Lean Validation in the Pharmaceutical Industry in Ireland

By

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STUDENT DECLARATION

I hereby confirm that this dissertation titled "Lean Validation in the Pharmaceutical Industry in Ireland", which is presented in partial fulfilment of the requirements for the award of the MSc in Pharmaceutical Business and Technology, represents my original work, under the supervision of Brendan McLaughlin.

I have appropriately indicated all sources used in the preparation of this study through accurate referencing. I also verify that I have neither copied nor plagiarised the work of anyone else.

To be filled by the Student:

Signed by:

Date: 20 May 2023

To be filled by the Supervisor:

Signed by: Brendan McLaughlin

Date: 20 May 2023

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Dedication

I would like to dedicate this dissertation to my best friend Ellen, who always believed in me, supported me and encouraged me to do my best in everything I do.

'The measure of intelligence is the ability to change' Albert Einstein

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List of Abbreviations

ASTM	American Society for Testing and Materials
C&E	Cause and Effect
CI	Continuous Improvement
CFF	Critical Failure Factors
CQA	Critical Quality Attributes
CSF	Critical Success Factors
EMA	European Medicines Agency
FMEA	Failure Mode Effect Analysis
KPI	Key Performance Indicators
LSS	Lean Six Sigma
PAT	Process Analytical Technology
PV	Process Validation
QbD	Quality by Design
R&D	Research & Development
RCA	Root Cause Analysis
SME	Subject Matter Expert
SMED	Single Minute Exchange of Dies
VSM	Value Stream Mapping

Abstract

Lean Validation in the Pharmaceutical Industry in Ireland

Laura Scully

In this study, it was shown that implementing Continuous Improvement (CI) initiatives has been done within Pharmaceutical Validation in Ireland, to some extent. 'Lean Validation' is a concept that involves the implementation of CI initiatives into the process of Validation. Within the Pharmaceutical Industry, there is an enduring interest for an organisation to reduce waste and improve the efficiency of a process. Validation is a core pillar of the Pharmaceutical industry and the process can often be long, tedious and inefficient. This ideology behind 'Lean Validation' is to use tools from principles such as Lean and Six Sigma to reduce waste and improve the Validation process. The objectives of this research were to explore the extent to which organisations are currently implementing 'Lean Validation' principles, what the current challenges with implementing them are, and what specific areas and tools could be the most beneficial to focus these initiatives on within the Validation process. This research was conducted using a mixed-method approach, consisting of a survey and interview.

The analysis of the data showed that CI tools and initiatives have been implemented within the Validation process, with the main goal of this to improve the efficiency of the process and to remove any aspect of the process that does not add value and can be considered 'waste' under Lean methodologies. The data showed there is some level of reluctance to implement CI within Validation, with the main challenges being lack of time and resources, and lack of engagement from personnel due to a 'fear of change'. The study concludes that CI initiatives can be beneficial for the Validation process in a number of areas and provides suggestions for Pharmaceutical organisations looking to implement them and recommendations for further study.

Chapter I

1. Introduction

1.1. Background of the Research

The pharmaceutical industry is a huge global industry, that is well regulated to ensure all products meet strict quality standards to guarantee the safety of patients who are administered them. These quality standards for Pharmaceutical products that are produced in Ireland must comply with the safety regulations set out by both the Health Products Regulatory Agency (HPRA) and the European Medicines Agency (EMA). Industry standards are published by regulatory bodies in order to provide pharmaceutical companies with a guide to adhere to, in order to ensure they remain in compliance.

Ireland is a large contributor to the manufacture and supply of pharmaceuticals around the world. There is a large presence of pharmaceutical organisations ranging from large international companies, to smaller start-up and R&D companies. The tax incentives and well-educated workforce are among the reasons why there is a significant amount of investment in the pharmaceutical industry in Ireland (IDA, 2023).

Validation is one of the most important aspects of the pharmaceutical industry as it guarantees the quality of the product which is ensures there is no risk the safety of the patient who is being administered the product. There are very strict regulations regarding the validation of pharmaceutical products, which are required to ensure that the process is robust enough to deliver safe and effective medicines, and that there are measures to ensure that any faulty or defective products will not be released to the market.

Validation can be a costly process for pharmaceutical organisations, both in terms of revenue and resources. The strict regulations in place makes changes or improvements to the validation process more tricky, as sufficient justification is required to show that a process will deliver quality goods prior to receiving marketing authorisation for a product. There are a number of activities associated with the validation process and many for companies the process is not streamlined and can result in a significant amount of work which can be considered unnecessary or ‘non-value add’ tasks.

Pharmaceutical organisations are always looking to make reduce the costs of product manufacturing. The most common way to do this, without compromising the quality of the product, is by implementing improvements to a process which will result in less waste, require less resources and lead to increased productivity. Recent events, such as Brexit and the COVID-19 pandemic have had an impact on the pharmaceutical industry and therefore companies have had to adapt and develop new strategies in order to remain competitive.

Continuous Improvement (CI) is the process of incorporating changes that have the potential to address known and predicted issues associated with a process in order to improve its efficiency or reduce the amount of resources required to complete a task. There are a number of approaches to this, many of which have been adopted in the pharmaceutical industry in an attempt to improve efficiency and remove waste. Waste in this case can considered anything that does not add value. 'Lean' is an example of a core methodology that has been used for CI in order to achieve this by removing this waste, using a number of tools for process improvement.

1.2. Purpose of the Research

Recent years have seen an increase in the cost of drug development and consumables, as well as inflation. Therefore, it is rational that companies are looking to make savings where possible. As the pharmaceutical industry is a tightly regulated industry it is not in the interest of many organisations to opt for cheaper options for consumables and equipment, which have the potential to impact the quality of the product. The risk is simply too great, as a defective product can result in lawsuits, product recalls and damage to the company reputation. Therefore, companies must be strategic in their cost-cutting approaches in order to ensure there are limited negative repercussions.

Validation can often be a tedious and expensive task for pharmaceutical companies. There are a number of reasons why CI initiatives are attractive to large organisations, such as pharmaceutical companies. By streamlining and improving the process of the validation, there will be more resources available for the organisation to invest in other departments, such as Research & Development (R&D), which can result in the development of new treatments and medicines for patients.

A more efficient process that results in less waste will also have a positive impact on the environment, which is also a very relevant consideration as global enterprises are facing increased pressure to combat their environment impact. It is also in the interest of the company stakeholders to maximise the profit from the manufacture of the products.

Many CI initiatives and tools have been implemented successfully into the manufacturing process for pharmaceutical products, which has been thoroughly discussed in the published literature to date. However, improvements in the validation process are not widely reviewed in the current literature, which is why this research aims to focus on the advancement of CI methodologies within validation in the pharmaceutical industry to date.

1.3. Research Aims & Objectives

1.3.1. Research Question

The main aim for this research is analyse gather information from individuals in the pharmaceutical industry in Ireland to answer the following research questions:

- To what extent do Lean and other CI methodologies currently play a part in the Validation process of pharmaceuticals in Ireland?
- What Lean or CI tools could potentially help to optimise the Validation process?
- What challenges are currently associated with the implementation of CI initiatives within the validation process?

1.3.2. Research Objectives

- **Objective 1:** Determine the extent, if any, to which Lean and other CI tools are currently being implemented in validation in the pharmaceutical industry.
- **Objective 2:** Explore Lean methodologies and other CI tools that could potentially optimise the validation process in the industry
- **Objective 3:** Analyse the current challenges, both observed and potential, that could be associated with the implementation of Lean Validation.
- **Objective 4:** Assess the potential impact and benefits of optimising the validation process through Lean and other CI principles.

1.4. Scope of the Study

The scope of this research is to assess the implementation of CI initiatives into pharmaceutical organisations in Ireland, specifically within validation. This includes all aspects of validation, including validation of manufacturing processes, analytical methods, cleaning, equipment, instrumentation and IT.

The term 'Lean Validation' for the purpose of this research is used to describe all types of CI initiatives that are implemented into the validation process within pharmaceutical organisations, which include tools and concepts from both Lean and Six Sigma methodologies.

The scope of the research is limited to the pharmaceutical industry in Ireland, which will therefore limit the sample population to organisations that have facilities within Ireland. However, 9 of the top 10 global pharmaceutical companies are established in Ireland, which means that the sample population in Ireland could reflect the trends within large organisations outside of Ireland, as global companies have a tendency to embrace a similar culture globally.

1.5. Overview of Dissertation

	Title	*Overview*
Chapter I	Introduction	Purpose and significance of study. Description of research topic and objectives.
Chapter II	Literature Review	Critical analysis of secondary literature available regarding the topic. Identification of gap for research focus.
Chapter III	Research Methodology	Discussion of approach to research, including research philosophies and conceptual framework.
Chapter IV	Results & Analysis	Presentation of findings and interpretation of results.
Chapter V	Conclusions & Recommendations	Discussion of conclusions drawn from result analysis and recommendations for further research. Includes limitations of research.

Table 1: Overview of Structure

Chapter II

2. Literature Review

2.1. Overview

Innovation is a fundamental concept for the pharmaceutical industry to develop new medicines for patients. With the high costs associated with new drug discovery through Research & Development (R&D), pharmaceutical companies are always looking to adopt new ways to cut costs, without compromising on quality. There are a number of drivers for the implementation of Lean for the pharmaceutical industry. A lean process can reduce the safety risks that can be associated with an inadequate process. However, many large-scale commercial manufacturing facilities have been slow to implement these new approaches. The heavy workload associated with validation/re-validation of a new process is among the contributing factors for this.

2.2. What is Continuous Improvement (CI)?

A common goal for a pharmaceutical manufacturing site is to achieve operational excellence. Continuous improvement (CI) is an ongoing effort to maximise the efficiency of a process or service. This is achieved by making changes to eliminate waste or improve quality. It can enable a company to gain a competitive advantage, cut costs and increase production capacities. It is important to challenge the traditional way for completing a task and embrace new ways to do things (Stevens, 2010). While CI is a necessary task for all pharmaceutical organisations who wish to stay competitive, implementing it successfully has not always been a straight-forward task. In the past, achieving the desired result from a CI project has been reported to fail in up to 70% of cases that have been deployed (Albliwi *et al.*, 2014). Lean & Six Sigma are the most popular strategies for enabling CI in a variety of sectors, including in the pharmaceutical industry.

2.2.1. Lean

Lean is a concept that was developed for the automobile industry in Japan by Toyota, which aims to remove waste from a process (Dave, 2020). It has become a universal methodology that has been adopted by many disciplines, and is commonly seen in the pharmaceutical industry. Lean manufacturing can be used to reduce costs and increase competitiveness of an entire organisation. Waste can be considered any activity that does not add value to the process. The ideology behind Lean is based on identifying all waste in a process, and eliminating it

(Wahab *et al.*, 2013). The typical cGMP approach to manufacturing focuses on quality first and foremost, whereas the Lean approach focuses on quality balanced with improved productivity (Pavlovic, 2012). 'Muda' is the Japanese work for waste. There were 7 types of waste originally identified by Ohno, but there are now 8 categorised forms of waste that are widely discussed across the literature which are presented in Figure 1.

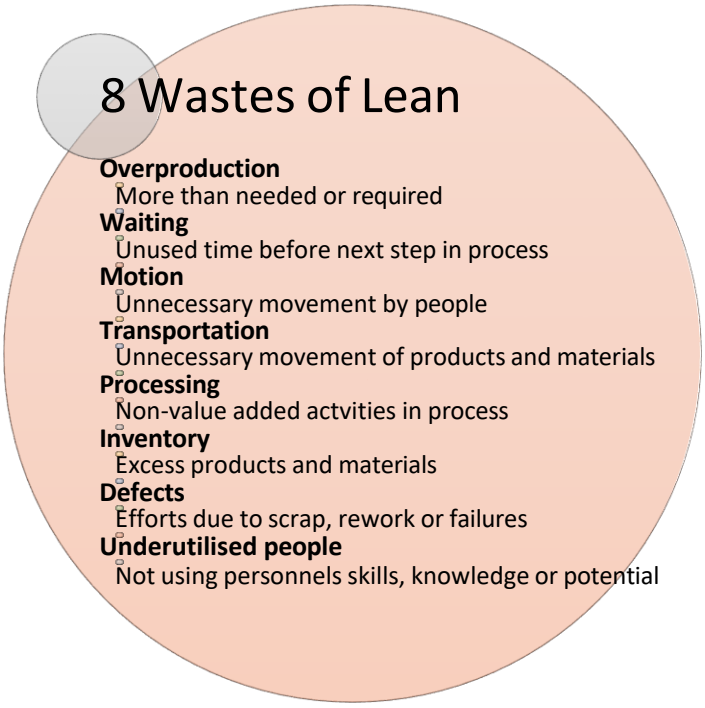

Figure 1: 8 Wastes of Lean, adapted from Wahab et. al *2013*

2.2.2. Six Sigma

Six Sigma is another methodology that aims to reduce variability or defects in a process, which was introduced in Motorola (Antony *et al.*, 2017). It is based on the DMAIC model, which stands for the steps 'Define-Measure-Analyse-Improve-Control'. This 5-step practice is used to identify the root cause of defects and remove them from the process. The process is then continued for each new problem, which is why the model is commonly visualised in a continuous circle, as shown in Figure 2 below which has been adapted from Yang et. al (Yang *et al.*, 2020). Lean tools are considered less technical, such as visual process mapping, whereas Six Sigma analysis is usually used for more complex problems and is based on statistical analysis, Design of Experiments (DoE) and hypothesis testing (ASQ, 2023).

