detailed understanding of the system. They can be sensitive to parameter values which may not be accurately known and are therefore required to be determined experimentally. They are also difficult to adapt and scale as any change to the model will require manual intervention.

Sub-Modelling can be used in mechanistic models to divide the model into the specific and distinct components of the larger system that are being studied. This modular organisation offers a number of advantages including facilitating understanding, making sub-models reusable for other contexts and also reducing the computational burden of the overall model. This type of approach yields a model that is more flexible and scalable, for instance if a bioreactor were to be scaled up only the physical sub-model would require updating while the kinetics sub-model would remain fit for purpose. This type of approach is illustrated in Figure 11 (Moser *et al.*, 2020).

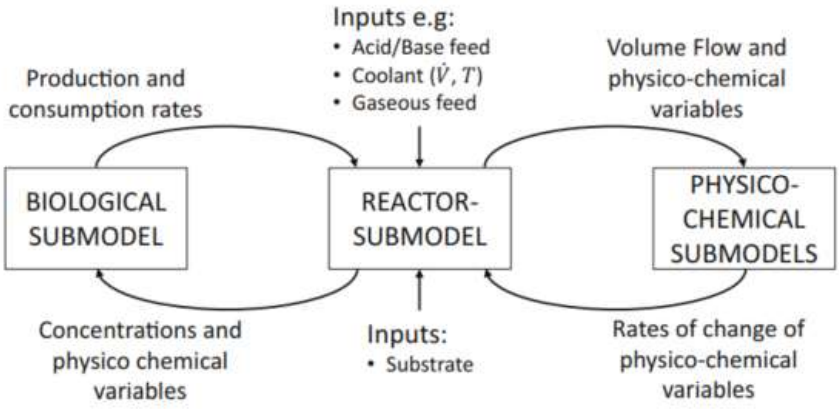

Figure 11 – Sub-modelling approach to Digital Models (Moser et al., 2020)

Data-Driven Models:

Data-driven models rely on purely statistical methods and machine learning algorithms in order to learn patterns from historical data, which are then used to form and refine models. The advantage to these models is that they do not require a detailed understanding of physical principles and can be developed quickly (relative to mechanistic models) if sufficient data is made available. The disadvantage to this is that if the data used to 'train' these models is insufficient or non-representative of the normal operation then they are unlikely to provide insight into the underlying process mechanisms or have much ability to simulate various process outcomes.

Spahn *et al.* (2016) developed a data-driven model using flux-balance and Markov chain analysis which describe protein glycosylation, a common CQA in recombinant biotherapeutics. The significance of this method was that it avoided the need for kinetic and physiochemical data and offers a more accessible platform for Digital Twin modelling. Glycosylation involves complex reaction pathways (Figure 12) where each glycan can be regarded as a different state in a network and then a stochastic number assigned to it to describe the probability of generation and another number to describe the flux (i.e. the rate of generation). A matrix was then developed (Figure 13) which assigns a number based on the likelihood of transition from one state to another, this matrix was then computationally solved to minimise the error between this model and an experimental dataset which it was found to predict well (Imai-Nishiya *et al.*, 2007).

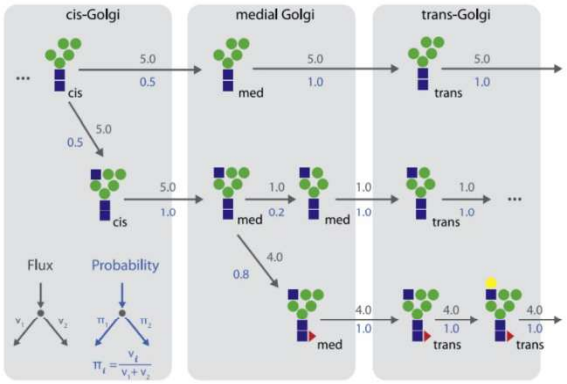

Figure 12 – Glycosylation reaction pathway (Spahn et al., 2016)

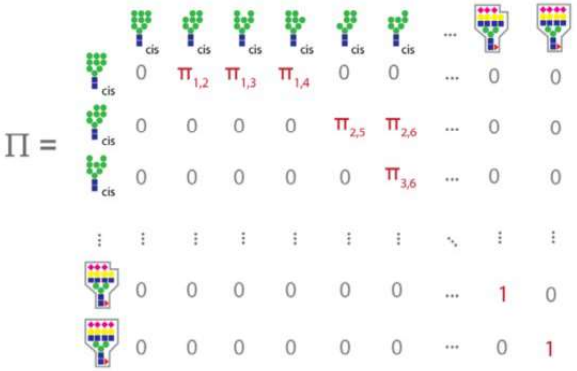

Figure 13 – Markov Matrix (Spahn et al.*, 2016)*

Hybrid Models:

Hybrid models combine mechanistic and data-driven model elements in order to realise the advantages of each. They utilise a framework of mechanistic principles in order to achieve a simulation close to that of experimental data. However, they then refine their model using historic data. These models can be refined using data prior to initiation of the physical twin run but then also during this run using live data from the ongoing operation if this is built into the design strategy. The benefit of this approach is that the process understanding gleaned is similar to a mechanistic model but also provides the adaptability and flexibility of a data-driven model (Banerjee *et al.*, 2024). Sokolov *et al.* (2021) highlight three features of Hybrid modelling which allow them to overcome challenges seen with purely mechanistic or data driven models: (1) As there is an underlying structure or backbone to the model the dimensionality of the model refinement is greatly reduced compared to a purely data-driven model. This significantly

reduces the burden on understanding the relationship between CPPs and CQAs during the model validation stage. While a mechanistic model would also require fewer experiments, these would need to be conducted in a non-simulated fashion where the effort is much greater. (2) Hybrid models have a better extrapolation ability than that of mechanistic models as they predict beyond the experimental settings tested. This is crucial for meaningful what-if analysis and process optimisation. (3) They are generally scale independent and can be scaled up easily. They are also modular in nature which means they can be transferred between projects of the same common type.

2.2.5.2 Adaptability and Machine Learning

Artificial Neural Networks (ANNs) in Data-Driven or Hybrid Models:

ANNs are a key tool in refining Data-Driven and Hybrid models by detecting historical and real-time data to detect patterns and by filling knowledge gaps to enhance model accuracy. ANNs as a computational strategy are increasingly prominent in the technology sector given their prominence in areas such as Facial Recognition, Natural Language Programming models and Stock Market Prediction. They mimic the human brain by processing data through layers of 'neurons' where each neuron takes an input such as a time and spatial data point in a processing trend, assigns random weights and biases to calculate an output, and then compares this output with the expected data (for example experimental data). Loss functions can then be used to minimise this error by adjusting and the weights and biases applied during the neuron's processing. This type of Machine Learning is a key building block in producing truly adaptive Digital Twins (Dmitriy and Vasilyev, 2020).

The type of ANN selected is crucial to its model refinement and predictive ability. One study on a continuous powder caffeine blending process found that when using a simple regression ANN as discussed above the model could not accurately account for disturbances in feed inputs to the blender and was unable to predict the composition of the outlet as measured by an NIR probe (Figure 14)

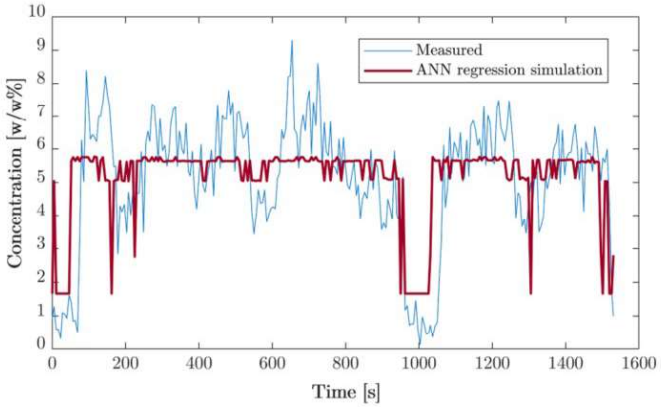

Figure 14 – Simple regression ANN (Beke et al.*, 2021)*

However, a more complex Nonlinear Autoregressive with Exogenous inputs (NARX) ANNs gave predictions much more closely aligned with the measured data (Figure 15). This is because NARX ANNs have a temporal structure and incorporate past values of the time series and exogenous inputs.

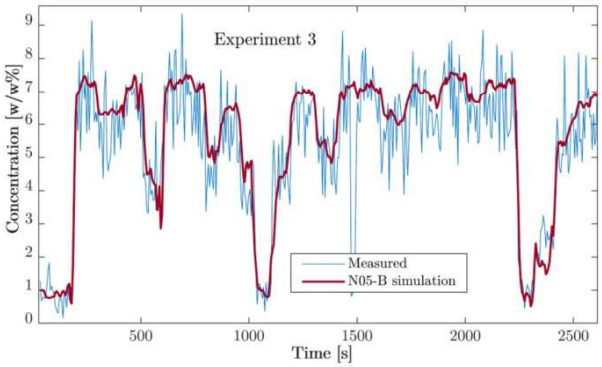

Figure 15 – NARX ANN (Beke et al.*, 2021)*

Multivariate Statistical Analysis (MVSA) in Data-Driven or Hybrid Models:

Digital Twins generate vast amounts of data from traditional and soft sensors. MVSA is an important tool that can handle these multiple variables and identify how their interactions impact on process optimisation and quality control. Techniques such as Principal Component Analysis (PCA) and Partial Least Squares (PLS) can be used to analyse the historical data and uncover hidden patterns and correlations and this assists in predictive maintenance and defect detection.

PCA is used to transform data into a new set of variables known as principal components. These are linear combinations of initial data sets and are weighted according to the variance they result in on the dependent variable under measurement. This is significant to Digital Twins for a number of reasons including that it reduces computational requirements, data is simpler and easier to visualise and finally that it can prevent adaptive models overfitting to parameters in the training data that are not significant.

PLS is useful in regression analysis of models with highly correlated variables as they are orthogonal with respect to one another so they each capture different aspects of the data. Leeming *et al.* (2023) used a PLS regression analysis to model the supersaturation process of a 500mL hexamine-ethanol recrystallisation process. The data fed back to the model allowed for both a predictive model (Figure 16) and also a powerful QbD type analysis of how the different variables such as cooling rate and initial seed mass would affect the response variables.

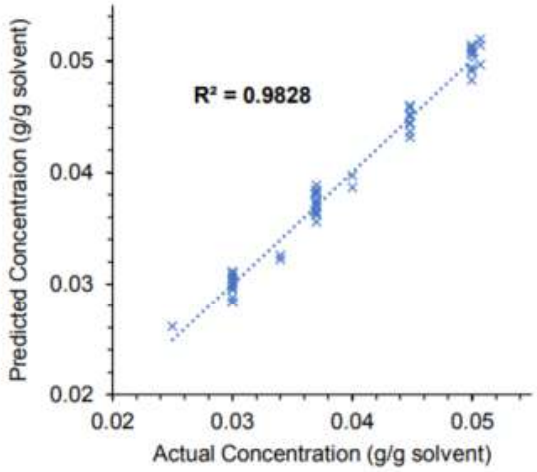

Figure 16 – PLS Regression analysis adaptive modelling of hexamine-ethanol recrystallisation process (Leeming et al.*, 2023)*

2.2.6 Regulatory Landscape of Digital Twins

While Digital Twins present ground-breaking possibilities for manufacturing optimisation, the integration of these must adhere to the stringent regulations defined by bodies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). At present the validation of many of the features related to Digital Twin technologies such as PAT sensors, data integrity and the QbD of the model can be deduced from the regulatory guidelines. However, there are many features required to implement a full Digital Twin framework that are not clearly laid out, such as how to validate a model to allow it to modify the behaviour of a process in real-time without the labour and time intensive activities associated with traditional change management.

Despite this, the regulatory agencies have identified there is a need for clarity. In 2023 the FDA Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) body released two discussion papers on the use of Artificial Intelligence (AI) and Machine Learning (ML) in both drug development and manufacturing. This paper discusses the applications of AI in manufacturing, many of these align with the use cases of Digital Twins including process design, advanced process control and process monitoring for fault detection. It also acknowledges issues including a lack of clarity in how AI will be subject to regulatory oversight and that standards will likely be required for validating and developing AI models (FDA, 2023). As an example of this lack of clarity, the FDA Modernization Act 2.0 allows the use of computational methods as an alternative to animal testing for clinical trials, but it stops short of specifically mentioning Digital Twins and at the time of writing there is no specific regulation regarding the use of these technologies in clinical trials (FDA, 2022).

The EMA has developed a 5-year AI workplan to develop roadmaps in conjunction with stakeholders to address requirements related to (1) Guidance, policy and product support, (2) Tools & technologies, (3) Collaboration and change management and (4) Experimentation. The experimentation brief specifically identifies that Digital Twins is a tool requires extensive ‘Technical deep dives’ (EMA, 2023).

2.3 Conclusion

This literature review explores the applications, benefits and challenges to Digital Twins in the pharmaceutical and biopharmaceutical industries. These technologies present promising opportunities in the optimisation of manufacturing processes by utilising real-time data integration, predictive modelling, and advanced process control. The framework of a comprehensive Digital Twin includes a physical model, virtual model and bidirectional data communication. However, there is limited evidence of this type of Digital Twin in industrial manufacturing. A significant challenge is the requirement for compliant model validation and the limited regulatory guidance available. The importance of other ‘Digital 4.0’ tools such as PAT and cloud computing is discussed. While Digital Twins have obvious benefits to the industry, advancement is required in the areas of regulatory guidance and data management.

2.4 Conceptual Framework

A conceptual framework of the proposed research is presented in Figure 17 below. The independent variables which are under investigation are the barriers to Digital Twin technologies and the Business benefits that adoption of these can provide. The relationship that is to be determined is how these impact on the current prevalence of these technologies in the Irish Pharmaceutical and Biopharmaceutical industries. This relationship is to be determined using in person interviews and an online survey. Moderator variables that may affect the strength of this relationship are organisational size and the technological maturity of a company. A control variable that could impact on the reported results from the survey are whether a participant's company has had success or failures with these technologies and so the perceived benefits will be included as a question in the survey.

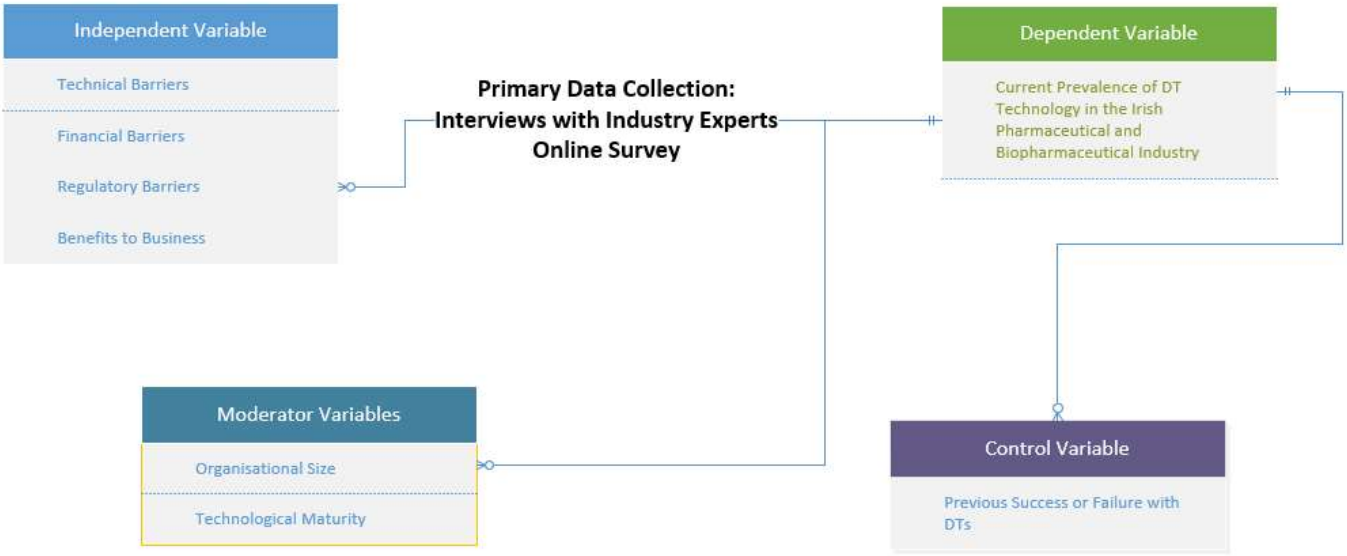

Figure 17 – Conceptual Framework

3.0 Research Methodology

3.1 Research Overview

The aim of this research is to investigate the awareness of Digital Twins in the Irish Pharmaceutical Industry and the perception of their potential benefits along with the technical and regulatory barriers to the adoption of these in the traditionally cautious Pharmaceutical and Biopharmaceutical manufacturing sectors. This chapter will establish the research paradigm, design and approach used in order to carry out this research.