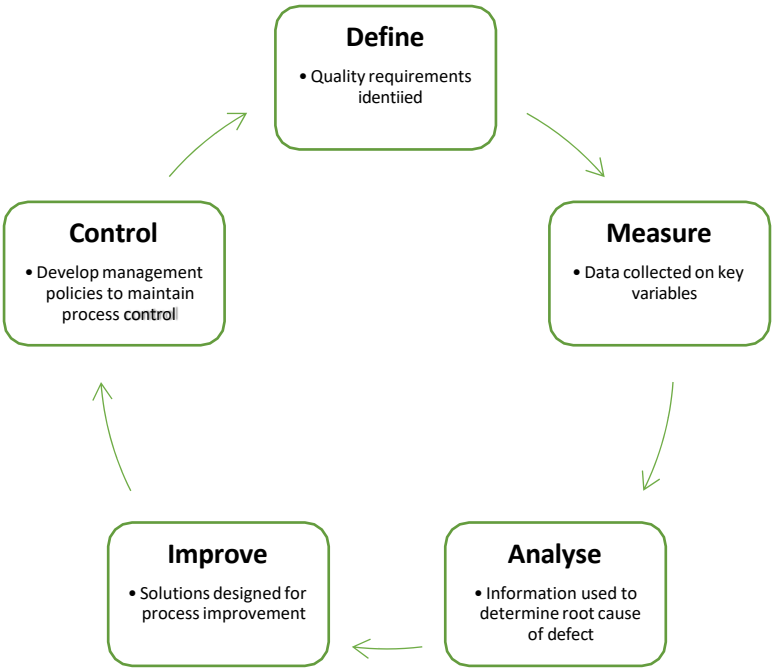

Figure 2: Six Sigma process 'DMAIC', adapted from Yang et. al *2020*

Six Sigma level quality aims to minimise variability and reduce failure to approximately 3 per one million units. Achieving Six Sigma quality indicates a well-controlled process that will perform almost always as predicted. Witcher discusses the importance of achieving Six Sigma quality and claims that incorporating FDA guidelines on Process Validation (PVs) is the best approach to achieve it. This approach describes using the FDA's PV framework throughout the 3 stages of a product lifecycle. Witcher claims that the FDA's PV guidance is the most important tool as it focuses from the beginning of Process Design to Qualification to Continued verification (Witcher, 2018) (FDA, 2011).

Quality by Design (QbD) is not the same as Six Sigma but the principles are very similar. QbD is a concept which, like Six Sigma, aims to reduce defects by creating a process that is reliable and delivers high-quality results. QbD is achieved by identifying characteristics that directly impact the quality of the product, and building the process around achieving these Critical Quality Attributes (CQAs) (Yu *et al.*, 2014).

2.2.3. Lean Six Sigma

Lean Six Sigma (LSS) is where Lean approach is combined with Six Sigma methodologies in order to greater reduce costs (Albliwi *et al.*, 2014). This approach is also popular in the

pharmaceutical industry. This approach can account for the limitations observed with both methodologies. Six sigma can be better suited for more complex problems that require advanced statistical analysis, where as Lean is more suitable when the issue does not require copious amounts of data collection and analysis. Individuals can be certified through a belt system, which are considered an important aspect to successful LSS development (Antony *et al.*, 2017).

2.2.4. Continuous Improvement Tools and Principles

There are a large number of CI tools that can be used or implemented in line with Lean and Six Sigma methodologies. The top 5 CI tools used in pharmaceutical companies, according to a study by McDermott et al. were Cause & Effect (C&E), 5-whys, 5S, Process Mapping and Failure Mode and Effects Analysis (FMEA), which were selected from a list of 25 CI tools presented (McDermott et al., 2021). Alkhoraif et al. also identify common Lean tools through reviewing the literature surrounding Lean implementation in small and medium sized enterprises, which include VSM, 5S, Kanban and Kaizen (Alkhoraif *et al.*, 2019). VSM and 5S are typically implemented early in the Lean process, which are effective at addressing at eliminating simple 'waste' from the process (Barclay *et al.*, 2021).

5S, similar to Six Sigma, is another cyclical 5-step methodology for process optimisation. The steps includes 'sort, set in order, shine, standardise, and sustain'. It aims to remove some of the 8 wastes of Lean from a process. This tool is used to organise and standardise the workplace through establishment of a systematic process and elimination of non-value add tasks (Trubetskaya *et al.*, 2022).

Kanban is considered a more advanced Lean tool, which aims to improve process flow through visual, real time representation of work which is driven by communication and full transparency. This is typically adopted after more basic Lean tools have been successfully implemented (Barclay *et al.*, 2021).

Gemba, which has been adapted from the Japanese word 'gembutsu' which means 'real thing', is another simple tool for Lean practices. It is an observation technique to understand how work is performed and requires the participants to engage where the process takes place, which is commonly the manufacturing floor for Lean pharmaceutical manufacturing. This was used in

Byrne *et al's* approach for problem solving and helped in this case to identify 4 categories of defects that were observed, from which the team could identify the most common cause of stoppages across all production lines (Byrne *et al.*, 2021).

Just-in-time (JIT) methodology negates the waste of excess inventory from having a surplus of product or capacity, which will have higher operating costs. It involves working based on demand. This concept is considered more difficult to implement in smaller organisations as the negotiating power is not as strong as with larger enterprises, who rely heavily on establishing strong relationships with suppliers (Alkhoraif *et al.*, 2019).

Root cause analysis (RCA) is a vital aspect of CI methodologies, including Lean and Six Sigma. This entails considering all possible causes for a detect or problem and determining the true root cause for the problem occurring. A number of commonly used tools are used for this, such as '5 why's', Cause & Effect' (C&E) and fishbone (or Ishikawa) diagrams to examine all possible root causes and narrow down options.

Value Stream Mapping (VSM) is a tool used to visually represent the current process flow. This is a way to highlight opportunities for improvement by identifying waste and creating a plan for the future process (Khan *et al.*, 2020). VSM was used by Byrne et al. when implementing LSS improvements into a pharmaceutical company. This tool identified one particular department within the manufacturing process that was a bottleneck and it was discovered that current run-rate of the packaging department was 1 million tablets a week less than the customer demand. They were able to use this information by focusing on identifying the root cause for this (Byrne *et al.*, 2021).

2.3. Validation process

While the pharmaceutical manufacturers must be consistent with their strict compliance with regulatory guidelines on validation in order to guarantee quality and safety of their products, they must also be willing to embrace some forms of continuous improvement if they wish to remain competitive (Stevens, 2010). Validation can be a costly process that can quickly drain resources from manufacturing organisations. Aside from being a regulatory requirement, there are a number of advantages for a well validated system for the pharmaceutical manufacturer.

These include increased production, output, and reduced complaints, rejections and cross-contamination, which result in less rework and less waste.

There are a number of challenges associated with validation of a new pharmaceutical process or product, that must be overcome in order to acquire regualotory approval for manufacturing. These can include ensuring the facility is fit for purpose, creating clear and concise documentation, and defining and agreeing on specific roles and responsibilities (Chang, 2011).

There are a number of areas of validation that could benefit from CI initiatives, such as Lean. Challenges regarding the documentation of the validation project has been identified as a potential area for improvement. In some cases the instructions for a task, or the paperwork for recording the task can be vague, due to a lack of thorough understanding of the process steps. It is possible in these cases that not enough detail will be collected, which can mean the information can be hard to verify. In contrast to this, if precise specifications are unknown prior to completing a step it could result in excess, irrelevant information being recorded. This inefficiency can result in wasted resources, and rework in some cases.

There are a number of areas within validation of pharmaceutical products that can present specific and unique challenges. For example, inadequate change management can cause disruptions and delays to the validation process. A lack of clarity, communication and competent guidance can lead to an inefficient change control process and result in reluctance to engage in revalidation projects that could potentially benefit the organisation in the long run. Another example is analytical method validation, which can be very time consuming. Simple issues like poor technical transfer documents can hinder this process significantly. Similar examples can be seen in Facilities, Equipment, IT and instrument validation.

2.4. Limitations to CI implementation

There are a number of factors that can limit CI implementation in the pharmaceutical industry as a whole, such as lack of financial and physical resources, or risks to data integrity. Success can often rely on a number of factors including organisational culture, clean communication and support from management, and adequate training (McDermott *et al.*, 2021). With validation being a key aspect of pharmaceutical manufacturing, dedicating key resources to non-essential tasks like CI implementation can be of lower priority to some organisations. A

strong risk-based approach could be a potential solution to overcome some of these issues (Stevens, 2010).

ASTM E2500 'Standard Guide of Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment' is a guideline published by ASTM (American Society for Testing and Materials) on how to manage a risk-based approach to validation of systems and equipment. It was developed based on the principals discussed in ICH and FDA guidelines to validation of pharmaceutical systems (ASTM, 2020). This approach to validation differs to the classic approach based on the use of risk management tools to assess the 'risk' associated with each aspect of a system based on the high level risks with a greater potential impact to product quality. In contrast, the classic approach assumes the impact of all aspects are equal (Levenson, 2019). The goal is to provide a level of flexibility within the industry, which can provide a more efficient process, using a well-defined, systematic approach which can improve compliance. There is a higher level of responsibility for the personnel involved to effectively assess and justify the level of risk of each attribute to product quality and patient safety (Pharmaceutical Technology Editors, 2009). This model is similar to the 'Quality by Design' approach in that the process requires a high level of SME involvement in the project design and process knowledge to be completed effectively. Despite the publication of the standards in 2007, the effectiveness of using ASTM E2500 for system validation is not widely discussed in the literature.

2.5. Use of Lean and CI in Pharma

Byrne *et. al* present a case study which introduces a Lean Six Sigma approach to a pharmaceutical manufacturing facility in Ireland, in an attempt to improve efficiency and boost productivity. In this case study a pharmaceutical manufacturing facility implemented a Lean Six Sigma methodology to reduce manufacturing downtime. The company produced pain relief tablets and it was currently experiencing an increased product demand due to the COVID 19 pandemic. A problem-solving approach was adopted in order to identify and eliminate waste and classify problem root causes using a customised 7-step approach, which followed the Lean Six Sigma methodologies. Step 1-5 of the process included identifying the top losses or problems within production through VSM. The scope of problems was then narrowed through 'loss stratification' in order to focus on the most problematic areas, from which, specific

projects could be selected based on their potential impact. The problem solving aspect followed a '6-step problem-solve' which was similar in structure to DMAIC framework.

In the attempt by Byrne et al. to determine the root cause of tablet defects they allowed all of their observations and data generated to show the true root causes and they redefined their initial problem statement (Byrne *et al.*, 2021). This shows that they were not biased towards the outcome or what was causing the issues. A willingness to adapt and change outcomes is essential for effectively implementing Lean methodologies that will address the true root cause. The benefits for the project were calculated to show improvements in downtime minutes, lost tablets and rejected tablets to the benefit of €446,460 per year. It is worth noting that a 20% contingency was included for the cost improvements to account for potential variability with regards to the equipment adjustments, which means the results can be considered practical and fair. The learnings from this study were also to be applied to multiple sister manufacturing sites globally (Byrne *et al.*, 2021).

A study by McDermott et al. aimed to investigate specific challenges or barriers for Irish pharmaceutical companies to implement CI methodologies. An online survey was conducted with all participants of the study currently employed by multinational pharmaceutical companies based in Ireland. This study concluded that 97% of participants have witnessed some form of continuous improvement approach within their company, at some stage. This included methods such as Lean, Six Sigma and Lean Six Sigma, with 51% of participants expressing that all 3 were used in their organisation (McDermott *et al.*, 2021).

The reasons for CI implementation were analysed, with 'productivity' being shown as the highest driver, 'quality' being close behind, with 92% and 83% of respondents considering the drivers for CI, respectively. Customer focus, safety and financial focus were also considered high drivers (McDermott *et al.*, 2021). This finding is consistent with the top benefits, according to Antony et. al which identified increased financial savings and customer satisfaction, and reductions in cycle time, inventory and costs from quality defects (Antony *et al.*, 2017).

The areas that were identified as having the strongest level of CI tools in use by McDermott are 'deviations', 'internal audit systems' and 'corrective and preventative action (CA/PA) systems'. The survey followed a mostly closed-ended question, which enabled quantitative

results analysis. To identify the Critical Failure Factors (CFFs), the participants were asked to pick the 5 that they felt were most applicable from a list of potential challenges. A 'reluctance to embrace CI culture change', 'a lack of education' and 'poor management communication' were identified as the top challenges from the options listed. These tools can be considered basic CI tools, commonly used for fundamental problem-solving. More complex tools were utilised less, indicating a greater focus on training could be required. Of the participants of this study, 9% worked in Validation. 24% of respondents were from the manufacturing area and worked directly on the production floor. It can be noted that CI initiatives, such as Lean, are more commonly implemented in manufacturing areas (McDermott *et al.*, 2021).

Nenni *et al.* discuss a case study of a multinational pharmaceutical company, implementing a Lean Management approach with 2 main projects for production: Re-engineer the layout flow and introduce a pull-system. VSM was used to identify waste which could be eliminated from the process, including rework and overproduction. The layout was redesigned in order to create a continuous flow and use the production space more efficiently. These projects are another example of successful Lean implementation in a pharmaceutical organisation (Nenni *et al.*, 2014).

Trubestskaya *et. al* investigate the implementation of Lean concepts into the Irish Medical Device industry, which like the pharmaceutical industry, must operate under very strict regulatory guidelines in order to guarantee product quality and patient safety. Despite this, there is evidence to support the successful implementation of Lean tools into the industry across large, medium and small enterprises, through the use of a variety of Lean tools and improvement of culture (Trubetskaya *et al.*, 2022).

Rybski e*t. al* discuss training a pharmaceutical company on Lean. Some of the key concepts identified for training topics are Lean tools such as 5S, VSM, 7 types of waste. 'Roles and responsibilities' and 'performance management' are also identified as key topics which indicates an understanding that personnel involvement is a critical factor to successful Lean implementation. Role-play is also used in order for participants to understand other's position and situation, which is claimed to strengthen participant acceptance of the Lean framework (Rybski and Jochem, 2016). In the case of Chowdary and George, effective use of 5-whys and VSM in developing an improved process is discussed. This is another example that a solid

understanding of the pharmaceutical manufacturing process was required to identify the issues that were hindering the process (Chowdary and George, 2012).

There are a number of topics identified that are observed across the literature regarding the implementation of CI methodologies, specifically Lean and Six Sigma. While there is a lot of overlap between the specific topics, the main themes discussed include: People, Process, Resources and Regulations. These factors were analysed in the literature for criticality to success for attempted CI implementation in general, and specifically in the pharmaceutical industry.

2.5.1. People

2.5.1.1. Culture

A culture of 'respect for the power of people' forms a strong base for the Lean principles, which can motivate people to learn and improve processes. Houborg describes a case study of a pharmaceutical company, 'Lundbeck', implementing Lean process improvements through a number of Kaizen events which significantly reduced lead time and increased productivity, the foundation of which relied heavily on adopting a culture of change with involvement from all levels (Houborg, 2010). A common challenge for the implementation for CI includes the adoption of a culture where CI is openly accepted and encouraged across a company. Resistance to culture change was identified as the greatest failure factor for the implementation of CI across the Irish pharmaceutical industry also (McDermott *et al.*, 2021). According to Antony et. al, if this issue is not addressed at the beginning, it is likely that the initiative will not last and will eventually be forgotten about (Antony *et al.*, 2017).

The issue of culture change was also discussed by Albliwi *et al*. This paper discussed the Critical Failure Factors (CFFs) observed for Lean Six Sigma across a number of sectors, including manufacturing. This is explored through a literature review of 56 published papers. It identifies 34 common factors that can impact the success of Lean Six Sigma including lack of commitment from management, training and education, communication and resources. The literature included in this review was published between 1995 and 2013, however, many of the failures highlighted in this paper are also observed in more recent accounts of CI failures. This paper discusses CI as a whole across many sectors, and does not focus specifically on the pharmaceutical industry (Albliwi *et al.*, 2014).

Research by Barclay *et al.* concluded that having a culture of continuous improvement, by embracing learning, is a strong indicator of the organisation's readiness to implement Lean methodologies. It is argued that a company whose employees can confidently say 'Failures are seen as an opportunity for improvement' and 'we are always making small improvements in our process' are ready to embrace Lean (Barclay *et al.*, 2021).

2.5.1.2. Management

Management openness and support is considered an enabler for CI implementation, including recognition of best ideas, and should be addressed as early in the process as possible. Similarly,

a lack of management attention is considered a factor for initiatives not being sustained (Antony *et al.*, 2017). This trend is also observed within smaller organisations implementing Lean tools (Alkhoraif *et al.*, 2019). McDermott's research identified that 49% of participants felt that CI was integrated or very integrated into the Management Review Process, which suggested a moderate commitment from leadership to implement CI within the Irish Pharmaceutical Industry (McDermott *et al.*, 2021).

2.5.1.3. Communication

Clear communication is an essential factor for successful Lean implementation. While smaller organisations may be at a disadvantage in some aspect, it can be argued that communication is more straight forward and employees work more closely together in smaller companies, which can be beneficial for introducing Lean initiatives (Alkhoraif *et al.*, 2019). Analysis by Laureani and Antony revealed communication as one of the top Critical Success Factors (CSF) for CI implementation across all organisations, regardless of size or industry (Laureani and Antony, 2012).

2.5.1.4. Training

Lack of training is also discussed as a CFF for the implementation of LSS, which can be due to the perception the training can be waste of money (Albliwi *et al.*, 2014). Training is a fundamental aspect for providing the base for a Lean enterprise to develop. A higher level of Lean training delivered can be linked to a stronger Lean culture, who are ready to embrace change (Barclay *et al.*, 2021). Identifying the correct team to solve a problem requires an assessment of individuals knowledge on the process. The typical size of team for a specific improvement project is 3-7 people (Byrne *et al.*, 2021). Sufficient training being a CSF for Lean Sigma implementation was similarly portrayed by Laureani and Antony as well as Seickmann *et al.* (Laureani and Antony, 2012) (Sieckmann *et al.*, 2018).

2.5.2. Process

2.5.2.1. Understanding of CI concepts

Sreedharan's analysis into CI CSFs also concluded that awareness and understanding of tools is essential for the success of Lean, Six Sigma and LSS implantation (Sreedharan *et al.*, 2018). This is reiterated by Seickmann *et al*., who delve into Lean implementation specifically for small and medium sized pharmaceutical production companies, who argue that management should have a clear understanding of the concept of a Lean Production System in order to successful implement one (Sieckmann *et al.*, 2018). To further this, Antony et. al also identified that limitations for LSS implementation includes a lack of clear standardised framework to follow (Antony *et al.*, 2017).

2.5.2.2. Process efficiency & knowledge

Inadequate process controls and Quality Control systems were identified as another limiting factor for Lean implementation (Alkhoraif *et al.*, 2019). Research by Garza-Reyes *et al.* supported this, concluding that the European Pharmaceutical industry was not at a sufficient level of Lean readiness. This study categorised the areas for potential Lean readiness. Based on the 'processes' within the industry, it would only require minor developments to achieve a state of readiness in this category. The 'process' category includes aspects such as 'elimination of unnecessary steps', 'a smooth and continuous process flow' and 'controlled and organised work zones', all of which are considered essential practices for successful implementation of Lean (Garza-Reyes *et al.*, 2016).

2.5.2.3. Clear defined goals & sufficient analysis

A clearly outlined strategy for achieving Lean should be pre-determined for successful implementation. Sufficient methods for monitoring data such as Key Performance Indicators (KPIs) and defect rates should be up-to-date and easily accessible in order to keep track of progress (Garza-Reyes *et al.*, 2016). Linking Lean Six Sigma into the organisation's business strategy has also been identified as a CSF (Laureani and Antony, 2012). Setting clear expectations for implementing LSS was also identified by Sreedharan as a critical factor for success (Sreedharan *et al.*, 2018).

2.5.2.4. Effective project selection

Byrne *et al.* clearly identifies the need for problem identification and subsequent appropriate project selection. The impact or benefit of each project should be assessed in order to maximise the potential success. A matrix to assess low to high 'impact' and 'effort' can be an effective strategy for project selection (Byrne *et al.*, 2021). The importance of effective project selection is reiterated in the review paper published earlier by Albliwi which highlights multiple accounts of poor project prioritisation as a key factor for CI failure (Albliwi *et al.*, 2014). This is also reiterated in Antony *et al.* who suggest project selection, prioritisation and tracking as key factors for successful introduction of LSS (Antony *et al.*, 2017).

2.5.2.5. External operation & Supply Chain

The scope of Lean implementation is often limited to the internal manufacturing sector of organisations, and does not commonly apply to the full value chain and reach more external aspects, such as the supply chain. This is discussed in the review by Alkhoraif *et al*., who assess the implementation of Lean in small and medium sized enterprises (Alkhoraif *et al.*, 2019). This finding is also supported by Argitantari *et al.*, who discuss the Lean application to Pharmaceutical Supply Chains and how it receives considerably less focus than manufacturing operations (Argiyantari *et al.*, 2020). Laureani and Antony also determined from their research into CSF for Lean Sigma implementation that extending these methodologies to supply chain is considered a low priority factor (Laureani and Antony, 2012).

2.5.3. Resources

2.5.3.1. Funding

The implementation of Lean methodologies can require significant financial investment prior to observing any benefits, which can be an inhibiting factor for many organisations. Alkorhaif *et al*, argue that this is particularly evident in smaller organisations, who are less likely to have excess financial resources to invest in these initiatives (Alkhoraif *et al.,* 2019). This point is also supported by Trubetskaya *et al*. who debate the larger organisations are usually better positioned to overcome the common obstacles that are observed with CI implementation. A case study by Chowdary and George on Lean implementation to a pharmaceutical manufacturing operation also discuss the importance of accurately assessing the cost of Lean projects prior to implementation. It is a priority for a company to justify the initial cost to implement the initiative, versus expected savings (Chowdary and George, 2012).

2.5.3.2. Equipment & materials

Outdated production machines can disrupt process flow. In the case of Nenni *et al*., the machines were updated with more technologically advanced models, which enabled a reduction in cycle time and supported the implementation of continuous flow. The upgrade also allowed for a more efficient use of the space within the production facility (Nenni *et al.*, 2014). Facility layout is also identified as an area of focus by Chowdary and George, who assess the floor plans to optimise equipment layout. 5S of the layout is also an effective method to maintain good housekeeping (Chowdary and George, 2012).

2.5.3.3. Time management

Insufficient time management can hinder Lean implementation, particularly for individuals with specialised knowledge and skills in the Lean tools (Alkhoraif *et al.*, 2019). This exact concept, however, was not as commonly addressed in the literature.

2.5.4. Regulatory Constraints

A strong focus on regulatory compliance can make it difficult to make process changes to commercially approved products. Regulatory CI actions that impact the manufacturing process may impact the drug characteristics and therefore may require a level of submission or notification to regulatory authorities. It is important that a formal change management process, which incorporates adequate risk assessment is completed for any significant changes to a process. This extra workload therefore discourages more drastic changes and result in a focus on the use of tools that would only address more basic issues, that would not affect product functionality and safety (Trubetskaya *et al.*, 2022)

There is also a fear that changes to a process, if not performed appropriately can be result in product defects. Defects often result in an increase in workload, rework and resources for corrective actions, which is essentially an increase in process 'waste'. A fear of product recall that may occur due to a quality defect as a result of CI is concern of organisations looking to update their process (McDermott *et al.*, 2021). Recalls are bad for the reputation and subsequently the revenue of an organisation.

Regulatory pressure to remain compliant can be considered a challenge, but the organisation must be able to quickly adapt to new and updated legislation to maintain adequate levels of quality (Trubetskaya *et al.*, 2022). Interestingly, McDermott et al. revealed that a regulatory focus was ranked as the lowest driver for CI (McDermott *et al.*, 2021).

High costs and heavy workloads are associated with revalidation on any process change that can come from Lean or Six Sigma implementation, which can make pharmaceutical organisations reluctant to make changes to their process. Pavolic discusses that this is an inhibitor for process improvements, which is why the pharmaceutical industry is behind other manufacturing industries in embracing Lean and Six Sigma initiatives (Pavlovic, 2012).

Audit preparation to ensure the company is always audit ready for all regulatory visits can take resources that would otherwise be used for CI. There has recently been an increase in regulatory bodies working together to assess the impact of potential collaboration for mutual recognition agreements (MRA's) on drug inspections between EMA and FDA, which could potentially

reduce the level of duplicate inspections (McDermott *et al.*, 2021). This demonstrates an effort to reduce the regulatory pressure on pharmaceutical manufacturers.

2.6. CI implementation in the Pharmaceutical Validation process

If changes are made to a validated manufacturing process once marketing authorisation for a drug is acquired, it must be assessed to determine if there is risk associated with the change. This can include changes that affect the manufacturing process, materials, equipment or tests. The process for re-validation of any aspect of the process must therefore must be considered before any changes are made to ensure there is no risk to compliance. Any CI initiatives therefore, must be assessed as they may impact the drug performance or manufacturing process. In this case notifications or submissions to regulatory bodies may be required if the process will differ from the original approved marketing authorisation.

A risk-based approach may be a solution to ensure regulatory requirements are met in the validation process. In the case where the impact to the product quality from the changes are determined to be minimal, using a risk-based approach, the changes may be documented in the product annual report to the FDA (FDA, 2014).

A significant challenge highlighted for implementing Lean Validation is a tightly regulated work environment, such as the one evident in the pharmaceutical industry in Ireland. It can be noted that in the study by McDermott *et al*. that 45% of participants voted that regulatory compliance is a barrier to CI programs. These respondents identified 'Fear of extra validation activity' as the main reason for barriers to CI in a regulated environment, of which 75% agreed (McDermott *et al.*, 2021). There are some published works discussing Lean implementation for the manufacturing processes, however there are limited publications focusing on a Lean approach to validation within the pharmaceutical and biopharmaceutical industry.

2.6.1. Possible Applications of Lean in Validation

Automation of the validation process can aid in efficient data collection and storage, while eliminating the processing of redundant information. Process Analytical Technology (PAT) aims to focus on a science-based approach for Good Manufacturing Practices (GMP), by designing, analysing and controlling the process through critical parameters (Kirshcner, 2010). The principle of PAT is based on attaining a thorough process understanding, which can lead

to more a focused Quality by Design approach, by highlighting trends and closing gaps in process development (Chew and Sharratt, 2010). This tool therefore has potential to minimise waste in the validation process.

Value Stream Mapping (VSM) is a valuable lean tool that can be effective in maximising efficiency and time for a process, by assessing the current flow and determining a more optimal future process flow. It can be effective in reducing bottlenecks, set-up times and process downtime, commonly seen in manufacturing processes (Khan *et al.*, 2020). This lean tool is conventionally used for optimising a manufacturing process or service, however, there could be potential for it to be applied to a validation process.

Failure Modes and Effects Analysis (FMEA) is a tool used to assess the potential impact if a failure or defect was to occur in a certain step of a process. The idea is to assess the risk associated with a step and determine if actions need to be taken to prevent the fail, depending on the chances of occurrence and potential impact (Lewus and Sidor, 2007). This tool also has the potential to benefit the validation process, as validation is one of the activities carried out early in the cycle of product introduction, and therefore solving any potential problems that may occur down the line will reduce the negative impact later in the process.

While the literature on CI implementation in validation procedures is limited, a variety of CI tools are commonly adopted in the pharmaceutical industry and the potential for their application should be explored to implement further improvements across the industry.