3.2 Research Paradigm

The research paradigm selected to guide how this research has been conducted, the methods that are used, the nature of the questions asked and how the findings will be interpreted is that of pragmatism. The reason for this is it gives flexibility in method selection and allows for focus on practical outcomes – this is pertinent as the recommendations made will be to the industrial manufacturing industry. It embraces both qualitative and quantitative approaches in order to address the research objectives effectively. The objectives to be researched in this body of work are novel and multifaceted so selection of pragmatism will allow the objectives to be prioritised above that of any specific methodology (Kaushik and Walsh, 2019).

3.3 Research Philosophy

A mixed-method approach will be employed in this body of work. Quantitative research that is based on objectivism is more likely to provide data that is reliable, unbiased, and replicable. Findings are often generalisable to the wider population if the research method is well defined and the quantitative nature reduces the influence of personal biases (Conrad and Serlin, 2011).

The benefit of the interpretive research methods of interviews is that they can reveal insights or complexities within different facets of Digital Twin implementation that could be missed if solely implementing a deductive method such as a survey. In this way the flexibility provided by interpretive data collection techniques can allow the methods to be adapted based on emerging data and return to previous subjects in an iterative manner.

3.4 Research Approach

The appropriate types of data collection method for this research topic are in-person and online meetings with industry experts in pharmaceutical manufacturing to provide qualitative data. This will be supported by an online survey to provide both quantitative and qualitative data with the questions as closely modelled to the interview questions as possible. This will be a mixed-method approach. Qualitative data is appropriate for the research objectives in exploring barriers to the widespread adoption of Digital Twins as well as identifying the benefits of this implementation for a number of reasons. The interviews will gather insight into experts' experiences and perceptions of this topic as well as their level of understanding and exposure as this is a novel area and some professions may have had little exposure to it. Furthermore, it is possible that some of these interviews will take on a discussion-like nature if the expert raises queries not considered in this research to-date, this may also generate interesting hypotheses for future research. This may also affect the questions asked in subsequent interviews, highlighting the benefit of the flexible nature of these interviews. I will aim to have a minimum of 4 research participants with detailed in-depth knowledge of Digital Twins and their application within the industry. Remote access will be sufficient for those interviewees not able to meet in person and my professional network should be

sufficient to reach out to participants from a number of companies based in Ireland. On the basis that there are 24,500 Pharmaceutical employees in Ireland (IPHA, 2024) and that a 10% margin of error is deemed acceptable, within this study a target sample population size of 96 participants is selected.

The results of the survey will enhance the quality of the qualitative data gathered in the in-person interviews as the statistical data obtained will be used to prompt discussion with the experts around the research objectives.

3.5 Research Strategy

3.5.1 Secondary Research Strategy

The secondary research conducted by literature review has identified that while there is detailed understanding of what a true Digital Twin is from the research community, it is unclear how well understood and indeed agreed upon this is by the industrial manufacturing community. Furthermore, it is not apparent whether the technical challenges faced by these researchers in the examples discussed in section 2.0 are reflective of those that the industrial manufacturing community is concerned with. Furthermore, as discussed in section 2.2.6 there is little evidence that the regulatory bodies have engaged with this topic in earnest.

3.5.2 Primary Research Strategy

The purpose of this research is to investigate Digital Twin technology use in the Irish Pharmaceutical and Biopharmaceutical industry. This technology is often discussed as being the future of the industry and integral to 'Digital 4.0'. However, it is hypothesised that the use of Digital Twin technology will not be prevalent in a majority of Irish Pharmaceutical and Biopharmaceutical organisations. Furthermore, it is hypothesised that there will be a significantly different level of knowledge of these technologies and the potential benefits they provide when comparing employees from different functional areas. It is anticipated that employees from Automation and IT roles will have a greater awareness of these technologies than Process Engineering, Quality, Validation and Operational staff.

This research is significant as Digital Twins are considered to be a cornerstone of 'Industry 4.0' which promises to revolutionise the manufacturing industry. This study will provide insight into its current implementation and the barriers to its adoption. By examining different levels of awareness and knowledge across functional areas it can inform training initiatives and ensure the relevant stakeholders have the knowledge required to fully harness Digital Twin technology. Furthermore, it holds significance for regulatory bodies as it can aid in developing policies and frameworks to encourage broader adoption in Digital Twin technology.

The objectives of this research are as follows:

1. To evaluate the current awareness level of Digital Twin technology:
    - Among employees in the Irish Pharmaceutical and Biopharmaceutical Industry.
    - How does this awareness level differ based on employees' position and functional area within the organisation.
2. To identify the key benefits of implementing Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

3. To investigate the technical barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the challenges in data integration, network infrastructure and technical skill base in Ireland.
4. To investigate the regulatory barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the data integrity, cybersecurity and GMP compliance challenges with a focus on FDA and EMA regulations.
5. To make recommendations for industry and regulators to prepare for widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

The results from the surveys and interviews will be used to test the following hypotheses:

H1: The majority of employees in the Irish Pharmaceutical and Biopharmaceutical Industry have low awareness of Digital Twin technology.

H2: Awareness of Digital Twin technology is significantly higher among employees in Automation and IT roles compared to those in Process Engineering, Quality, Validation, and Operational roles.

H3: Employees who are aware of Digital Twin technology perceive it as offering significant benefits, such as improved process efficiency, enhanced product quality, and reduced operational costs.

H4: The primary technical barriers to the adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry are related to data integration, network infrastructure, and the technical skill base.

H5: Regulatory concerns, particularly related to data integrity, cybersecurity, and GMP compliance, are significant barriers to the widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

H6: Regulatory frameworks and industry standards currently in place are insufficient to support the large-scale implementation of Digital Twin technology, necessitating new guidelines and incentives from regulatory bodies.

3.6 Sample Size Calculation

The initial sample size was calculated based on the following widely recognised statistical formula (Cochran, 1977):

$$n = \frac{Z^2.p.(1-p)}{E^2}$$

Where:

n = Initial Sample Size = 96.04
Z = Confidence Level Value based on 95% confidence level = 1.96
p = Population proportion value, most conservative value was selected = 0.5
E = Margin of Error = 0.1

This initial sample size was adjusted based on a finite population of 24,500 to give an n_{adj} = 95.7. Therefore, 96 participants was selected as the targeted survey sample size.

3.7 Data Collection Methods

3.7.1 Research Survey

A survey was used to gain an understanding across the different functional groups of Automation, Engineering, Quality, Validation, and Operations to address the research objectives listed in Section 3.5.2. The survey was conducted using Google Forms and comprised of 20 questions. Three of these questions can be considered to be administrative or 'gateway' type questions.

(1) Close-ended (CE): To obtain quantifiable data from participant in order to analyse this to help inform the Hypotheses in section 3.5.2.
(2) Open-ended (OE): To explore the different experiences from participants and potential insights which may not have been considered in the research planning stage.
(3) Likert scale (LS): To measure opinions and perceptions on a continuum and understand how this varies between participants and grouping of participants.

The survey contained an introduction to the research and purpose of the survey. Consent was gathered in Q1 and Q2 and the eligibility was gathered in Q3.

Q4-Q6 (CE) were used to obtain information on the participants' past experience, how many companies they had worked for and in what functional group. This was to support research objective 1.

Q7 (LS) & Q8 (CE) were used to obtain the participants' knowledge and perception of Digital Twin adoption. This was to support research Objective 1.

Q9 (CE) was to determine applications of Digital Twins from the participant's experience and Q10 (OE) was a follow-on question for further applications that were not considered in the survey. This was to support research Objective 1.

Q11(CE) & Q12(CE) were to determine what benefits the participants perceived Digital Twins to offer to the pharmaceutical and biopharmaceutical industry. Q13 (OE) was a follow-on question for further benefits that were not considered in the survey. This was to support research Objective 2.

Q14(CE) & Q15(CE) were to determine what Technical Barriers the participants perceived Digital Twins to face in the pharmaceutical and biopharmaceutical industry. Q16(OE) was a follow-on question for further Technical Barriers that were not considered in the survey. This was to support research Objective 3.

Q17(CE) & Q18(CE) were to determine what Regulatory Barriers the participants perceived Digital Twins to face in the pharmaceutical and biopharmaceutical industry. Q19(OE) was a follow-on question for further Regulatory Barriers that were not considered in the survey. This was to support research Objective 4.

Q20(OE) was to query from the participants for any further comments or feedback on Digital Twin use in the Pharmaceutical and Biopharmaceutical Industry in Ireland.

3.7.1.1 Sample Selection

Distribution was carried out by email which was selected for the ease of accessing participants. The survey was sent to groups of employees in 5 different pharmaceutical and biopharmaceutical companies in Ireland based on a professional network. Google Forms was selected as it allows data to be backed up and stored for integrity purposes and also it can be exported as a .CSV file which made data analysis convenient.

3.7.1.2 Data Analysis

LS and CE questions were analysed and presented for visualisation purposes using pie-charts and bar-charts. The data was presented according to different functional areas and also experience in order to investigate their effects. This is in support of hypotheses H1 and H2. OE questions were analysed by thematic analysis to identify patterns in the qualitative data obtained.

3.7.2 Research Interview

In order to support the quantitative data obtained from the survey, the interviews were carried out with Industry experts in Digital Twin implementation. For this role the questions were structured in a similar fashion so that the thematic data could be analysed in conjunction with the survey rates. The interviews were semi-structured in that the questions provided a framework to guide the process but also allowed for new additional topics to be discussed that were not originally considered while constructing the interview. The questions were sent to participants before the interview in addition to a PIL and an ICF.

The questions were structured into 4 sections based on the primary objectives they were to explore.

Section 1 was to support research objective 1. Q1 (LS) asked the participant to rate overall familiarity with Digital Twin technology in the industry. Q2 (OE) probed whether there is agreement in the industry on what is considered to be a Digital Twin. Q3 (OE) asked the participant how awareness of this technology varied by different roles within the industry.

Section 2 was to support research objective 2. Q1 (LS) asked the participant to rate the significance of the benefits offered by the adoption of Digital Twins to the Industry. Q2 (OE) asked the participant to detail what these benefits are.

Section 3 was to support research objective 3. Q1 (LS) asked the participant to rate how significant the technical barriers to the adoption of Digital Twins within the industry are. Q2(OE) asked the participant to detail these challenges and also asked for whether these are specific to data integration, network infrastructure and the technical skill base in Irish industry. Q3 (CE) asked if the existing network infrastructure in industry is adequate for the adoption of Digital Twins.

Section 4 was to support research objective 4. Q1 (LS) asked the participant to rate how significant the regulatory barriers to adoption of Digital Twins are within the industry. Q2(OE) asked the participant to detail these challenges. Q3 (OE) asked if the regulatory bodies have provided adequate guidance for the adoption of Digital Twins in industry.

3.7.2.1 Sample Selection

The interviewees were selected based on having significant experience of Digital Twins and 'Digital 4.0' within the Irish Pharmaceutical and Biopharmaceutical Industry. A mixture of interviewees from both the 'Customer' side of the businesses and the 'Service' side of solution providers was selected to get a balance of opinions. All interviewees were Subject Matter Experts (SMEs) within Computerised Systems, Industrial Automation, System Infrastructure and 'Industry 4.0'. Ideally 10 interviews would have been conducted to support this work however, due to time constraints only 4 were conducted as a part of this study.

3.7.2.2 Data Analysis

The data was collected by interview recordings of the online calls and then transcribed. Data was then analysed thematically to find patterns between the participants' responses. The findings of this research are presented back in a visual format by coding and grouping the data. The independence of thematic analysis from a specific theoretical framework is suitable for this work as the concepts of Digital Twins are relatively new and unexplored with respect to their place in industrial manufacturing. Furthermore, thematic analysis allows detailed insights to be discerned from the raw data. Computer software was used for this thematic analysis as it allowed for detailed cross-referencing between interview transcripts.

3.8 Time Horizon

The proposed timeline for this research is presented in the following Gantt chart:

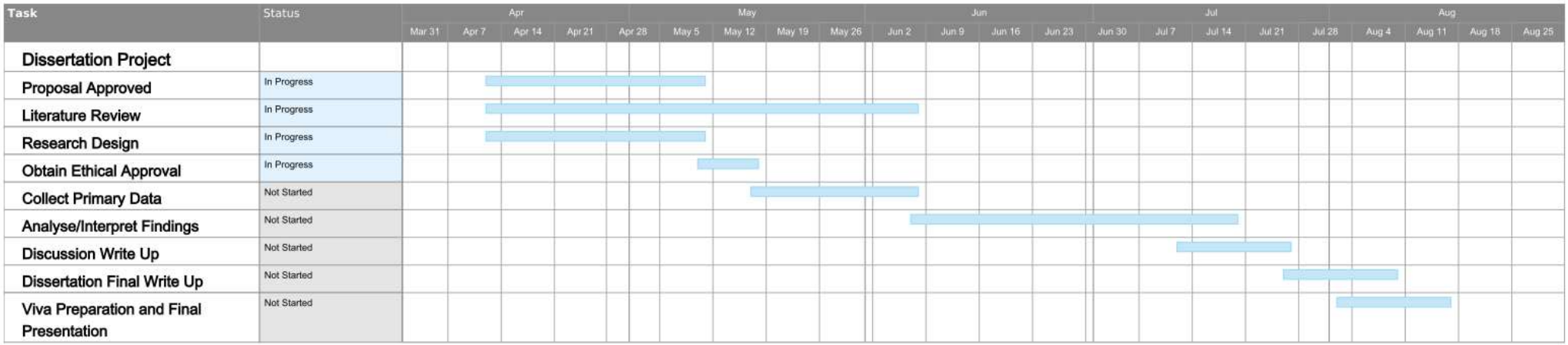

Figure 18 – Gantt Chart of Proposed Research

3.9 Sources and Selection of Participants

Participants for the survey were accessed through my professional network. Emails with the survey links were sent to groups of employees from 5 different Irish companies. Three of these companies operate within the Biopharmaceutical sector, one operates within the Pharmaceutical sector and the remaining company operates within both sectors. The four Interviewees were selected based on their industry expertise in the areas of Automation, 'Industry 4.0', Digital Twins, System Infrastructure and AI. Interviewee 1 is the CEO of a Digital Learning Twin company based in Dublin with over 10 years' experience in this field and was approached through LinkedIn. Interviewee 2 is the 'Digital 4.0' lead in a global Biopharmaceutical firm. Interviewee 3 is the Automation Strategic Lead in a global Biopharmaceutical firm. Interviewee 4 is the Director of Automation in a global Biopharmaceutical firm. Interviewees 2,3, and 4 all have over 20 years' experience in their fields.

3.10 Inclusion and Exclusion Criteria

The inclusion criteria for the survey and the interview were that participants must be currently employed or previously employed in the Irish Pharmaceutical or Biopharmaceutical industry. The exclusion criteria for the Interview process were a non-expert level of knowledge of Automation, 'Industry 4.0', Digital Twins, System Infrastructure and AI.