Chapter III

3. Research Methodology

3.1. The purpose of research

'Research' is defined as a systematic investigative process that aims to determine outcomes and draw conclusions on a particular subject. The purpose of completing research is to explore the information and data that is gathered and available, in order to draw conclusions on the specific objectives that are set out prior to beginning the research. The purpose of this research is to explore the hypothesis that the implementation of CI initiatives may have the potential to improve the efficiency of the pharmaceutical industry.

3.2. Collection of Primary Data

The main aim of this research is to explore the concept of 'Lean Validation' and other means of CI implemented into the Validation sector of the pharmaceutical industry in Ireland. CI initiatives are common across the pharmaceutical industry within the manufacturing process, which is well documented in the literature, but there is limited research into the implementation of these initiatives specifically in the validation sector. The main objectives of the research are to determine to what extent have CI initiatives, including Lean or Six Sigma tools, been adopted into the validation sector and what are the drivers and challenges associated with this.

The research strategy will be conducted through a mixed-method approach, consisting of a qualitative and quantitative data analysis. The design of the primary data collection will involve a survey and an interview with eligible participants who have experience working in the pharmaceutical industry in Ireland.

The survey design will consist of both open and closed-ended questions in order to perform quantitative and qualitative analysis. It will be created on Google Forms and will be distributed online though email, WhatsApp and LinkedIn to professionals who were employed in the pharmaceutical industry in Ireland. The survey was structured to gather additional information from individuals specifically with experience in the Validation sector or in implementing CI initiatives in the pharmaceutical industry. The format of the closed-ended questions in the survey will be 'Yes or No' where the participants can provide one answer, or in the form of multiple choice questions, where all options that apply can be selected. The open-ended

questions will allow for the participants to type their opinion or perspectives into the open space provided.

The interview will be conducted with a Subject Matter Expert (SME) in the validation process. The participant is employed as a 'Validation Engineer' in a top ranking multi-national pharmaceutical company, with over 5 years of experience in the industry. The interview will consist of both open- and closed-ended questions in order to attain an appropriate level of detail on the subject of CI implementation specifically within the validation process. Open-ended questions will be used in order to gather an unbiased perspective and care will be taken in selecting the questions to ask to ensure the answers of the interviewee are not influenced by 'leading questions', based on the information highlighted through the secondary research.
This is to guarantee questions are appropriate and cannot be misinterpreted (Burgess, 2001).

3.3. Analysis of Primary Data

Both the interview and the survey will be analysed with different approaches based on the nature of the data collected. The questions for both will be designed to gather information that could be compared and data that could potentially complement each other.

The survey data will be analysed using separate approaches for both the quantitative and qualitative data collected, which will come from the mix of open- and closed-ended questions within the survey. Different forms of data analysis will be performed depending on the nature of the question and subsequent data collected.

A quantitative approach will be used to analyse the initial closed-ended questions. This will be conducted by exporting the data collected from the Google Form to Microsoft Excel to perform numerical analysis to determine the significance of the data. Conclusions will be drawn on the data based on the statistical results.

A qualitative approach will be used to analyse the open-ended questions from the survey. Individuals who confirm to have experience in either CI implementation or in the Validation process will be subsequently asked open-ended questions, which will be analysed using an interpretivism approach to assess if there are any common themes that emerge from the data.

Interview data will be analysed with a primarily interpretivism approach, in order to gain insight into the opinion and perspective of the interviewee. The data collected will be qualitative in nature and therefore must be analysed appropriately, ensuring to remain objective so that interview data is not biased or inaccurately analysed. Identification and analysis of the themes that emerge from the data collected will be performed. This data will also be analysed in conjunction with the data and conclusions drawn from the survey, in order to determine if there are similarities or discrepancies between them.

3.4. Justification for Chosen Methodology

A mixed-method approach, consisting of quantitative and qualitative analysis, is considered the most appropriate technique for the nature of this research. While validation and continuous improvement (CI) implementation are well understood and researched concepts individually, the combination of the two is not widely discussed in the current literature. Therefore, a mixed-method approach to the study, through survey and interview, is the most comprehensive way to satisfy the research objectives.

3.4.1. Research philosophy

There are 4 main types of research philosophy, which include positivism, realism, interpretivism and pragmatism (Saunders *et al.*, 2019).

- Positivism – this approach is based on the belief that the research setting and research subjects are independent of each other, and one will not have an impact on the other. This is usually explored through a highly structured, quantitative approach and is analysed objectively.
- Realism – is based on a 'natural' setting of the world, regardless of whether it is perceived that way or not. This objective approach aims to explain the underlying mechanisms on why certain circumstances are observed.
- Pragmatism – this approach is based on the researcher focusing the research exclusively on practical and relevant issues. This can therefore be conducted using a variety of research methods, depending on the research subject.
- Interpretivism – typically analysed through a qualitative, subjective approach. This philosophy is based on the belief that our ability to interpret the environment is relevant and valuable. This approach can be subject to bias by the researcher.

The philosophy of this research will be based on interpretivism and positivism approaches, as these philosophies are the most appropriate for the nature of the data to be collected. A positivism approach will be used to analyse the survey results through the quantitative analysis of the results and presentation of the findings through statistics. An interpretivism approach will be used to analyse the data of a qualitative nature from the interview and the open-ended questions from the survey. Due to the subjective nature of this philosophy, care must be taken to ensure the results are not subject to bias.

Saunders' Research Onion is a well-studied model that details the levels of decisions or 'layers' used to develop a research methodology. The outer level describes the research philosophy, which is the system of understanding or beliefs about how knowledge is developed (Saunders *et al.*, 2019).

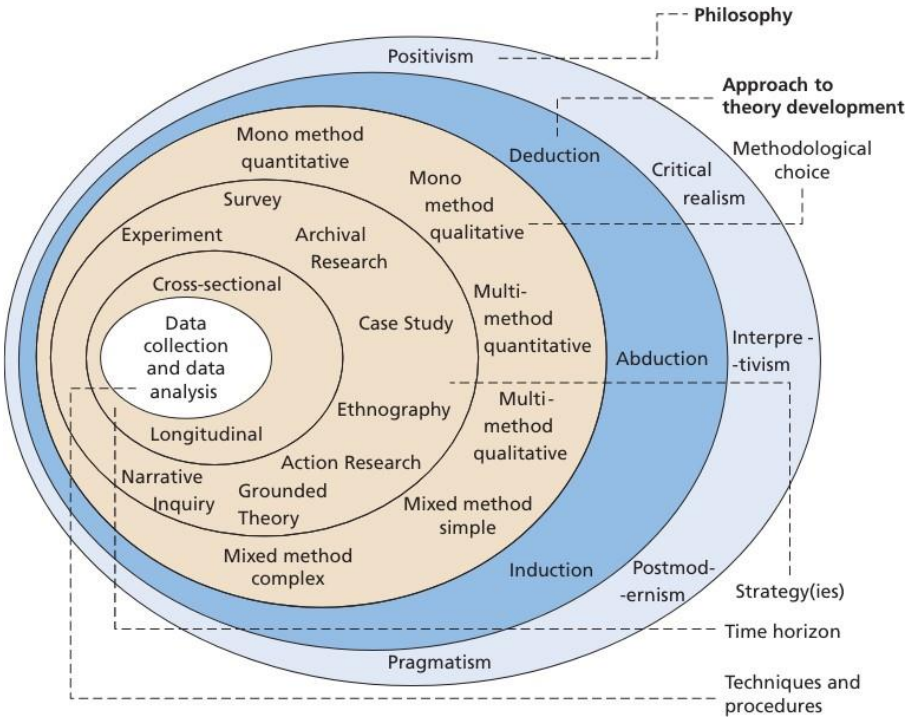

Figure 3: The Research Onion (Saunders et al.*, 2019)*

The main research philosophies that will be observed in the collection and analysis of this research will be interpretivism and positivism. The interpretivism philosophy will be applied to the qualitative analysis which will be gathered through the interview and the open-ended questions in the survey. There are 5 types of approaches to qualitative analysis of results. Ethnographic research is the most applicable to the nature of this study as the research is

focusing on the themes and tendencies for a specific group within the pharmaceutical industry, and their beliefs and behaviours regarding the subject (Elkatawneh, 2016).

The survey will capture a broader range of data and information in general which will be analysed through interpretivism and positivism philosophies. The data will also be statistically analysed to determine credibility and significance. A pilot survey will be created and sent to a number of participants to provide feedback on the format and structure of the survey prior to initiation of the data gathering. This feedback will be used to devise the survey questions to ensure there was no ambiguity with what data is to be collected, to ensure it is aligned with the research goals and objectives. The survey questions were designed to be unambiguous in order to incite reliability in responses. Reliability would be considered evident in a study if the study was to be repeated in the future and it was to incur consistent and reproducible results.

3.5. Target participants

The research purpose and aims of the study will be explained to participants prior to agreeing to partake in the research. They will be informed that the research is being conducted for the purpose of the author's dissertation for the completion of MSc in Pharmaceutical Business and Technology with Griffith College and Innopharma. Participants have the right to withdraw consent for participation at any point in the process, which will be highlighted prior to commencing data collection.

The target participants for the survey are employees in the pharmaceutical industry in Ireland. The survey will be generated online and will be distributed to participants through email, WhatsApp and LinkedIn. The respondents will be asked a qualifying question as for the survey to determine if they are eligible to participate in the research, which will ask if they have experience in employment in the pharmaceutical industry in Ireland.

The initial questions in the survey are applicable to all respondents who work in the pharmaceutical industry, regardless of the department or sector. Individuals who confirm that they work specifically within Validation or CI implementation will be asked further open-ended questions to gather their opinion and personal experience, which will be analysed through an interpretivism approach.

Participants who work in or have been involved with validation will be asked their opinion on whether Lean or other CI initiatives are evident in the validation process. It will then assess what they believe the greatest challenges and drivers to CI implementation are in validation. Furthermore, participants who have been involved in forms of CI implementation will be asked if they have experience working on these specifically within the validation process.

Inclusion criteria

The participants are required to be working or have experience working in the pharmaceutical industry in Ireland to be considered eligible to partake in the research. Individuals with experience in Validation and CI implementation will be asked additional questions based on their experience.

Exclusion criteria

The responses from participants who do not meet the inclusion criteria or do not agree to the voluntary participation section of the survey will not be considered for the data analysis. These criteria will be determined from Question 1 and 2 of the survey, which are marked as required to ensure this information was documented prior to data collection.

3.6. Conceptual Framework

The literature review has indicated that there is limited information in the current published literature regarding CI implementation into the validation sector of the pharmaceutical industry. While both topics are well documented and understood, the cross-over or interaction between the two is not widely discussed. An objective of this research will be to determine if the participants perceive the combination of the two practices together is as seldomly observed, as it is in the published literature.

Another one of the main aims for the research analysis process will be to identify any key themes that emerge from the data regarding the common tools, challenges and drivers associated with Lean or CI implementation in the Validation sector. The data will be compared from the interview and survey to draw conclusions on whether there is potential for 'Lean validation' to benefit the pharmaceutical industry.

As indicated in the literature there are a number of challenges associated with the implementation of CI methodologies within the pharmaceutical industry. These factors, which can be considered 'independent variables', are presented in the Conceptual Framework detailed in Figure 4 below. This model displays the hypothesis that there are currently a number of challenges associated with the implementation of CI within the validation sector in the pharmaceutical industry. The 'dependent variable', or effect in this case, is the level of success of CI implementation within the pharmaceutical organisation. The current hypothesis states that the perception of these challenges will impact the extent to which CI initiatives are implemented.

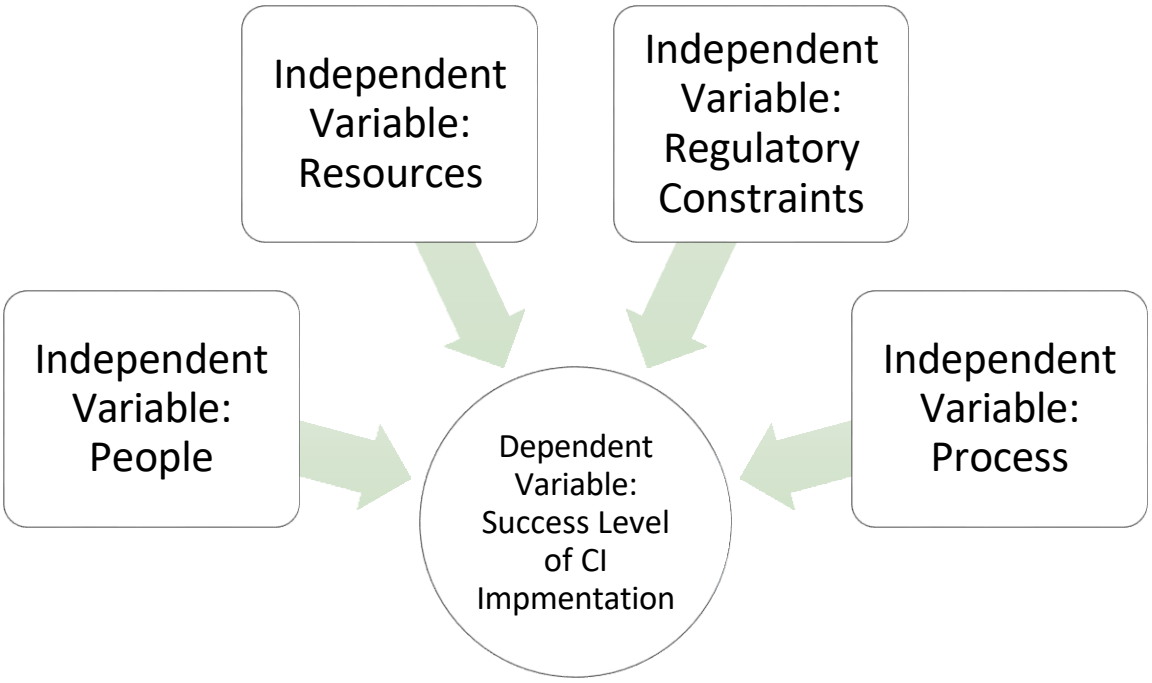

Figure 4: Conceptual Framework

3.7. Ethical Considerations

All primary data collection and subsequent analysis will be performed in compliance with the ethical principles of Innopharma and Griffith College. The anonymity and confidentiality of the participants will be protected throughout the research. The research does not involve any area that could be considered politically, racially or commercially sensitive. The participation of the research is completely voluntary.