3.11 Ethical Considerations

The primary data collection, synthesis and interpretation was carried out in an ethical manner. All participants were fully informed about the purpose, methods and any possible uses of the research and any risks that may be involved. All information supplied by subjects was treated confidentially and their identity was anonymised. Research was independent and there was no conflict of interest from the researcher to be declared. In the event of a conflict of interest from a participant they were given the option to withdraw from the study, and if they chose not to withdraw then this conflict of interest would also have been declared. Furthermore, at any time a participant could withdraw from this research for any reason. A PIL was given to each of the participants as part of the invitation letter which explained the background of the research, any risks and benefits and addressed the confidentiality they could expect. The participants were asked to sign an ICF. Privacy of participants was respected, and all findings will be disseminated in an appropriate manner. An ethics assessment and application form were carried out and on the basis that no confidential information pertaining to any organisation is disclosed within the research, ethics committee approval was not required.

3.12 Conclusion

A pragmatic research paradigm has been employed in order to develop a research methodology to investigate the awareness and adoption of Digital Twin technology within the Irish Pharmaceutical and Biopharmaceutical industries. The combination of quantitative and qualitative methods described is to investigate the six research objectives listed in section 3.5.2.

4.0 Findings and Analysis

4.1 Overview

This chapter analyses the findings from the primary research conducted to investigate the research objectives and hypotheses under test. Qualitative and quantitative data has been obtained through an online survey and interviews with four industry experts. The data was transferred to Microsoft Excel for visualisation and analysis.

4.2 Introductory Questions

It is crucial to receive appropriate consent from participants prior to conducting any research. This allows the research objectives, benefits and risks to be communicated to the participant and they are given the alternative option to not take part or withdraw. It is also made clear that participation is voluntary, and they have the ability to withdraw at any time.

4.2.1 Survey Introduction Questions

The survey introduction section contained the above information related to the background of the research and the voluntary nature of the participation.

Question 1 confirmed that the participant had read and understood this information. Of 112 participants who participated in the survey, 112 selected 'Yes'.

Question 2 confirmed the participant's consent to take part in the survey. Of 112 participants who participated in the survey, 112 selected 'Yes'.

Question 3 confirmed the participant's eligibility to take part in the survey. As this survey was specifically aimed at those that work or had previously worked in the Irish Pharmaceutical and Biopharmaceutical industries this was confirmed. Of 112 participants who participated in the survey, 109 selected 'Yes'.

4.2.2 Interview Introduction and Consent

The research objectives, requirements and information related to voluntary consent and confidentiality were provided to interviewees through the PIL (Appendix C) and consent was given by a signed ICF (Appendix D).

4.3 Demographics of the Population

4.3.1 Survey Population

There were 112 Participants that took part in the survey. Of these, 109 were eligible based on the fact that they worked in or had previously worked in the Irish Pharmaceutical or Biopharmaceutical industry. The level of experience across the survey population was categorised as '<5 Years', '5-10 Years', '10-15 Years', '15-20' Years and '>20 Years' with each category well represented as seen in Figure 19 below.

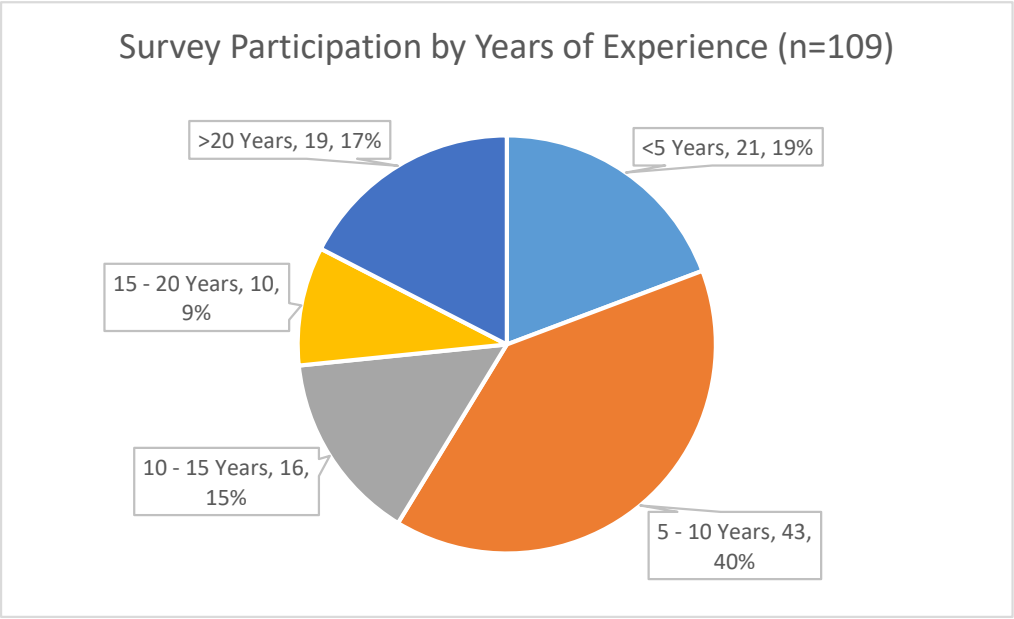

Figure 19 – Demographics of Survey Participants by Years of Experience

Information was also gathered according to the functional areas of the participants which can be seen in Figure 20 below. The groups of 'Automation/IT' and 'Operations' were well represented. 'Process Engineering', 'Quality Assurance', 'Technical Services' and 'Validation' were less well represented but still in sufficient numbers for the data gathered to be meaningful. 'Quality Control', 'Supply Chain' and 'Medical Affairs' were not well represented and therefore, it is difficult to draw meaningful conclusions about these groups.

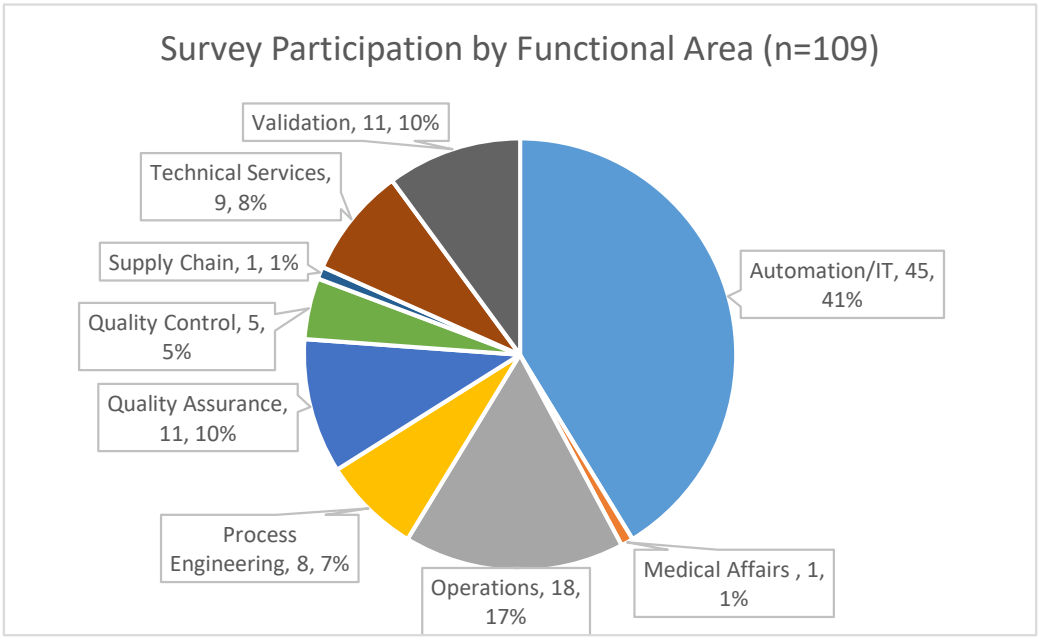

Figure 20– Demographics of Survey Participants by Functional Area

In order to understand the breadth of this experience and the exposure to different companies within Ireland participants were also asked how many different companies they had worked for over the course of their career. As can be seen from Figure 21, there is good exposure to different companies and their potential usage of Digital Twins.

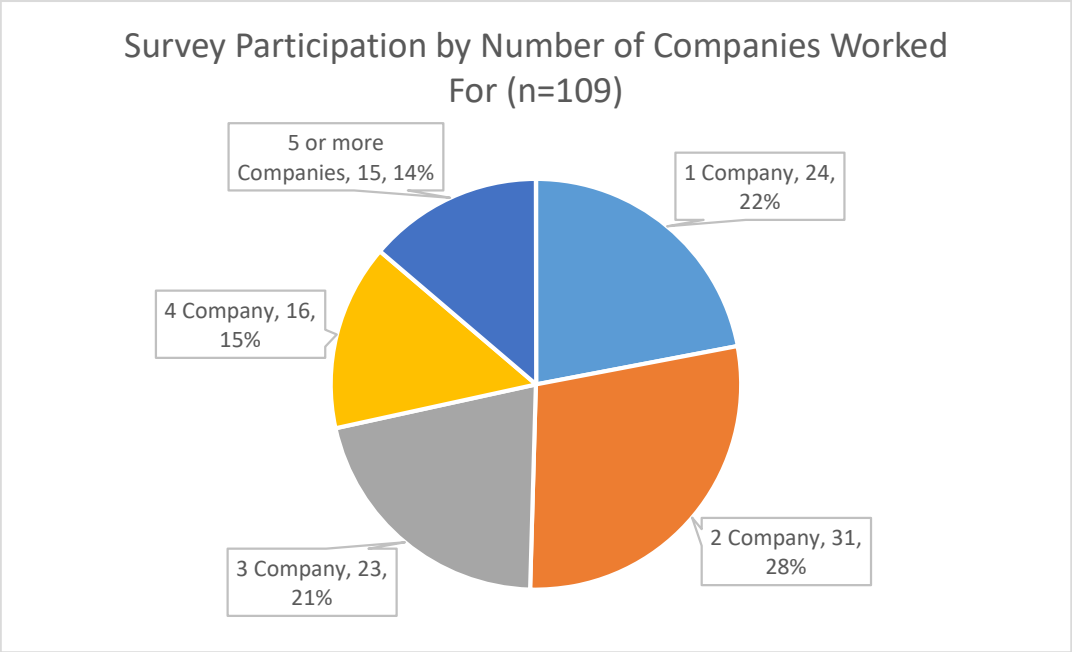

Figure 21 - Demographics of Survey Participants by Number of Companies

4.3.2 Interview Population

The four Interviewees were selected based on their industry expertise in the areas of Automation, 'Industry 4.0', Digital Twins, System Infrastructure and AI. They have also all managed projects and teams in these fields. Interviewee 1 is the CEO of a Digital Learning Twin company based in Dublin with over 10 years' experience in this field. Interviewee 2 is the 'Digital 4.0' lead in a global Biopharmaceutical firm. Interviewee 3 is the Automation Strategic Lead in a global Biopharmaceutical firm. Interviewee 4 is the Director of Automation in a global Biopharmaceutical firm. Interviewees 2,3, and 4 all have over 20 years' experience in their fields.

4.4 Introduction to Research Topic

The Research Topic that is investigated in this work is that of Digital Twin technology use in the Irish Pharmaceutical and Biopharmaceutical industry. Despite this technology being considered central to the future of the industry, it is hypothesised that there will be low awareness of it from employees of the industry generally. It is also hypothesised that the awareness will be significantly greater in those employees that are more involved in the implementation side of Digital Twin technology such as Automation and IT compared to areas of Process Engineering, Quality Assurance, Validation and Operational staff. The significance of this is that if Digital Twins to become a foundational tool for industry it would be required for most if not all of these departments to engage with the technology. This research aims to understand the advantages these technologies provide along with their regulatory and technical barriers. By examining different levels of awareness and knowledge across functional areas it can inform the need for targeted training initiatives and ensure that the relevant stakeholders have the knowledge required to fully harness Digital Twin technology. Furthermore, it holds significance for regulatory bodies as it can aid in developing policies and frameworks to encourage broader adoption.

The objectives of this research are as follows:

1. To evaluate the current awareness level of Digital Twin technology:
    - Among employees in the Irish Pharmaceutical and Biopharmaceutical Industry.
    - How does this awareness level differ based on employees' position and functional area within the organisation.
2. To identify the key benefits of implementing Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.
3. To investigate the technical barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the challenges in data integration, network infrastructure and technical skill base in Ireland.
4. To investigate the regulatory barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry. Specifically, the data integrity, cybersecurity and GMP compliance challenges with a focus on FDA and EMA regulations.
5. To make recommendations for industry and regulators to prepare for widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

The results from the surveys and interviews will be used to test the following hypotheses:

H1: The majority of employees in the Irish Pharmaceutical and Biopharmaceutical Industry have low awareness of Digital Twin technology.

H2: Awareness of Digital Twin technology is significantly higher among employees in Automation and IT roles compared to those in Process Engineering, Quality, Validation, and Operational roles.

H3: Employees who are aware of Digital Twin technology perceive it as offering significant benefits, such as improved process efficiency, enhanced product quality, and reduced operational costs.

H4: The primary technical barriers to the adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry are related to data integration, network infrastructure, and the technical skill base.

H5: Regulatory concerns, particularly related to data integrity, cybersecurity, and GMP compliance, are significant barriers to the widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

H6: Regulatory frameworks and industry standards currently in place are insufficient to support the large-scale implementation of Digital Twin technology, necessitating new guidelines and incentives from regulatory bodies.

4.5 Survey Data – Research Objective 1

4.5.1 General Industry Awareness of Digital Twin Technology

109 Employees in the industry were asked to assess their awareness of digital twin technology from five categories: 'No Knowledge', 'Some Knowledge', 'General Understanding', 'Good Knowledge' and 'Excellent Understanding.' Figure 22 shows the distribution of responses.

There is a significant cohort of 69 participants with 'No Knowledge' and this is characteristic of the negative skew towards lower levels of knowledge within participants. A chi-squared test was carried out to assess if there was a significant difference compared with an even distribution of knowledge. A p-value <0.05 (8.98×10^{-28}) was obtained which reflects this low level of awareness is significant.

This result indicates a need for increased education around these technologies. Targeted training initiatives to provide foundation level knowledge to those who will encounter the technology superficially and advanced training for those that will be directly involved in the implementation of these tools should be conducted. Strategic investments by major pharmaceutical players should be implemented now, in order to realise the potential of these tools at a later stage.

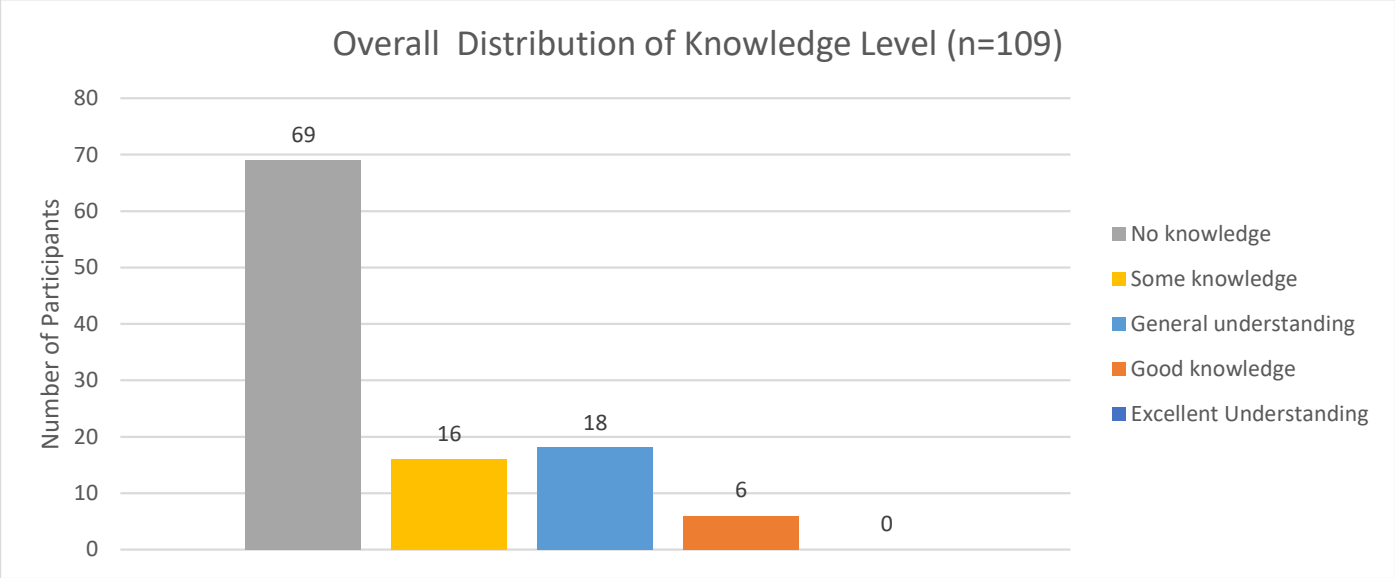

Figure 22 – Digital Twin familiarity within Survey Population

4.5.2 Industry Awareness of Digital Twin Technology relative to Years of Experience

The relationship between how knowledge levels varied according to Participants' years of experience was investigated. As before, knowledge levels were grouped into 5 categories and the results are displayed in Figure 23. In order to test whether these observed variations were statistically significant a chi-squared test was carried out and compared the observed data against an even distribution across the experience levels. The returned p-value was > 0.05 (0.45) which indicates that the knowledge of digital twins is not significantly dependent on years of experience.

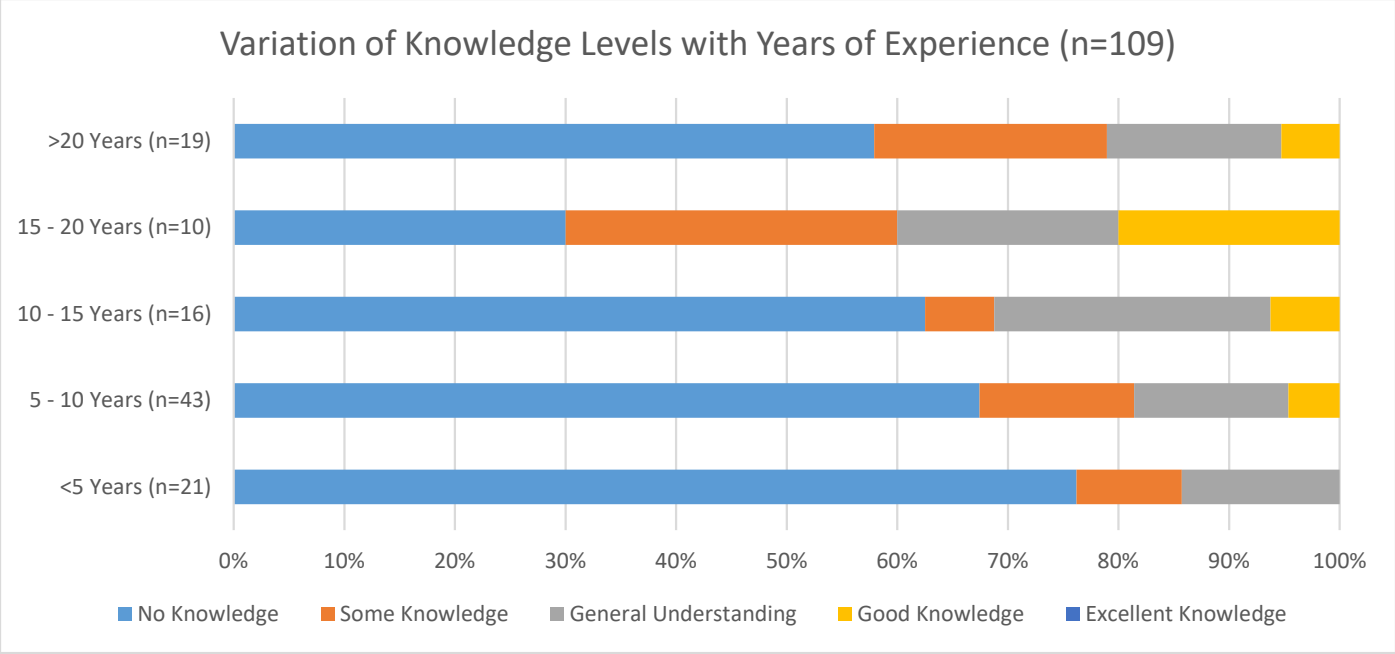

Figure 23 – Digital Twin familiarity relationship to level of experience

On interpretation of the results, there is a need for a broad-based approach when increasing the awareness levels of digital twin technology in the industry. The lack of a correlation between experience and knowledge levels would suggest that training initiatives should look to engage employees across experience levels.

4.5.3 Industry Awareness of Digital Twin Technology relative to Functional Area

The relationship between Industry Awareness of Digital Twin Technology relative to participants' functional area of work was investigated in order to investigate Hypothesis H2: Awareness of Digital Twin technology is significantly higher among employees in Automation and IT roles compared to those in Process Engineering, Quality, Validation, and Operational roles. The data was once again grouped into 5 categories and the results for each functional area are displayed in Figure 24.

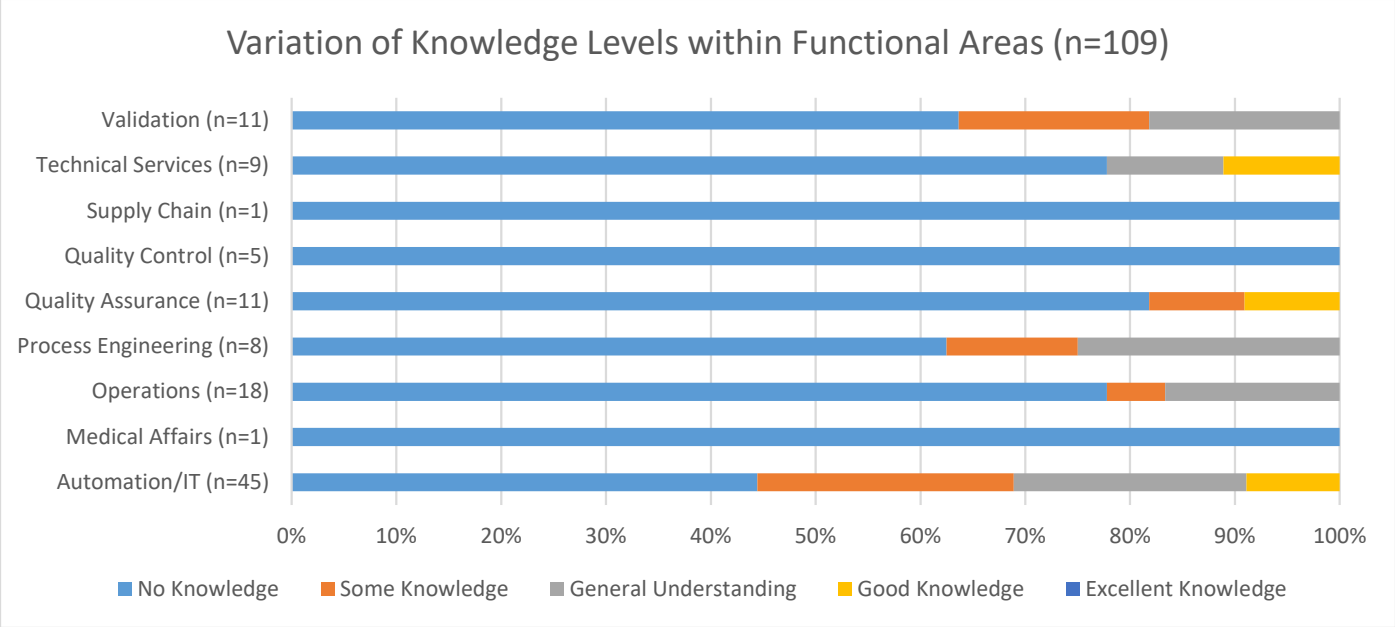

Figure 24– Digital Twin familiarity relationship to Functional Area

However, many of the functional area's sample sizes are deemed too small to provide a meaningful test to this hypothesis. Therefore, data was regrouped into two categories 'Automation/IT' and a 'Non-Automation/IT' group composed of the remaining results. This data is displayed in Figure 25.

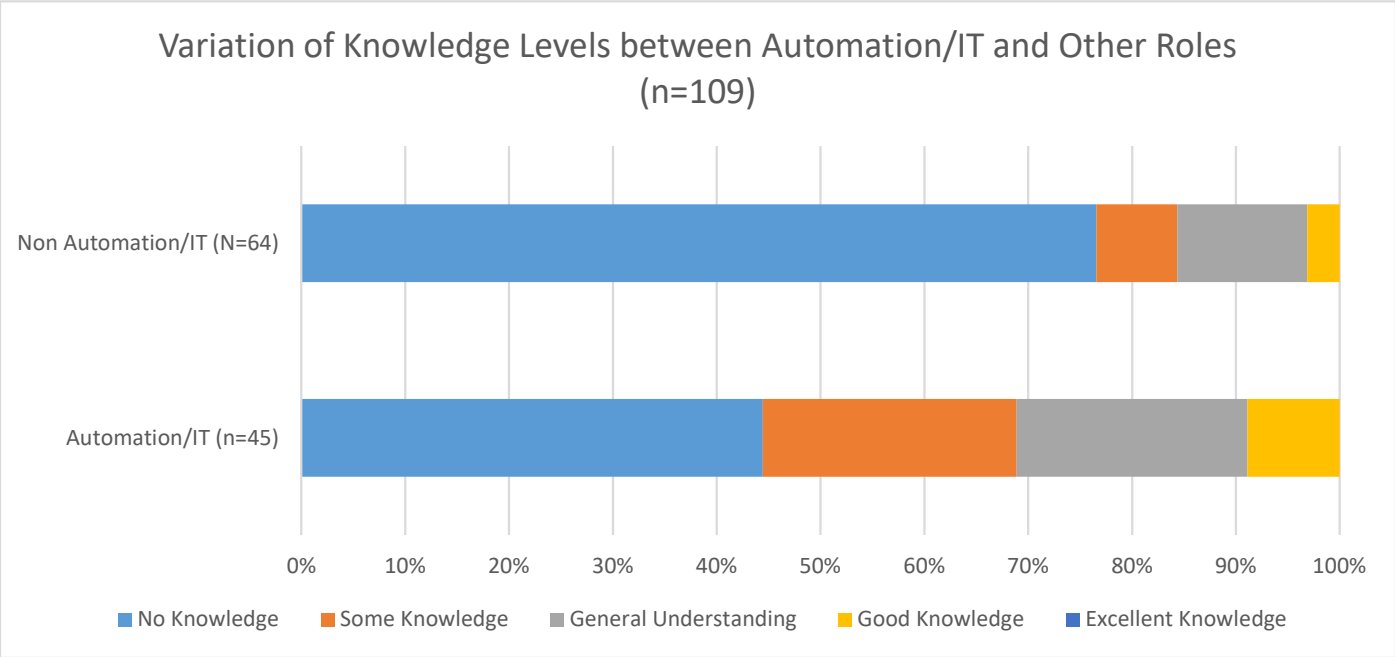

Figure 25 - Digital Twin familiarity relationship to Functional Area of Automation/IT and Other

On initial inspection, a significant proportion of the 'Non-Automation/IT' group reported no knowledge of Digital Twins. A small proportion indicated some familiarity with minimal representation in the higher knowledge level categories. In contrast, the 'Automation/IT' group displayed greater knowledge overall across the categories.

A chi-squared test was performed to compare the observed distribution from a uniform distribution to understand if the difference between the two groups was statistically significant. A p-value <0.05 (0.0062) was obtained which indicates this difference was significant.

4.5.4 Perception of Digital Twin Adoption

In order to research the perception of Digital Twin adoption within the pharmaceutical and biopharmaceutical industries, a targeted question was asked of the 40 participants that had reported better than 'No Knowledge' on whether they felt the Industry had widely adopted the technology. The data is presented in Figure 26.

A majority of participants (87%) responded 'No'. There is a majority perception that the technologies have not been widely adopted and the responses among those that consider themselves to have some knowledge in the field suggest that the technology can still be considered to be in the early development stage for the Irish industry.

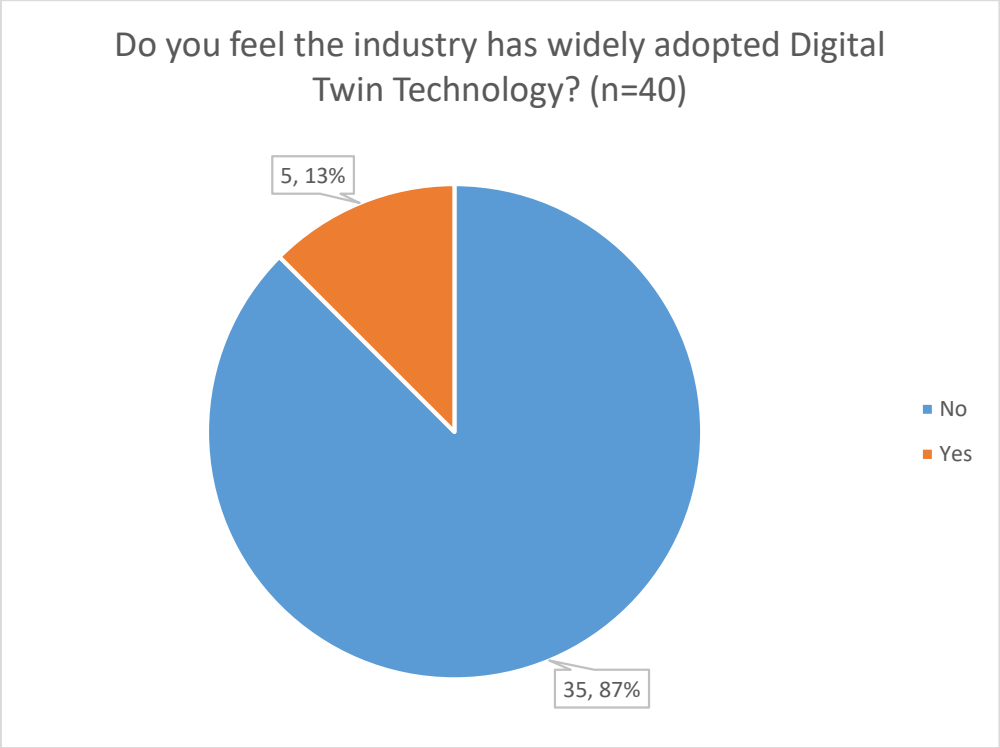

Figure 26 – Adoption of Digital Twins within the Industry

4.5.5 Applications of Digital Twins within Industry

The survey participants were asked to select the Applications of Digital Twins that they had seen implemented within the industry and the results are presented in Figure 27. The most frequently selected applications were those of 'Bioreactor Modelling at Plant Scale' and 'Entire Upstream or Downstream Processing Trains'. The former selection is unsurprising given the prevalence of Cell Culture experimental studies that were apparent in the Literature Review stage of this work. The latter category is likely to reflect Flowsheet modelling as an exhaustive literature review found no case of a comprehensive digital twin for an entire process train in the manufacturing industry and this would be a highly significant event in the world of Pharmaceutical and Biopharmaceuticals if it were to be implemented. 'Bioreactor Modelling at Pilot/Lab Scale' and 'Chromatography Unit Operations' were both reported with a frequency of 3. It is suspected that the prevalence of 'Bioreactor Modelling at Pilot/Lab Scale' is underrepresented in this survey as the respondents come from large scale manufacturing not research or lab environments. Interestingly, survey respondents reported experience of these tools used for 'Chromatography Unit Operations' which indicates that industry players are investing in technical unit operations with complex fluid dynamics. The remaining categories have 2 selections each which reflects that their usage may be more specialised however, that they are being explored is noteworthy.