The participants for the interview will be provided with a 'Participant Information Letter' which will provide information on the research process and participation details. They will also be asked to sign an 'Informed Consent Form', confirming that they are aware of the conditions associated with participation of the research.

Question 1 of the survey will include a participant involvement consent agreement and only respondents who agreed 'Yes' to the terms will be considered for the results analysis. The question will be marked as 'required' to ensure all participants are aware of their right to withdraw consent at any point. During the design process of the survey, it will be ensured that only questions relevant to the research objectives will be included. Names, ages or any other personal information that is not relevant to the research will not be requested. The names of the pharmaceutical companies where participants were employed will also not be collected for confidentiality purposes.

Responses only from participants who are deemed eligible to be included, by meeting the inclusion criteria, will be included in the analysis process to guarantee the integrity of the data and ensure to mitigate any misrepresentation of the findings. The handling and storage of the data will be controlled throughout to ensure the confidentiality and integrity of the data.

Chapter IV

4. Findings and Analysis

This section will present the results of the primary research conducted through the survey and SME interview. The data was analysed appropriately as described in Chapter III and is discussed below with regards to the research aims and objectives.

Through the distribution of the survey through email, WhatsApp and LinkedIn a total of 57 responses were gathered. Of these 57 responses, all participants except 1 met the inclusion criteria by agreeing to participation and having experience working within the pharmaceutical industry in Ireland. Therefore the sample population for the survey was 56. The survey responses from 1 respondent that did not meet the inclusion criteria was not included in the data analysis.

An in-person interview was conducted with a participant who is an SME in Pharmaceutical Validation, with extensive experience working with the requalification process. The interviewee was familiar with the term 'Lean Validation' and their understanding of the concept was that it was a process that involved optimising the validation process by removing waste.

4.1. Observation of CI initiatives within the Pharmaceutical Industry

Of the 56 respondents to the survey, 52 had observed the use of CI initiatives, including Lean or Six Sigma, within their pharmaceutical organisation. Refer to Figure 5, which shows a visual representation that 93% of respondents have seen some form of CI methodology introduced into their organisation in at least one department.

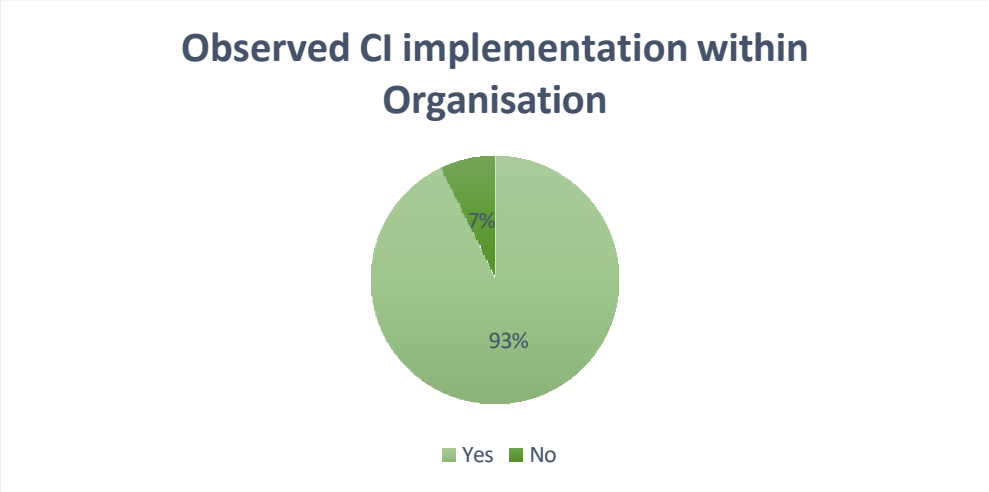

Figure 5: CI Initiatives implemented into participants organisation

4.2. CI Tools observed within Pharmaceutical Organisations

The CI tools that were observed within their organisations by the respondents are presented in Figure 6. A list of tools, which included common tools from Lean and Six Sigma methodologies was provided in the survey and the respondents were asked to select any and all that had been implemented within their organisation, regardless of department. The most common tools observed were 5S and 5-why's, which were observed in 90% and 88% of cases. Gemba, Fishbone Diagrams and Kanban were also popular tools that were all identified in over 50% of responses.

Single-Minute Exchange of Dies (SMED) was highlighted as the least common tool implemented with less than 10% identifying this tool as being used within their organisation, with Error-Proofing and Bottleneck identified in just 21%. As part of the answer to this question, the respondents were given the option to include any other tools that have been implemented that were not included in this list, for which 'Method 1' was the only tool identified by 1 participant.

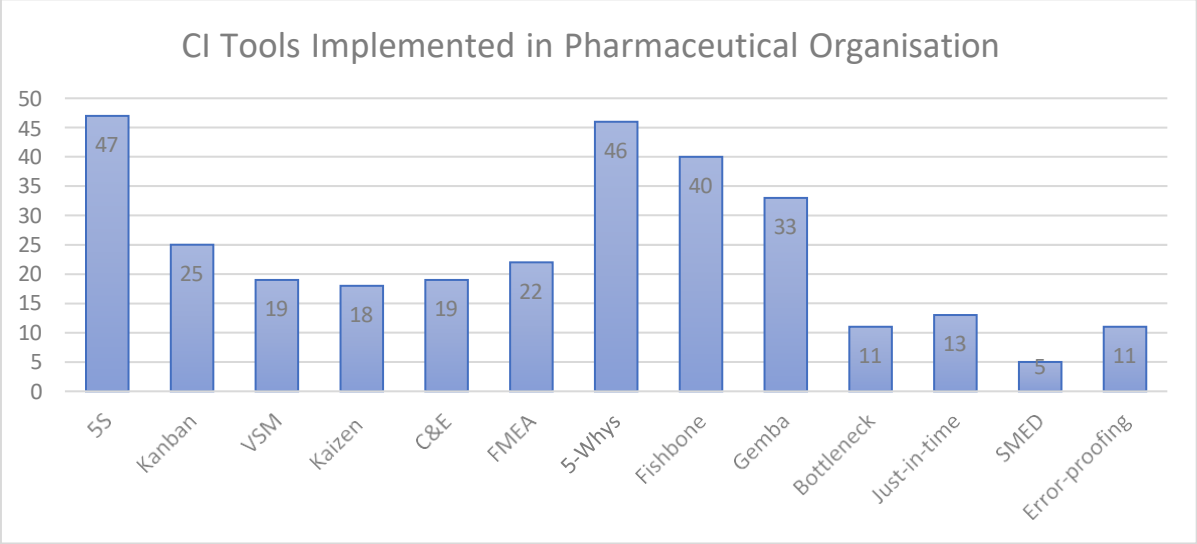

Figure 6: CI tools implemented in Pharma Organisations

4.3. Drivers for CI implementation

Participants were asked to explain what they perceived to be the main drivers, or motivation, to implement CI initiatives within their pharmaceutical organisations. This question was an open-ended question which allowed the respondents to offer their unprompted opinion on what they believe are the main motivations for pharmaceutical companies to embrace a culture of CI, and implement methodologies to achieve this. The responses were analysed and the main themes observed are summarised in Figure 7 below.

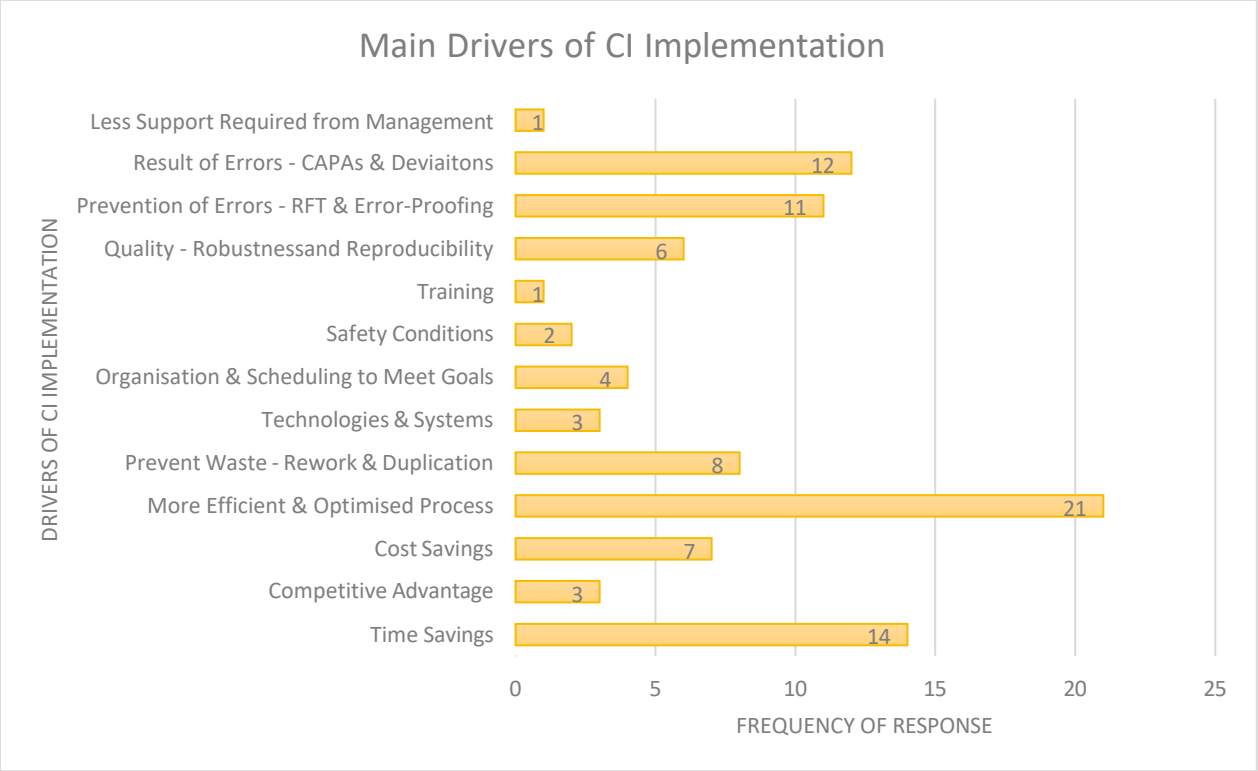

Figure 7: Main Drivers for CI Implementation

The main driver identified was to achieve a 'more efficient and optimised process', which was distinguished in 40% of responses. The second most common driver identified was to achieve 'time saving'. This highlights that for the respondents 'time' is perceived as a valuable resource for pharmaceutical organisations, as it ranked higher than 'costs savings' as a motivator to implement CI initiatives, with 27% identifying 'time' compared to 13% for 'costs' as a key driver. Similarly 'Time saving' and 'process efficiency' were themes also discussed by the interviewee for drivers of CI initiatives. Conversely, an aim to improve safety conditions, technologies and systems were less commonly identified as key drivers for CI implementation.

Other key drivers identified for CI implementation included actions that are taken as a 'Result of Errors', including quality events and deviations, as well as actions that are taken to 'Prevent Errors' or potential quality events. This indicates the respondents are aware of the importance of a process that has a quality on focus and controlling mistakes and organisations are prepared to invest in initiatives that will enforce this.

4.4. Main Challenges Associated with CI Implementation

Another open-ended question within the survey was used to assess the most prominent challenges that are associated with the implementation of initiatives. This was analysed by categorising the responses into key themes, which have been presented in Figure 8 below.