It is important to note that the frequency was low of all categories which supports the assumption that Digital Twins experience low adoption in the industry.

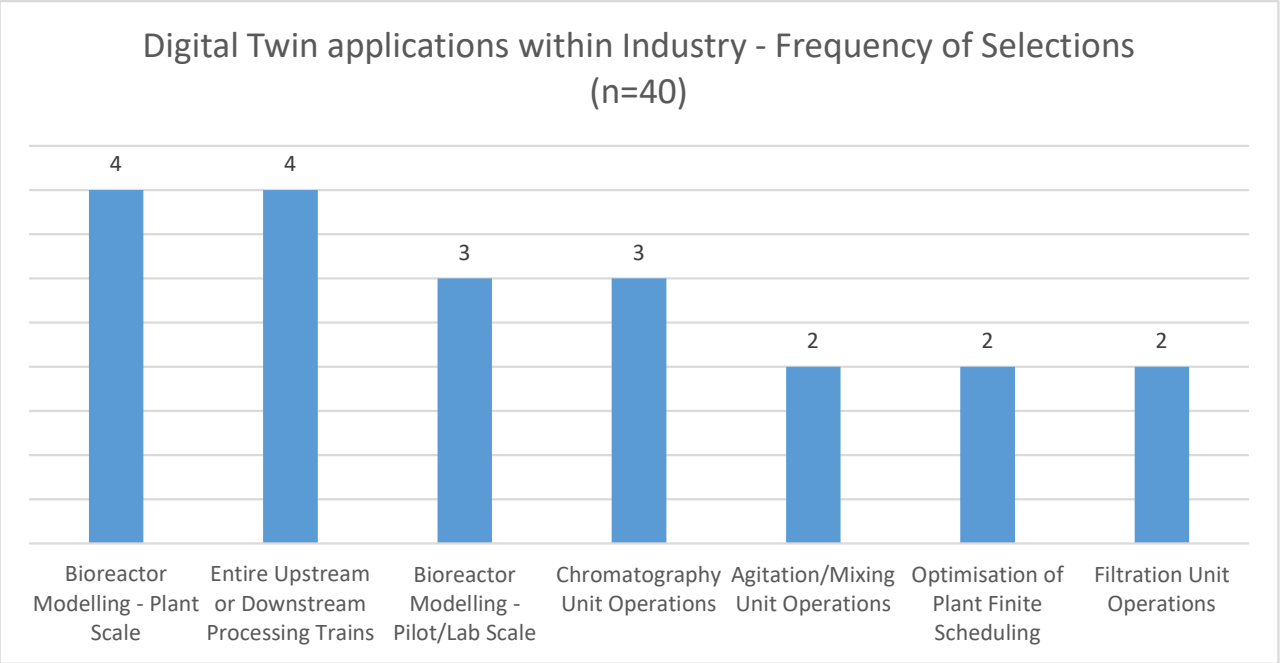

Figure 27 – Frequency of selection of Digital Twin applications within industry

4.5.6 Additional Applications of Digital Twins

Participants were asked to provide examples of additional applications that they had observed within the industry and the results along with the demographic details of participants is displayed in Table 1. Some notable results are discussed below.

One respondent noted that it has been used to support real time batch disposition which demonstrates the potential for it to enhance quality control processes to support decision making. Another participant indicated they had witnessed it used in predictive maintenance pointing to the ability of this technology to predict failure and optimise maintenance scheduling. Another reported having seen a Digital Twin tool used in the Oil and Gas industry which provides an interesting insight into the different stages industries are currently in. Two respondents both identified a use in Plant design and configuration, this is likely meant as flowsheet modelling.

Functional Area	Years of Experience	Additional Applications of Digital Twins
Quality Assurance	>20	In support of real-time batch disposition
Automation/IT	5 - 10	Not in pharma industry, but have used DeltaV Mimic OTS for oil and gas project.
Automation/IT	10 - 15	Not seen it used in industry successfully
Validation	15 - 20	Plant Design and Configuration
Automation/IT	>20	Plant layout and design
Process Engineering	5 - 10	predictive maintenance of individual equipment
Automation/IT	5 - 10	Small equipment

Table 1 – Additional applications of Digital Twins

4.5.7 Significance of the Benefits from Digital Twin Implementation

Of the 40 participants with better than 'No Knowledge' of Digital Twins, the overwhelming majority (98%) felt that significant benefits were offered by this technology. These results are displayed in Figure 28. This highlights strong recognition of the potential of this technology to industry, from those that have had some exposure to it. It would suggest that by raising awareness amongst groups that may be unaware of this technology but would benefit from it nonetheless, there may be more engagement from these groups. This is key as ultimately while this technology will be implemented by Automation/IT/Software engineers and process engineers, it will be operational groups that use the technology.

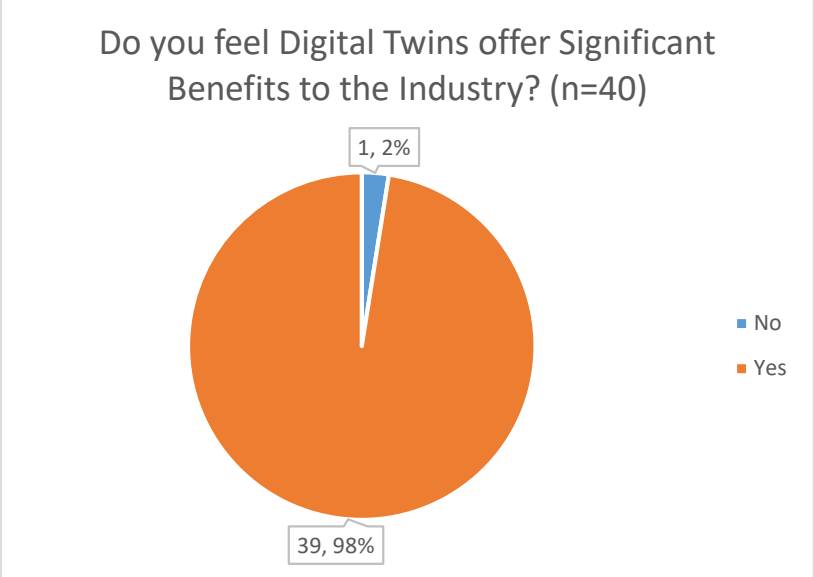

Figure 28 – Significance of benefits of Digital Twins

4.5.8 Perceived Benefits of Digital Twin Implementation

In order to research what these specific benefits are perceived to be, the 39 participants that answered 'Yes' to the previous question on the significance of the benefits of Digital Twins were asked to select from a number of categories on the benefits they felt applied to the industry. The results are displayed in Figure 29. Some notable points are discussed below.

The most frequently selected benefit was that of 'Greater understanding of manufacturing processing steps'. This underscores the belief that these tools can enhance the comprehension of complex multivariate processes. This aligns with the viewpoint discussed in section 2.2.2.2 of this work that Digital Twins are naturally complementary to a QbD approach of model validation. Following this, 'Improved process yields' and 'Enhanced decision making' were the next most frequently selected options. The first of these categories corresponds well with scientific research such as that observed in section 2.2.2.2 of this work where improved cell densities were observed as a result of predictive simulation. Interestingly, only a small minority of the participants felt that benefits would include 'Cost savings' or 'Delivering sustainability improvement'. That the former is not an apparent benefit could be one reason that adoption is slow. The auxiliary processes of sustainability such as utility generation and waste stream may not offer savings significant to justify the cost of Digital Twin implementation. On the other hand, the high value product stream of the process would present the required level of economic return.

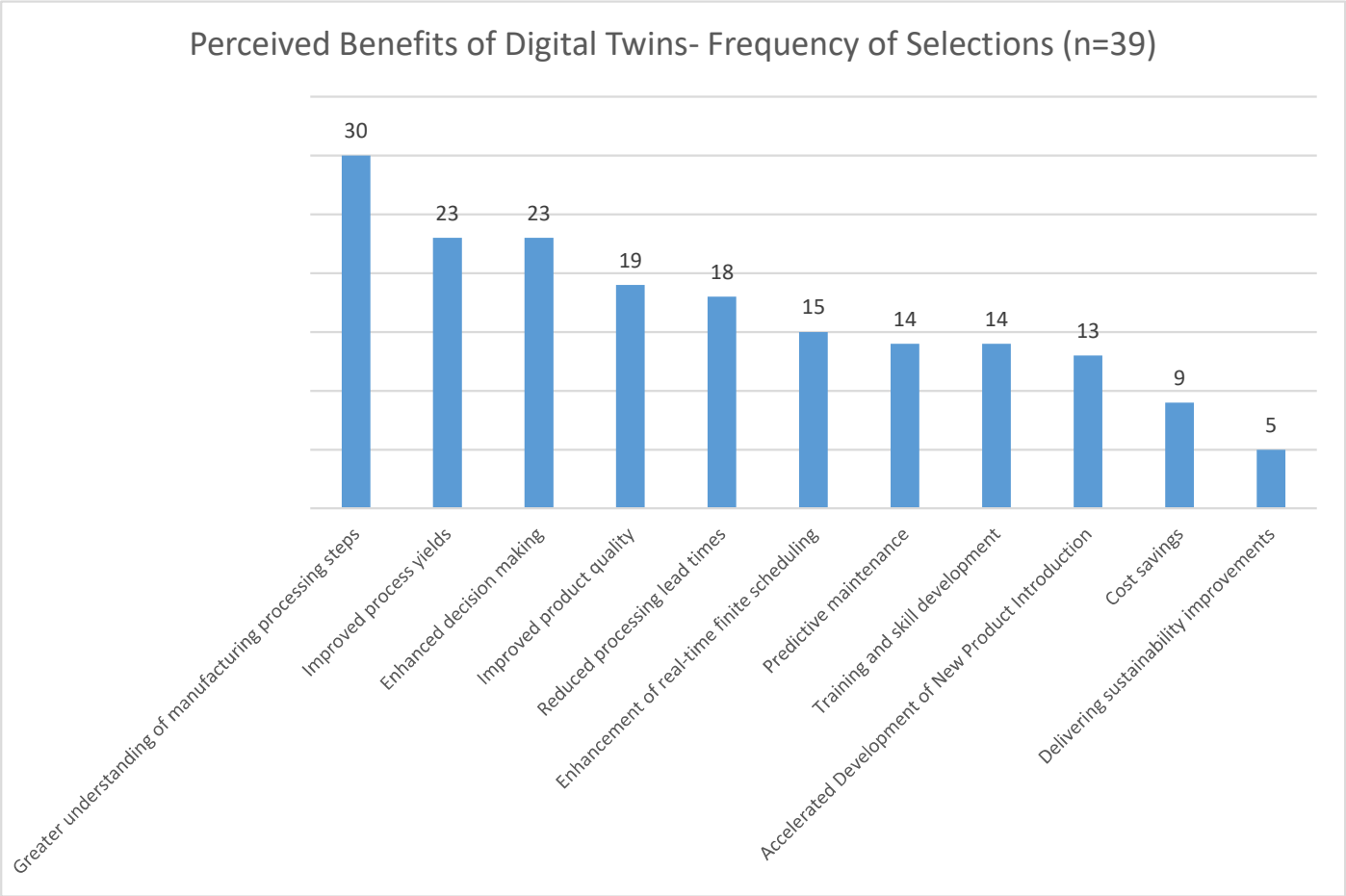

Figure 29 - Frequency of selection of Digital Twin benefits to the industry

4.5.9 Additional Benefits of Digital Twin Implementation

Participants were asked to provide additional benefits they felt Digital Twins offered to the industry and the results along with the demographic details of participants is displayed in Table 2. Some notable results are discussed below.

Functional Area	Years of Experience	Additional Benefit of Digital Twins
Automation/IT	>20	Early warning of process unit operation trending away from optimal output.
Validation	15 - 20	Reduction in Contamination Events

Table 2 - Additional benefits of Digital Twins

One participant felt that a benefit of digital twin could be as a way to detect process parameter drifting from their target range. While this is valid, it is captured in the existing categories in terms of the benefits it would yield, namely 'Improved process yields' and 'Improved product quality'. An interesting benefit suggested by a participant from the 'Validation' functional area was a reduction in contamination events. One possible way this benefit could be realised is a simulation of cleanroom environments and the effect of dynamic variables such as material and personnel flows.

4.5.10 Significance of the Technical Barriers to Digital Twin Implementation

Of the 40 participants with better than 'No Knowledge' of Digital Twins, the majority (80%) felt that there were significant technical barriers to the adoption of these technologies. The results are displayed in Figure 30. This suggests that industry stakeholders may feel greater investment in technological resources or organisational readiness is needed to facilitate the complexity involved in the implementation of a Digital Twin.

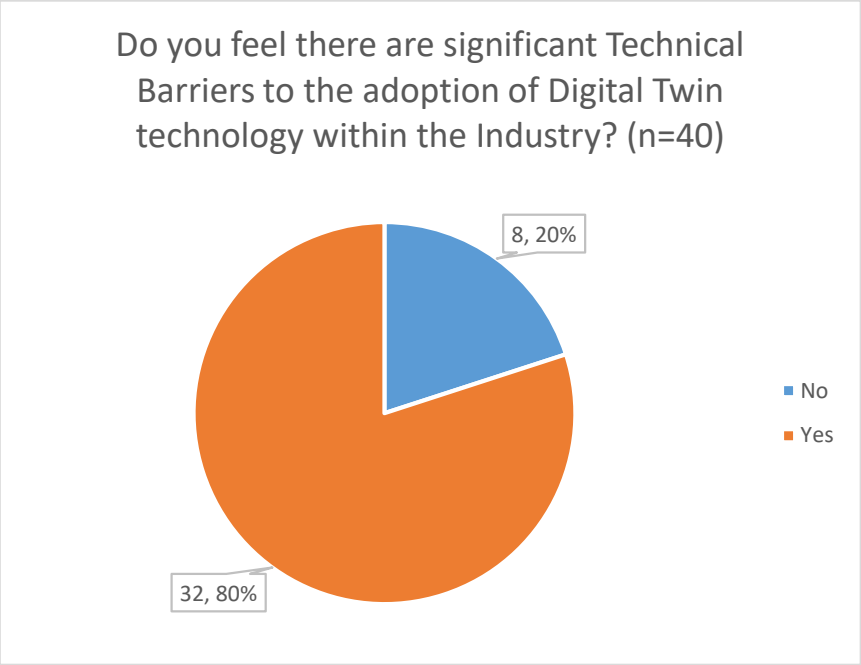

Figure 30 - Significance of technical barriers to Digital Twins

4.5.11 Perceived Technical Barriers to Digital Twin Implementation

To research what these technical barriers are perceived to be, the 32 participants that answered 'Yes' to the previous question on the significance of the technical barriers to Digital Twins were asked to select from a number of categories on the technical barriers they felt applied to the industry. The results are displayed in Figure 31. Some notable points are discussed below.

The most frequently selected category was that of 'Data Integration and Management'. This highlights the difficulty posed by trying to combine data from various sources and ensure it is able to form a cohesive model. Ensuring this data is accurate and real-time is likely a critical concern for any implementation project and reflects the problems in system interfacing that are discussed in section 2.2.3.3 and 2.2.4. This is closely related to the 'Interoperability issues between different systems' which was the second most frequently selected category and is likely to reflect scenarios where different vendors may not have designed their systems to work with one another and may even not license their software under these conditions. A smaller proportion selected 'Scaling to large scale manufacturing', 'Continuous Maintenance of Digital Infrastructure' and 'Availability of qualified workforce' which suggests that while these may be challenges - in scaling up digital twins from pilot projects to full production, maintaining the infrastructure to support them once established and ensuring organisations have the skill base to manage this technology - these are not chief concerns.

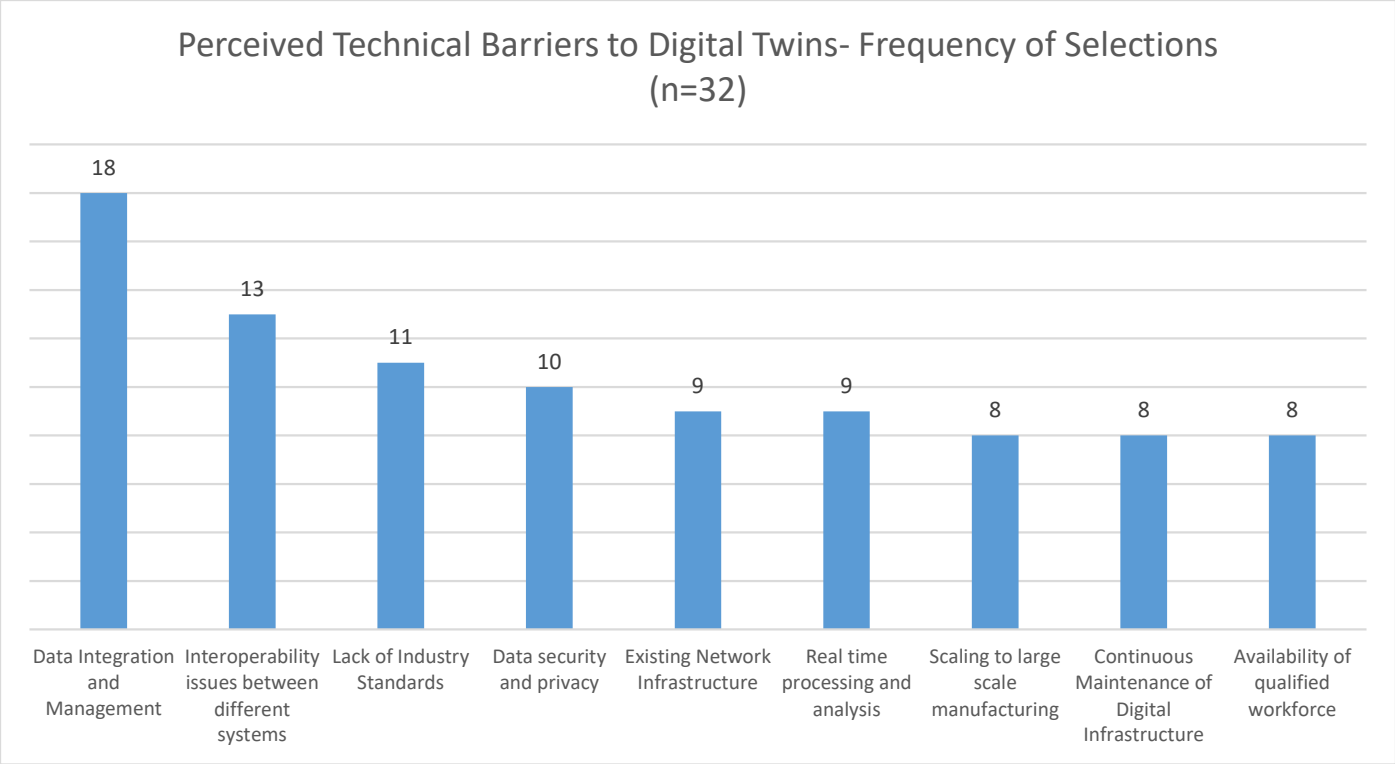

Figure 31 - Frequency of selection of Digital Twin technical barriers

4.5.12 Additional Technical Barriers to Digital Twin Implementation

Participants were asked to provide additional technical barriers they felt Digital Twins were faced with and the results along with the demographic details of participants is displayed in Table 3. Some notable results are discussed below.

Functional Area	Years of Experience	Additional Technical Barrier of Digital Twins
Automation/IT	15 - 20	Cost of maintaining an accurate digital twin is a significant barrier to entry for some companies
Process Engineering	5 - 10	Lack of awareness of DT and therefore lack of motivation for it be implemented
Automation/IT	5 - 10	Managing the equipment model and ensuring physical model can be mapped to a digital twin
Automation/IT	5 - 10	PAT technologies and integration into existing facilities that already have spent significant capital to manufacture in certain way. the risk of adopting a digital twin, will be slow and gradual
Automation/IT	5 - 10	Regulation in general

Table 3 - Additional technical barriers to Digital Twins

One participant commented that the financial barrier was not simply the capital expenditure involved in a Digital Twin project but also the requirement to commit to the operational expense of maintaining it. Another commented on the cultural barrier due to a lack of awareness of the technology, this chimes with the awareness gaps discussed in section 4.5.1 – 4.5.3. An interesting observation was that for those manufacturing centres which have already spent a significant outlay on establishing their processes, to integrate the tools necessary for a digital twin such as PAT will be a lengthy process.

4.5.13 Significance of the Regulatory Barriers to Digital Twin Implementation

Of the 40 participants with better than 'No Knowledge' of Digital Twins, 55% felt that there were significant regulatory barriers to the adoption of these technologies. The results are displayed in Figure 32. Opinion among the survey population is much more divided on the significance of these barriers than for the technical barriers. This could reflect that these barriers are genuinely not perceived to be significant, or it may reflect that digital twins are still in an early developmental stage in most manufacturing facilities and the regulatory barriers have not been widely experienced yet.

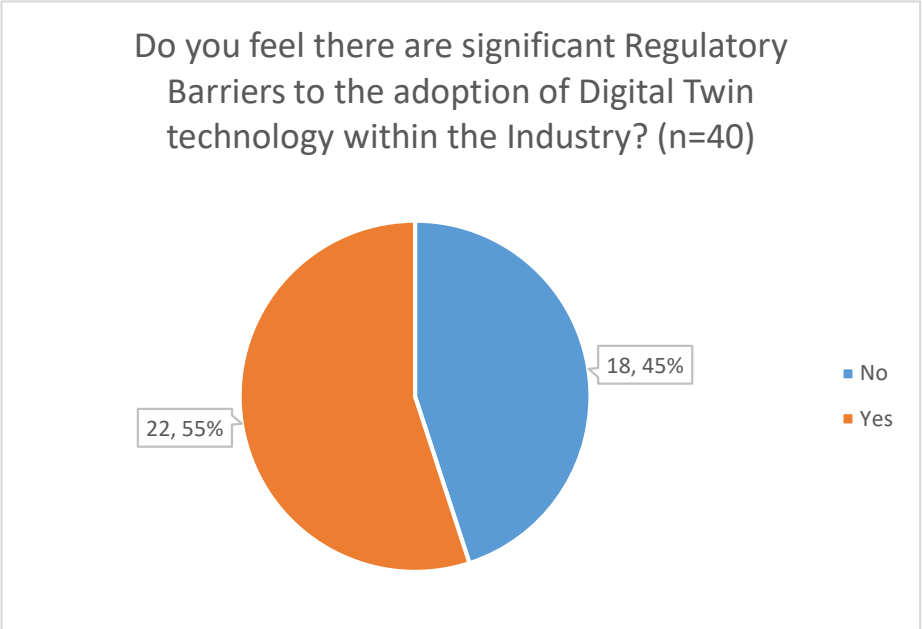

Figure 32 - Significance of regulatory barriers to Digital Twins

4.5.14 Perceived Regulatory Barriers to Digital Twin Implementation

To research what the specific regulatory barriers are perceived to be, the 22 participants that answered 'Yes' to the previous question on the significance of the regulatory barriers to Digital Twins were asked to select from a number of categories on the regulatory barriers they felt applied to the industry. The results are displayed in Figure 33. Some notable points are discussed below.

The most commonly identified barrier was that of 'Vendor supplied models - not GMP compliant'. This reflects a concern that while 'Off-the-shelf' models such as 'Simca' and 'Aspen ProMV' may avoid an organisation having to venture into new territory of developing out digital shadow and digital twins, the underlying models may not be acceptable to regulatory agencies. This is possibly due to limitations of proprietary software. The next most frequently selected category was 'Traceability of Data inputs, model changes and decision-making processes within digital twins' which would suggest that what regulatory agencies consider acceptable in the process validation workflow described in section 2.2.2 may not extend to the advanced process control nature of a bidirectional Digital Twin. Also highlighted by the participants is the lack of regulatory guidelines which reinforces the findings on this subject in section 2.2.6

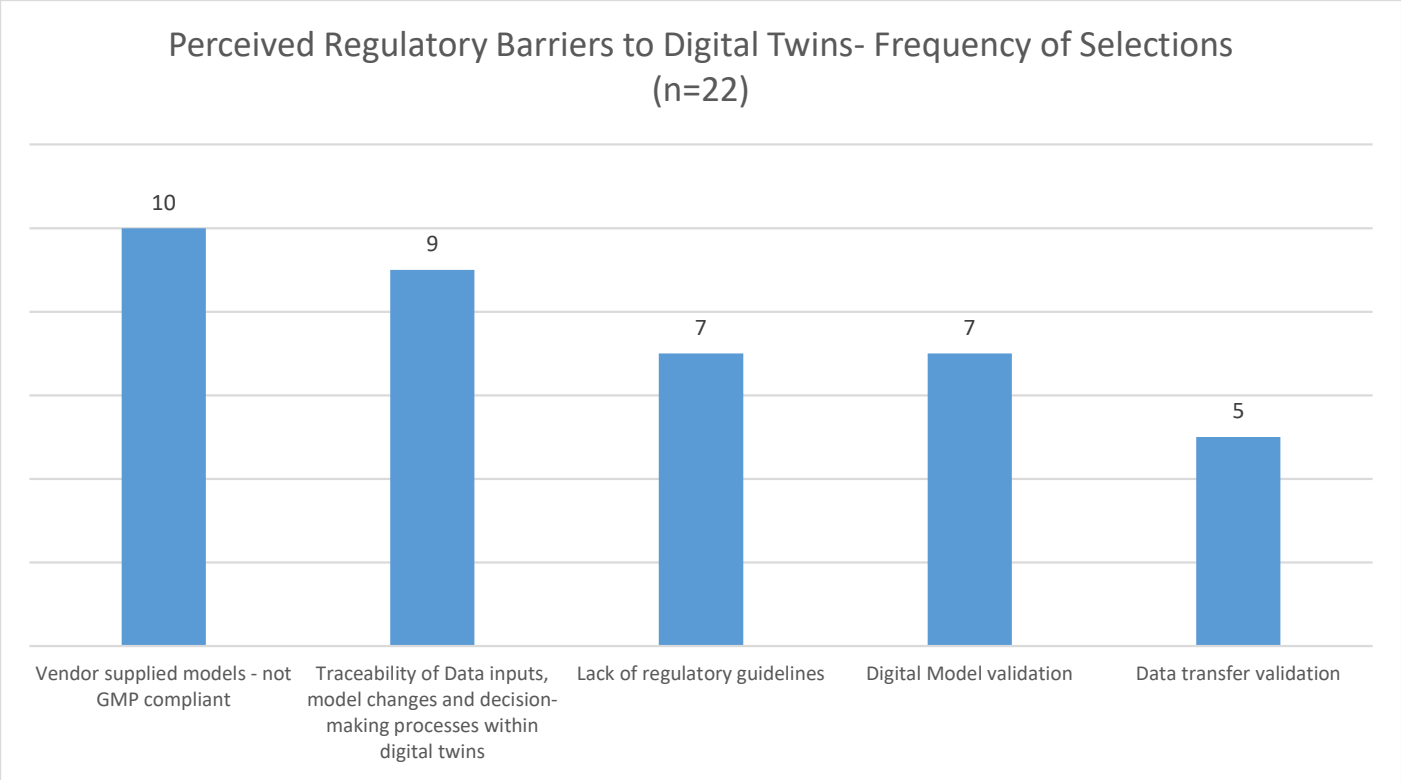

Figure 33 - Frequency of selection of Digital Twin regulatory barriers

4.5.15 Additional Regulatory Barriers to Digital Twin Implementation

Participants were asked to provide additional regulatory barriers they felt Digital Twins were faced with and the results along with the demographic details of the participant is displayed in Table 4. An interesting piece of feedback was provided in which an experienced participant within the 'Automation/IT' cohort did not agree with the premise that a digital twin needed to be regulated given the qualification and validation requirements on the physical component. It is possible that this participant's idea of a Digital Twin is that it is used purely for informational purposes. It is unlikely this participant envisaged it as a fully-fledged bidirectional data transfer tool used for advanced process control and simulation.

Functional Area	Years of Experience	Additional Benefit of Digital Twins
Automation/IT	>20	I don't get why the twin would need to be regulated? My understanding is it would just be used to pilot an idea. The Implementation would be on the physical asset which is heavily regulated.

Table 4 - Additional technical barriers to Digital Twins

4.5.16 Additional Feedback to the Survey

On completion of the survey, participants were asked for any additional feedback on Digital Twins which is presented in Table 5 below. An interesting observation commented on the significant implementation and support cost as a barrier for technology that is "still developing" and "not yet standardised". Another observation is given about the ambiguity of purpose with a digital twin and how this defines the route of delivery. An illustration of this is that a model to provide online process control would require a greater level of validation than one to provide process insight, which in turn would require greater validation than one for the purposes of training simulations for operators.

Functional Area	Years of Experience	Additional Feedback on Digital Twins
Automation/IT	>20	In general I think the perceived high implementation and support costs for Digital Twins across the whole process train is a barrier. Where specific cost/yield benefits may not be clearly identified as dramatically different from the benefits obtained by a combination of Process SMEs, already available data, and low level process modelling. Significant upfront investment with technology that is still developing and/or is not yet standardised across the industry.
Operations	5 - 10	Is it possible to integrate a digital twin into a continuous model would it be downstream as all of the unit operation would be linked.
Automation/IT	5 - 10	It will be highly helpful in preventing operator errors which is very much high in pharmaceutical industry.
Automation/IT	5 - 10	There is often ambiguity of how a digital twin would be used - is it for a performance tool or a GMP compliance tool. Both models offer a different route to delivery

Table 5 - Additional Feedback on Digital Twins

4.6 Interview Data- Thematic Findings

4.6.1 Confusion and Awareness Gaps

The interviews pointed to confusion and varying levels of awareness of digital twin technologies within the industry and what they entailed. Interviewee 1 considered the term 'digital twin' to be overly broad and prone to misinterpretation especially for those outside of technical roles. Furthermore, he felt that this created barriers to effective communication and adoption within industry noting from his personal experience of starting a company in this space "We did call it a digital twin and then immediately regretted it because that is such a broad term that it's almost counterproductive when you're trying to essentially communicate what you do." Furthermore, this participant emphasised this inconsistency stating that "there's a lot of different people saying a lot of different things about what a digital twin is". Interviewee 1 also alluded to a possible reason certain groups may resist engagement with these technologies and described how the dynamic and real-time closed loop control that is inherent to a comprehensive Digital Twin was mismatched with the regulatory requirements of the pharmaceutical and biopharmaceutical industries stating, "One characteristic of a digital twin is that it feeds back and adjusts dynamically, which does not fit with pharma at all" and that "That's not really conducive to GMP at all". Regulatory guidance prioritises maintaining validated states over the innovative benefits that Digital Twins may offer. As a result, this interviewee felt that "mechanistic" Digital Twins are applications with a "narrow focus" such as "to maximise cell culture yield or things like that".

This observation was reinforced by Interviewee 2 who rated familiarity in the industry as a whole as "a two out of five" and felt that this superficial level of knowledge was limited to automation and technical services role. Furthermore, this interviewee felt that within operational manufacturing roles such as "quality, operations and validation" the awareness would be minimal stating that they "wouldn't be familiar at all with digital twin technology. They're more focused on what they're manufacturing currently and not really looking to the future".