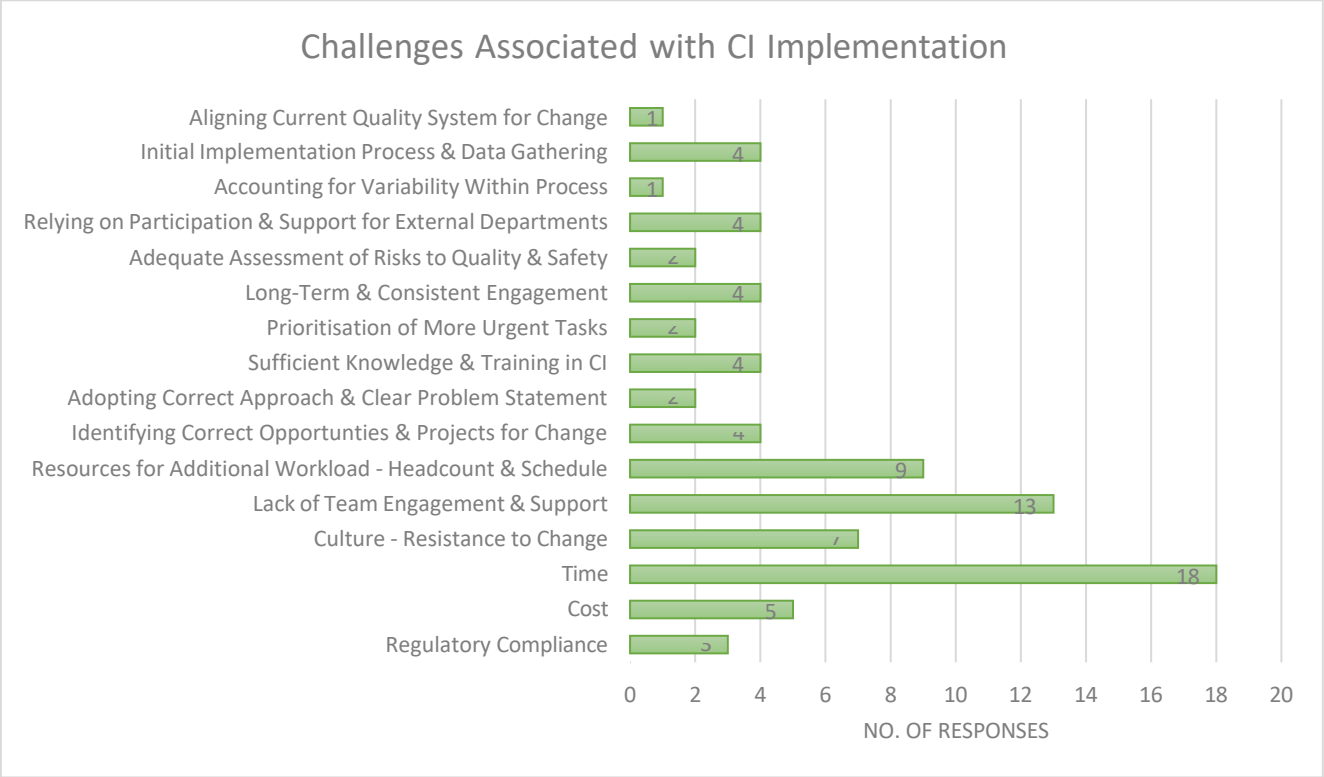

Figure 8: Main Challenges Associated with CI Implementation

The most commonly identified challenge was 'Time', with 36% of respondents listing this as one of the main challenges relating to CI implementation. Many of these respondents noted that a significant investment of time is required, particularly in the beginning of a CI project, in order to establish the project before any of the benefits are experienced. A common concern observed is that many teams are not prepared to invest the adequate amount of time and other resources to ensure that CI initiatives are implemented successfully. Other resources that were identified as critical were 'Adequate Headcount' and 'Knowledge of CI tools'.

The involvement of people within the industry was also a key challenge that was reported. A 'Lack of Engagement' from both the immediate validation team and from other departments were identified as factors that contributed to challenges in implementation. A company culture that exhibits a resistance to change is also a key challenge that was presented.

These findings are consistent with the result of the interview, which indicated that 'Lack of team engagement' and 'tight time constraints' contribute to the challenges of successfully implementing a CI initiative.

4.5. Participants with Experience in Validation

Of the 56 participants included in the sample population of the survey, 30 declared to have experience working specifically within the field of Pharmaceutical Validation. There 30 participants therefore were asked additional questions, based on their experience which related directly to CI implementation within Validation. These responses will be compared to the responses of those working in the Pharmaceutical Industry in general in order to determine if the themes identified follow a similar trend in the Validation sector.

4.5.1. Use of CI & Lean tools within Validation

Of the 30 respondents with experience working specifically with Validation, 18 (60%) reported having seen CI initiatives, such as Lean tools, used within the Validation process. Interestingly, 40% of respondents reported having never seen the use of CI initiatives within the field. This is a strong contrast to the 93% of respondents who have observed CI tools within some aspect of their pharmaceutical organisation, which indicates there may be some reluctance to implement CI initiatives during Validation.

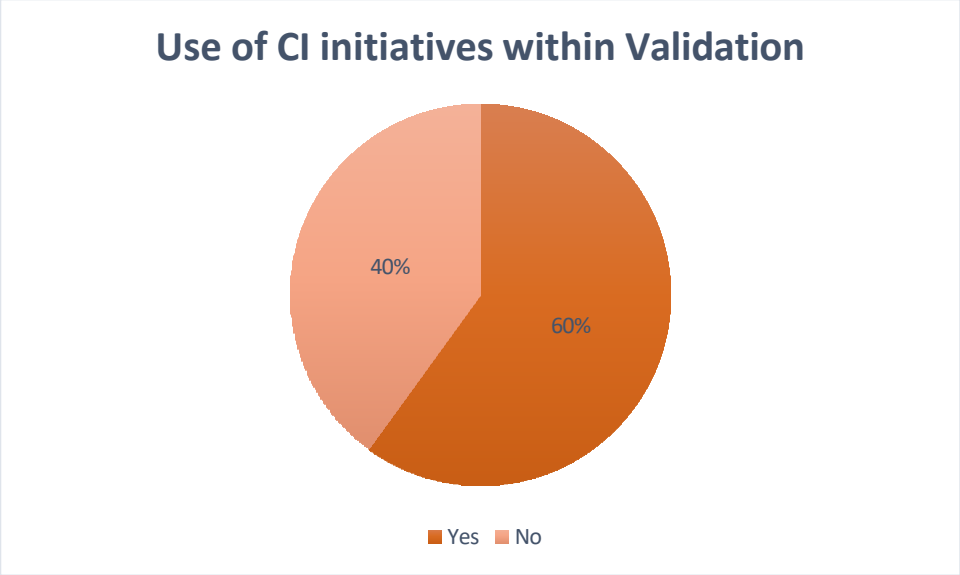

Figure 9: Use of CI Initiatives within Validation

In contrast, the interviewee expressed that the global pharmaceutical organisation where they are employed has made significant efforts to implement CI initiatives within the Validation department, which have included Lean tools and principles.

4.5.2. Areas within Validation in which CI initiatives have been implemented

The 18 participants who answered 'Yes' to having seen CI tools within Validation were asked specifically what areas they had observed this in. An open-ended question was used to gather their perspective and the main themes observed are summarised in Figure 10 below.

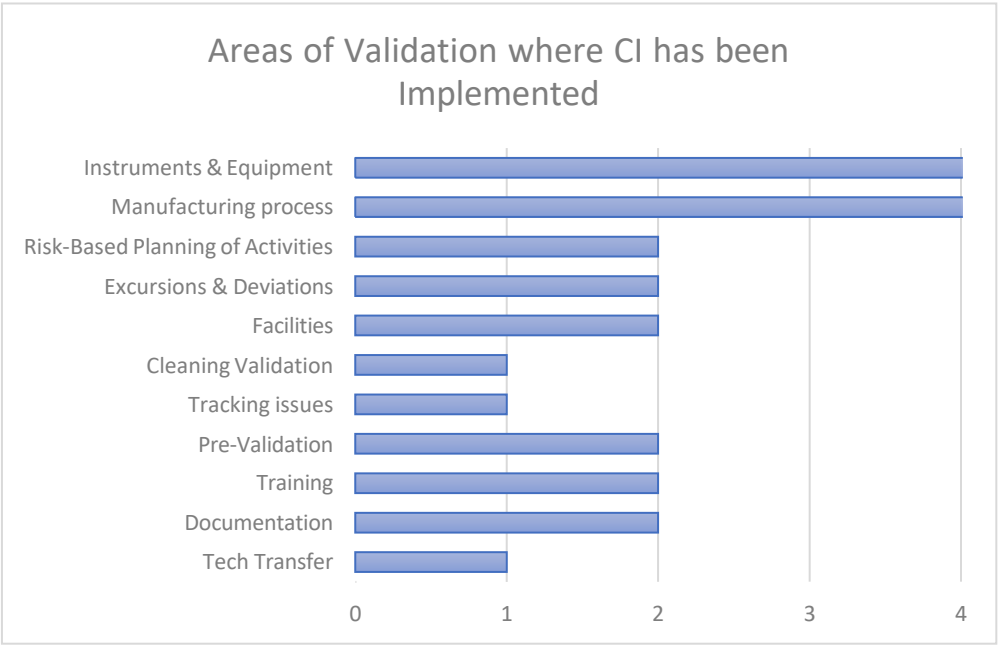

Figure 10: Areas of Validation Where CI has been Implemented

As the responses given were specific and there was not a very high level of overlap within the themes identified, Table 2 below provides more detail on the themes and contains more specific information answers provided by the respondents.

Theme Identified	*Additional Detail Provided*
Instruments & Equipment	Qualification of instruments; Temperature mapping; Requalification of equipment
Manufacturing Process	Specific manufacturing steps - Upstream, Downstream, Purification, Harvest; Scale-up; Establishing Standard Work; Development batches
Excursions & Deviations	RCA; CAPAs
Facilities	Validation of Labs; Cleanrooms
Tracking Issues	Visualisation of ongoing issues & resolution
Pre-Validation	Planning and scheduling of validation activities;
Documentation	Optimisation of format; Digitalisation for recording and storage

Table 2: Details of Themes Identified from Areas of Validation

The most common areas identified for CI initiatives being adopted within validation are for 'Instruments & Equipment' and for the 'Manufacturing Process', which we both mentioned in 22% of responses. As discussed previously from the findings of the Literature Review that CI tools, such as Lean and Six Sigma tools, are quite common and have a relatively high success rate of implementation within the manufacturing process of pharmaceutical products. As these initiatives are commonly established within the manufacturing process to improve efficiency, it could be argued that implementation of similar initiatives into the validation process for manufacturing could be more straight-forward, which would be supported by the observation that it is most commonly seen in this area of validation.

Similar areas were discussed by the interview participant, who mentioned there were a decent number of Lean tools implemented into the process of instrument and equipment validation. Training, documentation and deviations have also been areas of interest for incorporating these initiatives, which are in line with the results presented in the survey. A more specific example

of an area provided in the interview was within the storage space for equipment specifically used for the validation process, such as temperature mapping probes for qualification of instruments and equipment.

4.5.3. CI Tools implemented in the Validation Process

The participants with validation experience where then asked to select the CI tools that they have seen in implementation within the validation process, from the same list of tools that they previously selected from for CI implementation into their organisation in general. The CI tools that were selected are presented in Figure 11. 5S, FMEA, 5-Whys and Gemba presented as the most popular tools.

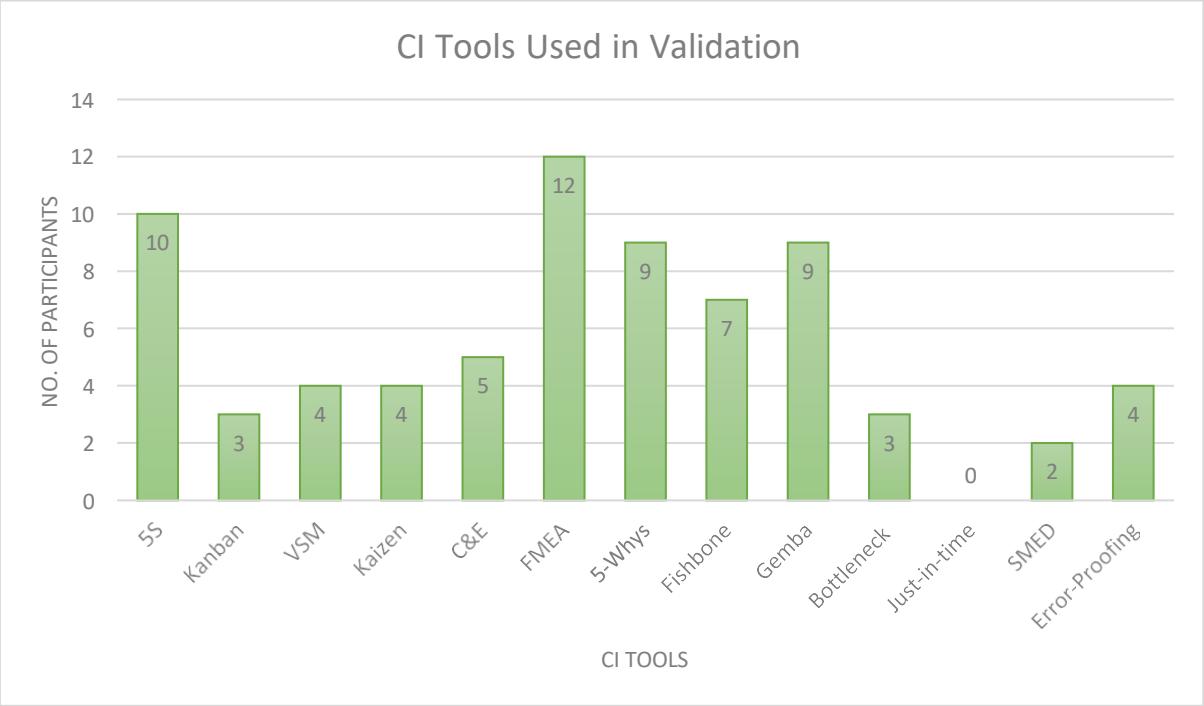

Figure 11: CI Tools Used in Validation Process

A comparison of the tools that have been implemented in the pharmaceutical industry both in general not specific to any department, and the tools identified specifically in the Validation process is shown in Figure 12 below. As the sample size for the tools used in organisations in general is larger, compared to Validation specifically, the figure presents the popularity of the tools in a percentage based on how often the tool was selected across the responses given.

It is evident that same tools have comparable levels of popularity across both groups of data. The main differences in the tools identified specifically for the Validation process is the use of FMEA, which was classified in 70% of validation-specific responses, compared to 42% for

generally used tools. This tool, and 'error-proofing' tools, were the only tools that were categorised as being more popular specifically in validation, compared to the general process.