These concerns around awareness were further echoed by Interviewee 3 who pointed out that while there is some understanding within industry, this is incomplete and lacks depth. For example, this interviewee pointed out that maintenance or calibration technicians may consider a Digital Twin to be "a training tool" that "walks them through how to do maintenance or how to do equipment checks". However, the same terminology is used by someone from a global technical services role that would consider a digital twin as a tool for "data process optimisation" or "pulling in data into let's say an algorithm or multivariate environment".

Finally, Interviewee 4 gave a more optimistic view and indicated that familiarity with digital twins is growing and is a widely discussed topic at conferences and amongst industry stakeholders and rated the level of familiarity as a "four out of five" citing "attending different conferences and talking to peers and talking to other stakeholders within our current company". However, this interviewee also acknowledged that awareness is not universal and that there is a knowledge gap between departments. Stating that "a global tech ops group or a team leading up an NPI would be very, very interested" and "aware of how powerful digital twin technology could be for them" and contrasting this with other functional areas "from operation's side of things in our current business, it doesn't seem to be too much uttering around it or push to introduce it. I think that might lead you to think that there's probably not a familiarity

of just how powerful a digital twin could be". Interviewee 4 in this way drew a link between appreciation of benefits of Digital Twins and readiness for adoption.

4.6.2 Potential for Operational Efficiency and Process Optimisation

An analysis of the interview questions related to the most significant benefits to Digital Twin implementation results in the emergence of the dominant theme of the potential for operational efficiency and process optimisation. Across the interviews, key areas that were highlighted included enhanced training, cost savings, process improvements and enhanced data-based decision making.

Interviewee 1 commented on a wide range of benefits and applications of digital twins, "faster training, more flexibility for moving people around, greater knowledge, resilience, faster investigations, more robust CAPAs, and then into process optimisation if you're in the digital model side, understanding bottlenecks, improving scheduling turnaround, asset management optimisation". This response highlights how Digital Twins can enhance operational workflows and improve overall efficiency.

Interviewee 2 highlighted the level of cost saving that Digital Twins could deliver citing a reduction in downtime, equipment-wear and also operational demands stating, "It'd be a huge business saving because obviously the reduced downtime, the reduced use on your equipment, the reduced operational requirement to carry out a process or to run your experiments". This Interviewee linked this last point to operational excellence and performance targets such as the "golden batch" and that "If you had a digital twin that you could simulate, you could speed up, you could make different changes to, you could understand and get closer to your golden batch" by "running thousands of simulations quickly and effectively". This approach alluded to is similar to the mDOE enhancements offered through simulation rather than traditional experimental methods as discussed in section 2.2.3.1. This interviewee also mentioned the benefit as a "virtual training tool".

Interviewee 3 identified the significant financial incentive offered in an industry with profit margins as pronounced as in pharmaceuticals and biopharmaceuticals and how from a critical perspective this should justify the high upfront investment "even marginal gains in yield are seen as highly valuable" and "absolutely worth the investment". However, this interviewee also highlights that right now these multivariate models of process steps are "viewed as one of many inputs" but this will potentially change as they "develop and you get bigger data sets and a better understanding". This interviewee also gave an insight into how this benefit of cost saving may need to be communicated to a global level within organisations as "sites are seen as cost centres within large organisations". This interviewee also identified training tools as a potential use case but felt that unlike process optimisations, this would not be a sufficient driver to necessitate the investment cost required as "it's a harder sell as a financial benefit". This interviewee concluded that while these benefits are significant "I just don't know that many sites are very far down along that curve yet".

Interviewee 4 focused significantly on operational efficiencies that could be realised by leveraging AI to analyse complex data sets more efficiently and that traditional analysis techniques were no longer fit for purpose "This is where a digital twin akin to probably AI can just do more with that data to parse it, to display it in different ways and means that we can find the golden nugget within that data that we're looking for".

4.6.3 Client vs. Vendor on Technical Barriers

A thematic analysis of the interviewee responses identifies a difference of opinions between the participants on the significance and nature of the technical barriers to digital twin adoption. It is worth noting that the more optimistic viewpoint came from interviewee 1 who represents the vendor side of Digital Twins whereas the remaining participants are from the client side.

Interviewee 1 disagreed with the premise of the question and the significance of technical barriers stating, “I don't think it's a technical barrier” and “I think it could have been done 20 years ago to be very honest”. What this interviewee identifies instead is a “regulatory barrier and an adoption barrier”. They continue “The barrier is fear of adoption, fear of change for our industry is really where I think it is” and as an example cites the resistance to a move to paperless systems. This participants impression is that the technology is feasible, but the broader organisational culture is a much more significant obstacle.

Interviewee 2 did identify a number of technical barriers to adoption. Firstly, in terms of the system infrastructure aspects “I think the scale of what you would need to capture of that amount of data from every angle, I think that would need a significant upgrade in terms of what your network would look like”. Furthermore, this interviewee also felt there is a lack of the advanced process control systems to measure CQAs such as those discussed in section 2.2.3.2 and that to upgrade this would require substantial investment, "Even some of the most advanced systems I'd see, I would still feel that would probably require significant investment in sensors and transmitters”. The technical barriers identified are not limited to infrastructure and also encompass process expertise “I think we lack the process knowledge and maybe we lack the data sets”.

Interviewee 3 discussed in-depth the complexities of data integration and how the lack of standardisation across control systems presents technical challenges. It was acknowledged that although large amounts of data are already available within automated systems and is often transferred to higher level enterprise systems such as ‘OSI PI’, to integrate that into a digital twin is a unique challenge because the technology is nascent and there is not one “dominant player in the market”. The next logical step this interviewee foresees is that this lack of standardisation will incur significant costs "If each product has a different variation of the same thing, that makes the overhead and building those models very complex”. This could then be exacerbated because of competing industry players with distinct designs "If that data pool doesn't become the standard for multiple sites or for the organisation going forward for 5, 10, 20 years, how quickly does that become redundant or have to be re-engineered?".

Interviewee 4 identified the financial and resource demands that are associated with digital twins and how there are high costs of implementation and continuous maintenance required. This interviewee stated the major barrier being “The significant outlay to introduce it, the modelling and the hardware and the software around the digital twins, but then the maintenance of it as well” and felt that for a comprehensive digital twin the demand could be upwards of “3 to 4 thousand hours to maintain such a system with a highly skilled engineer every year”.

4.6.4 Regulatory Barriers and Lack of Engagement from Regulatory Agencies

Several regulatory barriers that are hindering the adoption of digital twins in the pharmaceutical industry were highlighted by analysis of interviewee responses. A recurring outlook was that the framework itself is not in place and that this is a significant departure from the way regulatory agencies expect process validation and control to be conducted. This would align with the assessment of the regulatory landscape provided in section 2.2.6.

Interviewee 1 reflected that regulators are primarily concerned with “basic digitalisation” and that digital twins are “so far beyond what the regulators are dealing with”. He continues that “dynamic models that are adjusting processes on the fly without a human in the loop” is also unacceptable to those within companies in “decision making roles for QA and compliance”. This interviewee predicts that this technology is a much more long-term prospect stating, “we're 20 years away”. He also discusses that in his opinion because there is no regulatory guidance specific to digital twins it is this lack of guidance that fosters a fear of adoption and change within companies.

Interviewee 2 also identified regulatory resistance as a significant barrier and felt that simulated models were unlikely to be accepted in validation and approval processes. This interviewee echoes that of interviewee 1 in feeling that digital twin concepts were simply not within a regulators remit “if you're going to market or if you want to get approval on a particular product, the regulators aren't looking through that type of data”. This interviewee highlighted that this lack of preparedness was also present internally within companies “We don't have the capacity for our own quality and validation departments to be able to embrace that or to be able to understand enough about what we're trying to achieve”. This interviewee gave a similar assessment of the long-term nature of changing the landscape “we’re quite some distance away”. This interviewee also discussed how the level of data that a Digital Twin can process may actually hinder progress in the regulatory space stating “There may be such an amount of data that it will be very impenetrable”.

Interviewee 3 delved into the regulatory barriers and how distinctions would be employed based on the use-cases. The distinction was made between Digital Twins for decision-making along with a number of other inputs and a validated change process, versus their use in process control and stated that "I don't think the regulator has any objection to using a digital twin as a workplace tool or as a knowledge tool” but emphasised that in the process control space “regulators want you to understand your process” and that with advanced process control driven by a “black box or an AI” which “the technical services and quality team who are responsible for the product don’t understand” would likely be unacceptable to an inspection agency particularly given the complex nature of these models compared to traditional process control "This is a much more complex version of inputs driving maybe more complex outputs”.

Interviewee 4 also commented on the regulatory agencies limitation in staying up to date with the rate of current technology advancement and how to align this with a GMP environment stating "It's about how do you stand over those algorithms that you're introducing into your digital twin" the interviewee explained and questioned "Are you introducing some other element of machine learning that isn't maybe explainable to an agency and thus you can't stand over actually the computation and the result from that computation". This integration of complex algorithms

into highly regulated environment is challenging especially as the framework is not equipped to support these tools. However, this interviewee did highlight an alternative to ‘black box’ adaptive models that he felt would be more acceptable to regulators in this space. ‘Explainable AI’ makes the logic behind decision-making available and transparent. The Interviewee stated, "So it's being able to maybe pull it apart and actually validate how the AI has actually come up with that computation is important within GMP." This is one example of a tool that while requiring some level of trade-off in terms of computational ability, may allow these models to meet the stringent regulatory guidelines and add value to their implementation.

4.7 Summary

The data obtained and investigated within this chapter is used in order to test the following hypotheses:

4.7.1 Hypothesis H1: The majority of employees in the Irish Pharmaceutical and Biopharmaceutical Industry have low awareness of Digital Twin technology.

The results from the survey discussed in section 4.5.1 support this hypothesis with a significant skew towards lower levels of knowledge. Furthermore, the analysis in section 4.5.2 comparing this hypothesis against experience suggests this is unrelated to participants' level of experience within the industry. The results from the Interview analysis reinforce this viewpoint with three of the four interviewees describing overall awareness within the industry to be generally low. The fourth interviewee felt that the awareness was relatively higher however, they clarified this was more so with global technical roles and that it was not something that was being engaged with at an operational level.

4.7.2 Hypothesis H2: Awareness of Digital Twin technology is significantly higher among employees in Automation and IT roles compared to those in Process Engineering, Quality, Validation, and Operational roles.

The results from the survey discussed in section 4.5.3 support this hypothesis. The knowledge level was significantly higher within the 'Automation/IT' functional areas typically associated with 'Digital 4.0' project implementation. This was supported by the interview responses in which the participants generally felt that core operational roles were primarily focused on their validated manufacturing processes and maintaining these. It is also noteworthy that the interviewee's broadly felt that there was general confusion within the industry about what a Digital Twin embodied. This is supported to a degree by the additional regulatory barrier survey question where one participant did not understand why a Digital Twin would need to be regulated at all. It is likely this participant envisaged at most a digital shadow in the continuum presented in section 2.2.1.2.

4.7.3 Hypothesis H3: Employees who are aware of Digital Twin technology perceive it as offering significant benefits, such as improved process efficiency, enhanced product quality, and reduced operational costs.

This hypothesis is overwhelmingly supported by both the results to a 'Yes/No' question presented in section 4.5.7 and also the litany of benefits discussed by the four interviewee participants. The most frequently identified category by survey participants was 'Greater understanding of the manufacturing processing steps', along with 'Improved Process Yields'. Interestingly, while the former was identified by the interviewee responses also, interviewee's 2, 3 and 4 who all come from decision making roles within their organisation felt that the main benefit to justify the investment cost to a business would be improving process performance and yields.

4.7.4 Hypothesis H4: The primary technical barriers to the adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry are related to data integration, network infrastructure, and the technical skill base.

This hypothesis is supported by the results to a 'Yes/No' question presented in section 4.5.10. The most frequently selected category was that of 'Data Integration and Management'. This highlights the difficulty posed by trying to combine data from various sources and ensure it is able to form a cohesive model and aligns with the responses given by Interviewee's 2 and 3 in system infrastructure. Interviewee 4 also highlighted the costs associated with data management but from a sustaining perspective in addition to project start-up. Interviewee 1 gave the one dissenting

opinion on this topic and felt that the technical barriers were not significant, and the more significant barrier was cultural and organisational.

4.7.5 Hypothesis H5: Regulatory concerns, particularly related to data integrity, cybersecurity, and GMP compliance, are significant barriers to the widespread adoption of Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

The survey participants were divided on this subject, and it is not possible to accept or reject this hypothesis based on the survey results presented in section 4.5.13. It is possible that those who do not feel regulatory concerns present a barrier may be imagining a basic digital shadow model that is used for informational purposes and not a fully-fledged Digital Twin which is novel for regulators. Interviewee 1 supported this idea that regulators are not predicting a move toward these comprehensive Digital Twins in the short to medium term. He also felt that most companies were not interested, and the limitation of their needs would be served by a digital shadow tool.

Interviewees 2, 3 and 4 all highlighted the regulatory limitations as a serious concern and mainly focused on the uncertainty in how one would validate these models to operate bidirectionally from the simulated model back to the physical component. However, Interviewee 4 also highlighted 'explainable AI' as one tool that could present a solution which would suggest industry vendors have also identified these concerns and are attempting to counteract them.

4.7.6 Hypothesis H6: Regulatory frameworks and industry standards currently in place are insufficient to support the large-scale implementation of Digital Twin technology, necessitating new guidelines and incentives from regulatory bodies.

Of the 22 survey participants that felt there were significant regulatory barriers, only 7 identified 'Lack of Regulatory Guidelines' as a specific challenge. However, as discussed previously this may be due to the awareness gap on what a Digital Twin entails. This was highlighted in the additional survey response given by one participant: "There is often ambiguity of how a digital twin would be used - is it for a performance tool or a GMP compliance tool. Both models offer a different route to delivery". This view that the guidance necessary for comprehensive Digital Twins is unavailable was reinforced by interview participants with interviewee 1 reflecting that Digital Twins are "so far beyond what the regulators are dealing with".

5.0 Conclusions and Recommendations

5.1 Conclusions Based on Research Questions, Primary and Secondary Research

The conclusions obtained from this study are organised into the first 5 Research Questions that were outlined within Chapter 1, the sixth question will be discussed within section 5.3:

1. What is the level of awareness of Digital Twin Technology within the Irish Pharmaceutical and Biopharmaceutical industry?

The primary research carried out in this study demonstrates that the level of awareness within the industry is low. The survey results expanded upon in section 4.5.1 demonstrate that among the sample population there is a significant skew towards lower levels of knowledge. The insights gathered from thematic analysis of the interviews was that 3 of the 4 participants described the level of awareness as low and the fourth felt that the awareness was limited to those directly involved in Digital Twin implementation. This is aligned with the secondary research carried out in this study where a literature review found the majority of applications of Digital Twins were at Lab or Pilot scale and this technology does not appear to have permeated through to the plant-scale of manufacturers.

2. How does the awareness level of Digital Twin Technology within the Irish Pharmaceutical and Biopharmaceutical industry vary based on employees' position and functional area?

The primary research illustrates that the functional area that employees work in has a significant impact on their awareness of this technology with significantly higher levels within 'Automation/IT' roles. The thematic analysis of the interviews supported this in that participants felt that roles supporting day to day manufacturing were unlikely to engage with these tools. This engagement will be necessary for these tools to be adopted by the industry. There is also a general confusion in the industry around the definition and purpose of a Digital Twin.

3. What are the key benefits to implementing Digital Twin technology in the Irish Pharmaceutical and Biopharmaceutical Industry?

The primary research indicates that benefits available from adoption of these technologies are significant plentiful. The most frequently identified of these was 'Greater understanding of the manufacturing processing steps' (based on the survey data), and an improvement of process yields (based on the Interview responses). The interviewees that have a role in organisational decision making all highlighted that the benefits would need to have a financial element to justify the investment outlay required both from a capital and sustaining perspective. The benefits align with those observed from the research community. A significant number of studies demonstrate the ability of Digital Twins to improve process yields. Furthermore, as discussed in section 2.2.2 the greater process understanding obtained through Digital Twin insights is conducive to a QbD approach to validation.

4. What are the main technical barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry?

Based on section 4.5.10, there are significant technical barriers to adoption. Within the survey results, 'Data Integration and Management' is the most frequently identified. This difficulty in trying to combine data from various sources to ensure it can form a cohesive model supports the challenges identified in section 2.2.3.3 and 2.2.4 of the literature review. While there are different interfacing systems and communications standards available, each of these have their own drawbacks such as data integrity or payload transmission rate.

5. What are the main regulatory barriers to the widespread adoption of Digital Twins in the Irish Pharmaceutical and Biopharmaceutical Industry?

A significant majority did not agree there are significant regulatory barriers to adoption. The respondents that did feel this was significant most frequently identified that the available modelling software is not compliant with a GMP environment.

This is related to the next most frequently selected barrier in the survey which was 'Traceability of Data inputs, model changes and decision-making processes within digital twins'. This suggests that what regulatory agencies consider acceptable in the process validation workflow (described in section 2.2.2) may not extend to the advanced process control nature of a bidirectional Digital Twin. The interview responses suggested that the nature of the regulatory barriers is from a fear of adoption perspective within companies. Furthermore, the respondents felt there was uncertainty into how a fully comprehensive Digital Twin model with closed loop control could be validated in a way that is acceptable to regulators.

5.2 Contributions and Limitations of the Research

This study provides contributions in understanding the adoption of and challenges to Digital Twins within Ireland's Pharmaceutical and Biopharmaceutical sector. This key sector contributes to over 50% of the country's exports (IPHA, 2024). Findings and recommendations can be used to inform future decision making in order to make full use of these technologies and for the industry to maintain its competitiveness within the global market.

This study highlights a low-level of awareness of Digital Twin technology that should be addressed as a priority so that stakeholders are ready to make informed decisions on how to invest strategically in this field. This investment can be directed based on the technical barriers identified in this work. Within the primary research, addressing data and system heterogeneity emerges as a notable concern.

This research identifies how the regulatory barriers that companies will face depends upon the way they intend to use these technologies. This suggests that the burden of regulatory, maintenance and validation work should be planned in at the project initiation stage.

The major limitation of this study is that the time horizon was constrained which had implications for the extent of collection of both primary and secondary data. Ideally there would have been a more in-depth analysis of both of these. While the sample size for the survey overall was 112 with 109 eligible for the questions related to the first research objective on awareness, this was reduced to 40 for the remaining objectives based on the remainder of the

cohort having 'No Knowledge' of Digital Twin technology. This limitation is inherently likely in a survey about a novel technology where a low level of awareness is expected.

If one were to extrapolate out, in order to have a truly meaningful sample size for the second part of the survey then over 300 participants would have been required to participate in it from the outset.

Furthermore, ideally there would have been more respondents to the interview but again this was limited by the time horizon of this work and also that inclusion criteria for the interview were industry experts and it is difficult to find participants who meet that criterion when investigating a nascent technology like Digital Twins.

A further limitation of this study which was reflected in some of the additional feedback survey questions was that the concept of what a Digital Twin embodies is broad within the industry.

5.3 Recommendations for Practice and Future Research

Based on the conclusions of this study, the following recommendations are made for Industry:

Given that the awareness within the industry is low, it is recommended that industry leaders and decision makers make proactive steps to increase both this and also the comprehension around what this technology is and how the applications, benefits and challenges are dependent on where on the continuum from Digital Model to Digital Twin the technology lies.

Organisations should prioritise educational initiatives for their staff across all functional areas and levels of experience such that may come into contact with this technology in some form. This may take the form of workshops or seminars to demonstrate the practical benefits. Companies could further this awareness and comprehension by introducing pilot projects so that employees can engage with the technology at a small scale with a lesser requirement for investment. This would also allow them to develop out procedures and frameworks to use for future implementation of these projects at a larger scale. These projects should have a benefit to process yield to justify the capital investment required for further works.

In order to overcome technical barriers, the industry should collaborate closely with 'Digital 4.0' vendors and make clear their requirements for seamless data and system interfacing solutions which will not age out at a rate that makes the maintenance cost restrictive to the introduction of the technology.

Based on the conclusions of this study, the following recommendations are made for the regulators:

The overwhelming feedback from both the primary and secondary data gathered in this study suggests that the agencies need to provide clearer guidance in how organisations can go about adopting Digital Twin within their manufacturing processes. They should address the regulatory uncertainty in model validation and advanced process control through close alignment with major industry players and develop out case studies in how to qualify and validate these systems in a compliant fashion. It is advised that this guidance is developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It would be counterproductive for the European Medical Agency (EMA) and Food and Drug Administration (FDA) to develop separate contradictory guidelines in an already confusing area. Regulatory sandbox environments should be

established to allow organisations to collaborate on what is feasible and this would allow the regulators to develop their own internal expertise on this emerging technology. Agreement could be reached on the limits that AI could play in adaptive modelling and tools such as 'explainable AI' could be assessed for their suitability to support this.

5.4 Reflections

The Irish economy is heavily dependent on the success of its Pharmaceutical and Biopharmaceutical industries. The conservative approach of incumbent Tier 1 pharmaceutical multinationals, including those with facilities located in Ireland may potentially leave themselves open to industry disruption by smaller, younger competitors – with more flexible cultures and attitude to risk – more willing to adapt and incorporate these technologies and realise their potential efficiency benefits. The wave of 'Industry 4.0' technologies that are entering the community's discourse including PAT, AI, VR and Digital Twins promise such significant benefits that it seems impossible that they will not become foundational tools in the manufacturing industry.

The same conservative nature which has served the industry in Ireland well in the production of safe, stable, and efficacious drug products could ultimately cause those same industries to decline and fall behind other competitors in the global market. The questions posed in this study seek to mitigate against this future scenario.

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Appendices

Appendix A – Copy of Survey

This questionnaire is being carried out by Rory Shevlin, a MSc student in Griffith College, Dublin, Ireland. This research is in the fulfilment of a master's degree in Pharmaceutical Business and Technology at Griffith College Dublin.
The survey will take approximately 10 minutes to complete.

This short survey aims to ascertain the level of knowledge of Digital Twin Technology in the Irish Pharmaceutical and Biopharmaceutical Industry.

If you have any questions or comments to this survey please contact rory.shevlin@student.griffith.ie. Participation in this research is completely voluntary, and your response will be treated with uttermost confidentiality in that your identity will not be connected through the data of this questionnaire. Data gathered is confidential and any findings from this data will be anonymized.
All data generated from this will be stored in line with the General Data Protection Regulation (GDPR).

Thank You.
I have read and understood the above information.

Yes	
No	

[NOTE: A no answer will launch email to rory.shevlin@student.griffith.ie for any questions /clarifications]

I agree to undertake the survey:

Yes	
No	

[NOTE: A no answer will end the survey]

1. Are you employed or have you been previously employed in the Irish Pharmaceutical or Biopharmaceutical Industry?
   - ☐ Yes
   - ☐ No [NOTE: A no answer will end the survey]

2. For how many years were you/have you been employed in the Irish Pharmaceutical or Biopharmaceutical Industry
   - ☐ <5 Years
   - ☐ 5 - 10 Years
   - ☐ 10 - 15 Years
   - ☐ 15 - 20 Years
   - ☐ >20 Years

3. In what functional area have you been employed for the majority of your career in the Irish Pharmaceutical or Biopharmaceutical Industry
   - ☐ Automation/IT
   - ☐ Process Engineering
   - ☐ Quality Assurance/Quality Control
   - ☐ Validation Engineering
   - ☐ Operations

☐ Technical Services
☐ Other

4. During the course of your career in the Irish Pharmaceutical or Biopharmaceutical Industry, how many different companies have you been employed by?
   ☐ 1
   ☐ 2
   ☐ 3
   ☐ 4
   ☐ 5 or more

5. On a scale of 1 to 5 how would you best describe your level of knowledge of Digital Twin Technology?
   ☐ No knowledge [NOTE: This answer will end the survey]
   ☐ Some knowledge
   ☐ General understanding
   ☐ Good knowledge
   ☐ Extremely knowledgeable

6. Do you feel the industry has widely adopted Digital Twin technology?
   ☐Yes
   ☐No
   If yes, in what applications have you seen Digital Twin technology used across the industry (select all that apply)?
   ☐ Bioreactor Modelling - Plant Scale
   ☐ Bioreactor Modelling - Pilot/Lab Scale
   ☐ Agitation/Mixing Unit Operations
   ☐ Chromatography Unit Operations
   ☐ Filtration Unit Operations
   ☐ Entire Upstream or Downstream Processing Trains
   ☐ Optimisation of Plant Finite Scheduling

   Are there any other applications that you have seen used within the industry?

7. Do you feel there are significant benefits to adoption of Digital Twin Technology within the industry?
   ☐Yes
   ☐No
   If yes, which of these benefits are applicable (select all that apply).
   ☐ Reduced processing lead times
   ☐ Improved process yields
   ☐ Improved product quality
   ☐ Greater understanding of current processing steps
   ☐ Enhanced decision making
   ☐ Real-time finite scheduling
   ☐ Accelerated Development of new product introduction
   ☐ Predictive maintenance
   ☐ Training and skill development

☐ Delivering sustainability improvements
☐ Cost savings
☐ Unsure

Are there any other benefits to adoption of Digital Twin Technology?

8. Do you feel there are significant technical barriers to adoption of Digital Twin Technology within the industry?

☐Yes
☐No

If yes, which of these technical barriers are applicable (select all that apply).

☐ Data Integration and Management
☐ Existing Network Infrastructure
☐ Interoperability issues between different systems
☐ Scaling to large scale manufacturing
☐ Data security and privacy
☐ Real time processing and analysis
☐ Lack of Industry Standards
☐ Continuous Maintenance of Digital Infrastructure
☐ Availability of qualified workforce
☐ Unsure

Are there any other technical barriers to adoption of Digital Twin Technology?

9. Do you feel there are significant regulatory barriers to adoption of Digital Twin Technology within the industry?

☐Yes
☐No

If yes, which of these regulatory barriers are applicable (select all that apply).

☐ Lack of regulatory guidelines
☐ Digital Model validation
☐ Data transfer validation
☐ Vendor supplied models - not GMP compliant
☐ Traceability of Data inputs, model changes and decision-making processes within digital twins
☐ Unsure

Are there any other regulatory barriers to adoption of Digital Twin Technology?

10. Is there any additional feedback or comments you would like to provide regarding Digital Twin use in the Pharmaceutical and Biopharmaceutical Industry in Ireland?

Appendix B – Interview Questions

Objective 1: Evaluate awareness level and differences based on position

On a scale of 1 to 5, how would you rate the overall familiarity with Digital Twin technology within the industry?

☐1 Not at all familiar

☐2

☐3

☐4

☐5 Extremely familiar

From your perspective, how does awareness of Digital Twin technology vary by different roles within the industry?

Objective 2: Identify the key benefits

On a scale of 1 to 5, do you feel there are significant benefits to adoption of Digital Twin technology within the industry?

☐1 Not Significant

☐2

☐3

☐4

☐5 Extremely Significant

What are the most significant benefits that the industry can realize or anticipates from using Digital Twin technology?

Objective 3 Investigate technical barriers

On a scale of 1 to 5, do you feel there are significant technical barriers to adoption of Digital Twin technology within the industry?

☐1 Not Significant

☐2

☐3

☐4

☐5 Extremely Significant

What are the common challenges in data integration, network infrastructure, and technical skill base related to Digital Twins in the industry?

Is the typical existing network infrastructures in the Pharmaceutical or Biopharmaceutical industry generally adequate for the adoption of Digital Twins?

☐Yes

☐No

☐Not sure

Objective 4: Investigate regulatory barriers

On a scale of 1 to 5, do you feel there are significant regulatory barriers to adoption of Digital Twin technology within the industry?

☐1 Not Significant

☐2

☐3

☐4

☐5 Extremely Significant

If so, can you elaborate on what these regulatory barriers are?

On a scale of 1 to 5, how prepared do you feel the industry is to meet FDA and EMA regulations concerning the implementation of Digital Twins?

☐1 Not at all prepared

☐2

☐3

☐4

☐5 Extremely prepared

Participant Information Letter

ASSESSING THE INDUSTRY KNOWLEDGE BASE OF DIGITAL TWIN TECHNOLOGY IN THE IRISH PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRY

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

This study is the Dissertation component of an MSc in Pharmaceutical Business and Technology and will allow the completion of said course. It is to evaluate Digital Twin technology use in the Pharmaceutical and Biopharmaceutical industry. More specifically, the prevalence of it, key challenges and benefits to adoption of it in terms of financial, technical, regulatory and cultural and the awareness and industry readiness of it within different functional areas.

WHAT WOULD TAKING PART INVOLVE?

Participating in this study will involve giving a 20-30 minute interview on your opinions on Digital Twin technology and the current status of the Irish Biopharmaceutical industry within it. In the case that you are not aware of this technology as it does not pertain to your area then this is also valuable data and will be noted.

WHY HAVE YOU BEEN INVITED TO TAKE PART?

You have been selected to take part in this study due to your area of work and functional role with the Irish Biopharmaceutical Industry.

DO YOU HAVE TO TAKE PART?

Please note

- that participation is voluntary;
- that a decision not to consent will have no adverse consequences;
- that consent can be withdrawn at any time
- If you need to withdraw, please contact Rory Shevlin on +[redacted]

WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF TAKING PART?

It is possible that data obtained throughout this primary research will be published. All data will be anonymised and participants can withdraw at any time from this study.

WILL TAKING PART BE CONFIDENTIAL?

Confidentiality and anonymity for all participants that take part in this study will be maintained as all data will be anonymised prior to being synthesised into the dissertation report. Non-anonymised data will be held in the form of signed consent form and audio recording and collected and retained within the Griffith College Online repository as part of this research process. This data is not within public domain. Confidentiality may have to be broken when there is a serious risk of harm or danger to either the participant or another individual.

HOW WILL INFORMATION YOU PROVIDE BE STORED AND PROTECTED?

'Signed consent forms and original audio recordings will be retained in Griffith College Online repository, accessible to Griffith College staff and the researchers of this study until after my degree 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 legalisation you are entitled to access the information you have provided at any time.'

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The plans for this research consist only of submitting this dissertation for the purposes of completing this MSc course. All dissertation research projects and their content will be made accessible in the college library.

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

For further information please contact:

Dissertation Researcher - Rory Shevlin – rory.shevlin@student.griffith.ie

Dissertation Supervisor - Philip Byrne – Philip.Byrne@griffith.ie

THANK YOU

Consent to take part in research

ASSESSING THE INDUSTRY KNOWLEDGE BASE OF DIGITAL TWIN TECHNOLOGY IN THE IRISH PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRY

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

- I _____ voluntarily agree to participate in this research study
- I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind
- I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study
- I understand that participation involves giving a 20-30 minute interview on your opinions on Digital Twin technology and the current status of the Irish Biopharmaceutical industry within it 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 an MSc dissertation.
- If data is coming from within one company or specifically pertaining to the one company -I understand that I will adhere to all of the codes of conduct and employee confidentiality for company Alexion and there is no expectation to breach these by partaking in this research.
- 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 Griffith College online repository until the exam board confirms the results of the dissertation for which this research is being undertaken.
- 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 that to confirm the result of the dissertation for which this research is being undertaken.

- I understand that under freedom of information legalisation I am entitled to access the information I have provided at any time while it is in storage as specified above.
- I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

Researcher Details
Name: Rory Shevlin
Degree Programme: MSc Pharmaceutical Business and Technology
College Details: Griffith College Dublin
Contact number: +[redacted]
Contact mail: rory.shevlin@student.griffith.ie

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