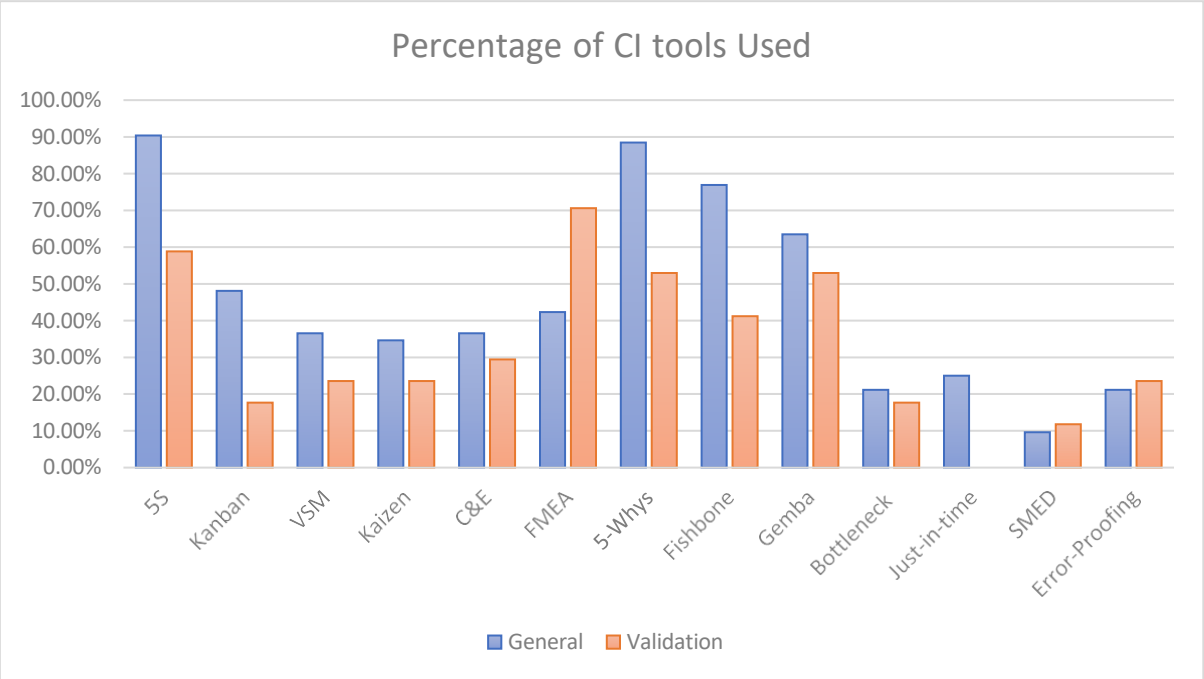

Figure 12: Comparison of Tools Implemented In General Vs In Validation

Similarly, the interview participant mentioned that some of the most common tools used are 5S and FMEA. In contrast, they identified Kanban as another one of the most popular tools, which was not as common in the survey results. The interviewee discussed a 5S and Kanban system that was introduced for the use and storage of validation equipment, to streamline the process and minimise time wasted searching for equipment in use and to ensure all GMP equipment was accounted for to guarantee compliance.

Furthermore, the interviewee highlighted the usefulness that VSM can have in areas of the validation process. Visually analysing current processes and assessing areas for improvement is a key method to remove waste. An example of the use of VSM in the Cleaning Validation process resulted in improved sampling maps designed to maximise efficiency of sampling routes, to reduce time waste.

4.5.4. Level of Success for CI Implementation within the Validation Process

The same participants were then asked to rate the level of success for the implementation of these tools within the validation process on a scale from 'Not at all Successful', 'Not very

successful', 'Somewhat successful', 'Quite successful' and 'Very successful'. The responses are shown in Figure 13. Interestingly, all respondents believed that the implementation of the CI tools were at least 'Somewhat successful'. 61% of respondents started that they believe the implementation of the tools and initiatives was 'Quite Successful'.

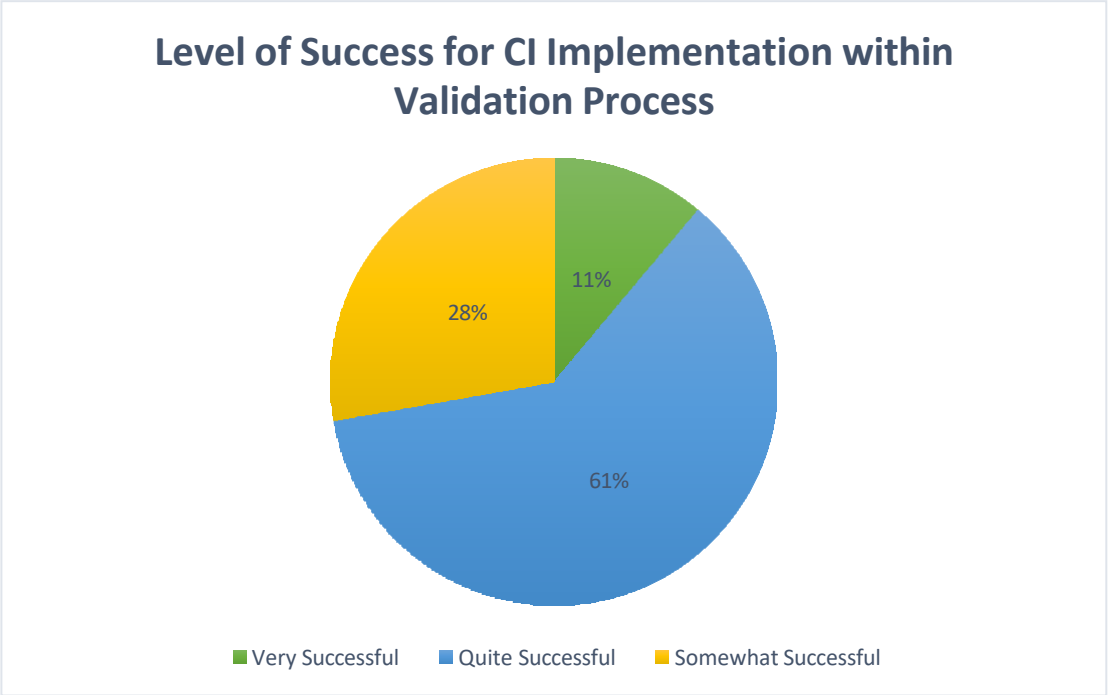

Figure 13: Level of Success for CI Implementation within Validation

4.6. Level of Reluctance to Implement CI Tools within the Validation Process

All respondents were asked a 'Yes/No' question on whether they perceived there to be a reluctance or hesitation to implement CI tools within the Validation process. To this the responses were split almost in half. 57% answered 'Yes', with 43% answering 'No', which is presented in Figure 14 below. The almost even split indicates that there is a considerable portion of participants that believe that there is some hesitation in attempting to implement CI tools within Validation.

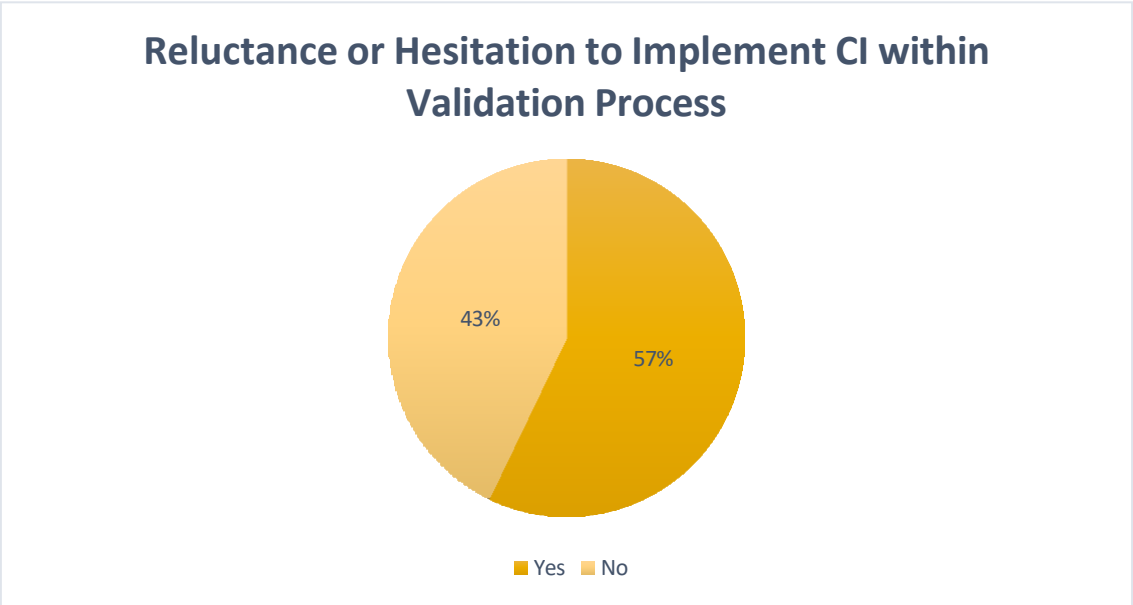

Figure 14: Reluctance to embrace CI within Validation

4.6.1. Factors Contributing to Reluctance of CI Implementation in Validation

In order to explore why there may be hesitation to embrace these CI initiatives within Validation, the respondents who answered 'Yes' to the previous question where then asked to explain their reasoning behind this and list the factors that they believe contributed to this. As this was an open-ended question, the results were critically analysed and the main emerging themes were selected and the frequency of these themes mentioned is summarised in Figure 15.

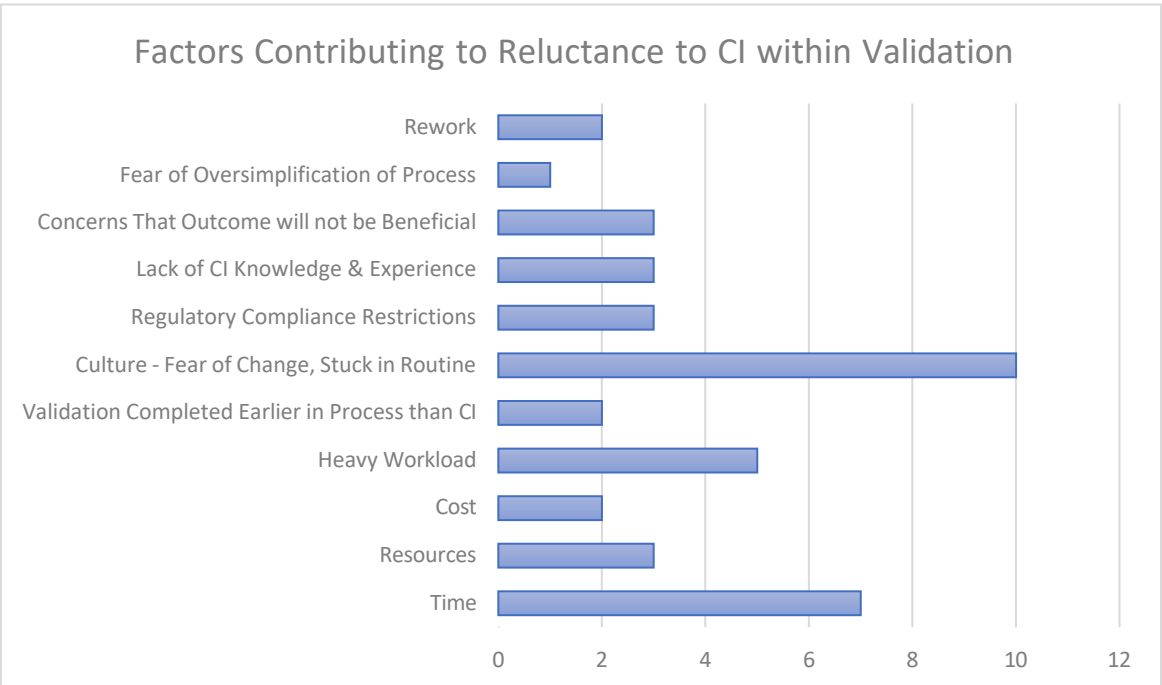

Figure 15: Factors Contributing to Hesitation for CI Implementation within Validation

Physical considerations for completing the tasks, which include factors such as 'Costs', 'Resources', 'Time' and 'Heavy Workload' were accounted for a substantial proportion of the factors. However, it is worth noting that the factors that were most frequently presented were related to people's attitudes towards the concept of embracing CI. This includes factors such as 'Fear of Change', 'Concerns of Insignificant Benefits' and concerns of 'What could go wrong', which have the possibility to result in regulatory incompliance and rework.

4.7. Areas That Could Potentially Benefit from a More Lean Approach

Participants were asked if they thought there were areas within Validation that could potentially benefit from a more Lean approach, to which, 93% responded that they believed there were, as presented in Figure 16 below.

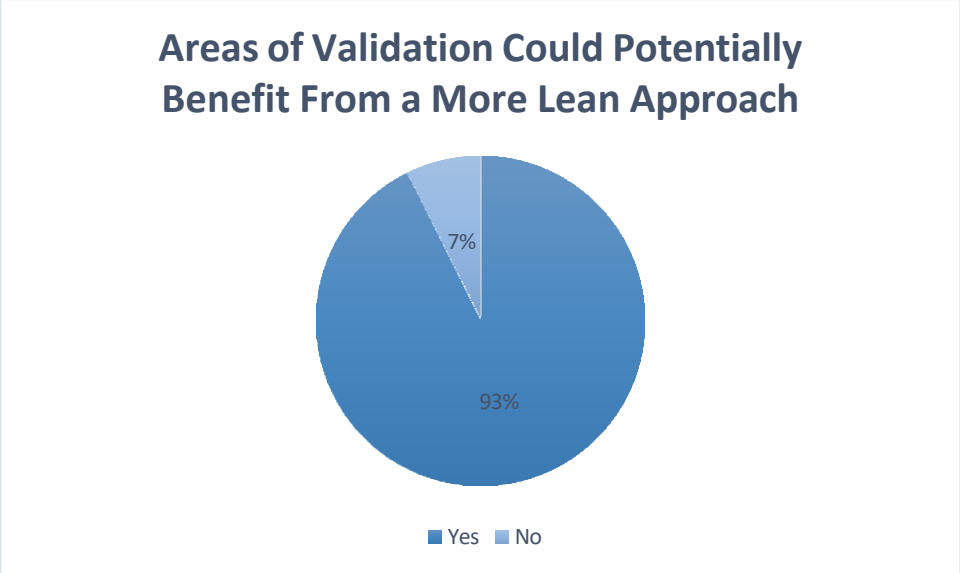

Figure 16: Areas of Validation Could Benefit from A More Lean Approach

4.7.1. Specific Areas of Validation that Could Benefit from CI Tools

The respondents who answered 'Yes' were asked to elaborate and mention what specific areas within Validation do they think could benefit from CI tools, such as Lean. The areas that were identified are presented in Figure 17. 'Documentation' & 'Instrumentation' were the key areas that were mentioned in the responses. 'Sufficient project planning' and 'adopting a risk-based approach' to the design of the validation process were also expressed as areas that could be improved as a result of CI.

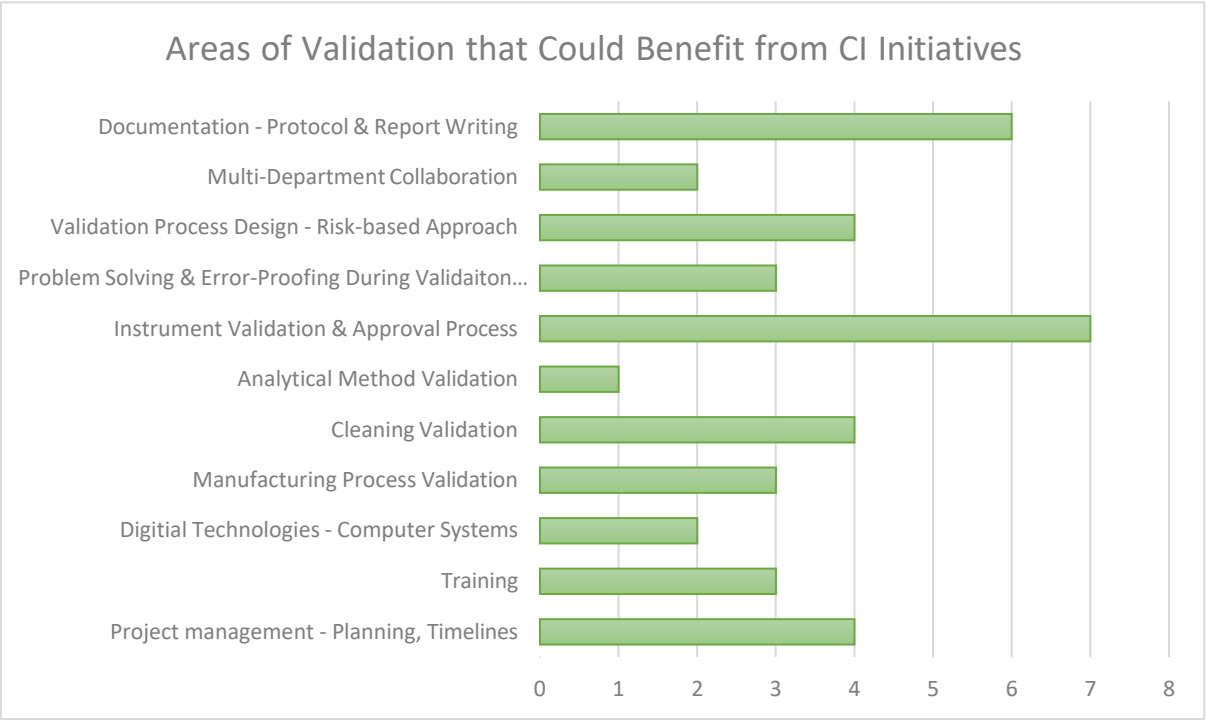

Figure 17: Areas of Validation that Could Benefit from CI Initiatives

Documentation was also one of the areas identified by the interviewee that has the potential to benefit from CI implementation. Streamlining the documentation process and removing any unnecessary information is key to keeping instructions for an activity clear, concise and to the point. The interviewee expressed concerns that key information in a procedure should be well highlighted so it is not missed among other, irrelevant information. A paperless approach, which will incorporate digitalisation strategies could also be a key focus for CI initiatives in order to effectively remove non-value added elements from the process.

Another area that was identified in both the interview and the survey was the Cleaning Validation process. The interviewee also expressed their view that Training is also an area that could benefit hugely from successful CI implementation, which is consistent with the observations from the survey. An example was provided which involved the digitalisation of a training process. Assessing the current process and identifying bottlenecks resulted in the training delivery method of a classroom format being updated to a video training, which made the training more easily accessible. This reduced the amount of resources, such as personnel and facilities, required to complete the training and also meant that training was always readable available so there was no time wasted in waiting for the training session to be delivered.

4.7.2. Why would the Validation Process not benefit?

The respondents who answered 'No' to the question of whether they thought there are areas of Validation that could benefit from CI implementation where asked a follow-up question of why they thought that CI would not be beneficial for the Validation process and the follow reasons were identified:

- There is too much work involved
- The requirements of validation to be met are too specific

4.8. Experience with Implementing CI initiatives in the Pharmaceutical Industry

All participants were asked if they had personal experience working with the implementation of CI initiatives, such as Lean tools and principles, within the Pharmaceutical Industry, of which 92% answered 'Yes'.

This group who answered 'Yes' was then asked a follow-up question if they had experience implementing these initiatives within the Validation Process. For this, only 49% of the respondents answered Yes', which is presented in Figure 18.

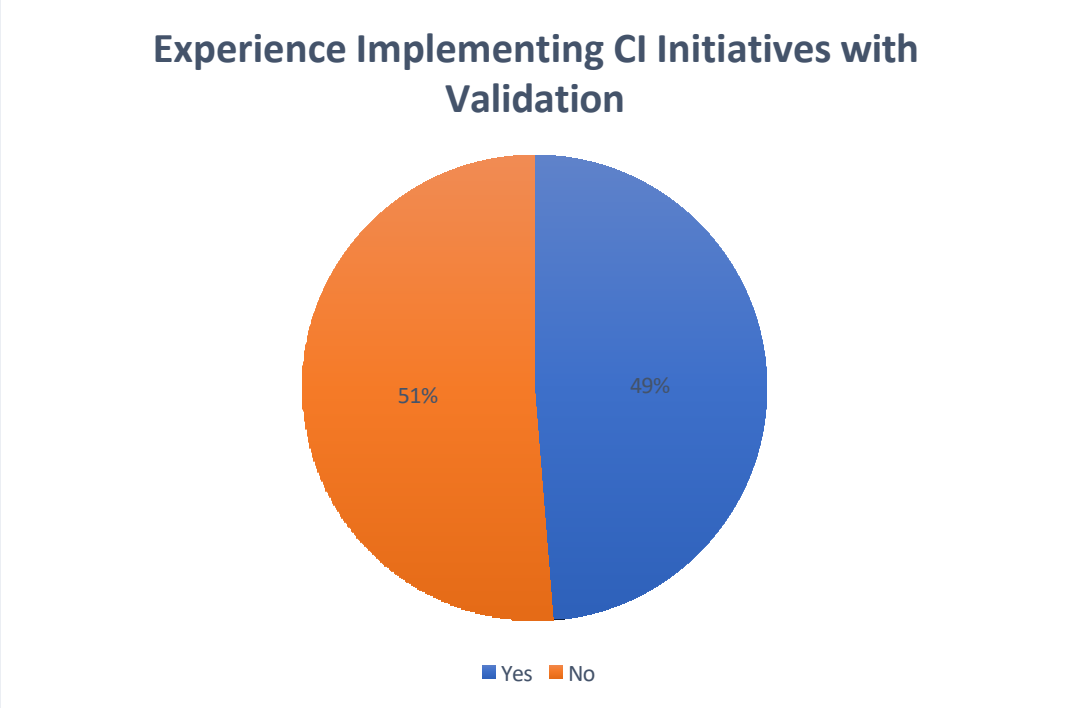

Figure 18: Participants with CI Implementation Experience Observed in Validation

The participants who answered 'Yes' account for 19 respondents, who have direct experience in implementing CI initiatives within some aspect of the Validation process.

4.8.1. CI Tools that could have the potential to Benefit the Validation Process

Finally, the respondents with experience in CI implementation of were asked an open-ended question on which tools they thought have the potential to be beneficial for the Validation Process. The frequency that these tools were given as an answer are presented in Figure 18. Many of the common tools that were reported to be observed by participants in previous questions, regarding CI implementation in the full pharmaceutical industry as well as specifically in the Validation process were given. 5-Why's was the most popular tool and it was within the top 3 tools observed for the previous 2 questions.

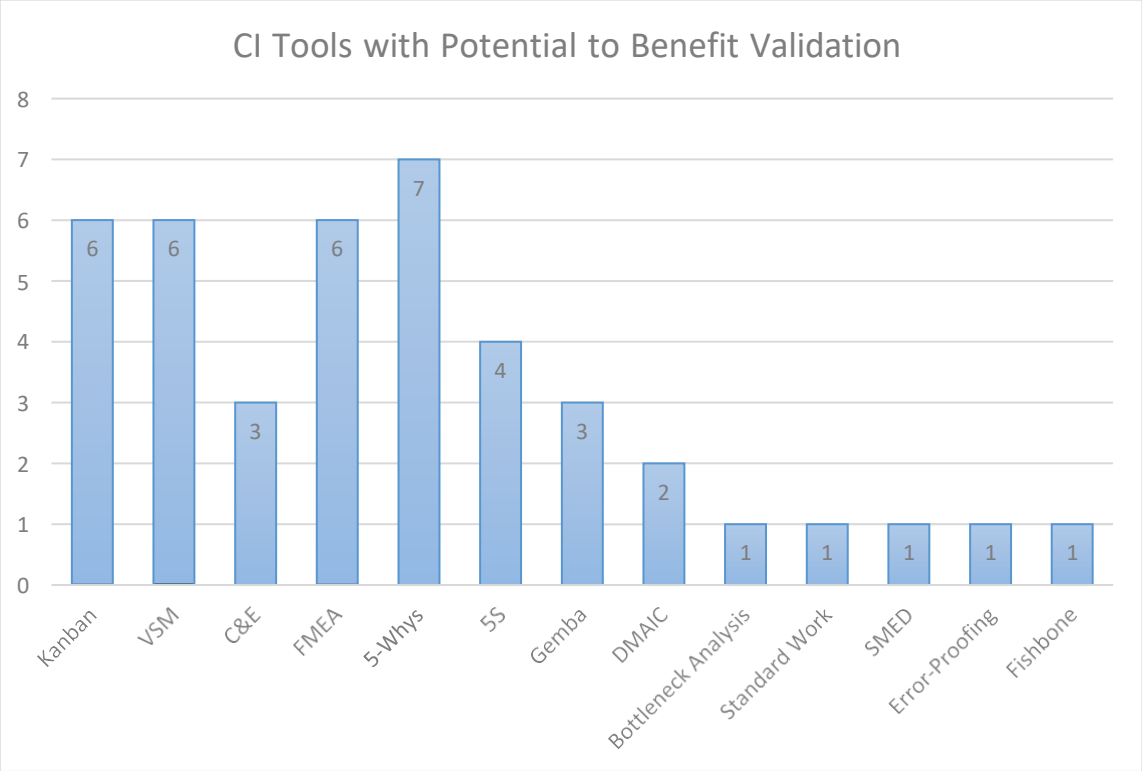

Figure 19: CI Tools with Potential to Benefit Validation

4.9. Analysis of Research Objectives

- Objective 1: Determine the extent, if any, to which Lean and other CI tools are currently being implemented in validation in the pharmaceutical industry.

This objective was assessed through qualitatively and quantitatively analysing the data from the survey and the interview. The survey revealed that 60% of participants who have experience in Pharmaceutical Validation have seen the use of CI tools, such as Lean tools, implemented within the Validation process in their Pharmaceutical organisation. This finding can be compared to the outcome of the more general sample population that was assessed in a preceding question, which found that within the pharmaceutical industry as a whole, 91% of respondents have witnessed the use of CI tools within their organisation in some form or department. This finding highlights the difference in approaches to CI implementation depending on the department and indicates a lesser focus on CI within Validation. With this being said, the results of the survey indicate that there is a respectable effort made within the Validation sector for the implementation of CI tools.

This observation was supported by the interview participant who reinforced the finding that there are efforts made within the Validation sector for the implementation of CI tools and initiatives. The focus on these initiatives indicates an understanding and appreciation for the potential benefits that CI tools can present to an organisation.

On the contrary, 40% of respondents to the survey indicated that they have not witnessed the use of CI tools or methodologies within the Validation process. This indicates that there may be some space to further incorporate the use of CI tools within the validation process within organisations that have not been attempted in the past.

It was identified through the survey results, that in common practice, CI initiatives are implemented at a later stage in the lifecycle of a product, after the validation process is complete. This can be due to the large initial investment that is validation requires with regards to time, funding and other resources.

- Objective 2: Explore Lean methodologies and other CI tools that could potentially optimise the validation process in the industry

Process optimisation to increase efficiency and reduce waste by removing non-value added activities from the validation process were highlighted as the key focus for CI implementation. The most popular tools identified from the survey that have been attempted to be implemented into the Validation process were FMEA, 5S, 5-Whys and Gemba. The majority of these tools were also identified as the most common among the CI tools implemented within the pharmaceutical industry, regardless of department. However, FMEA was the most popular CI tool identified for the Validation process, which was the sixth most popular choice of tool for implementation in general.

FMEA is a methodology that aims to predict potential failures in a given process. The popularity of this tool from the survey highlights that this type of tool can be beneficial as validation activities are typically carried out early on in the process for pharmaceutical production, and therefore the discovery and elimination of process failures before they occur is an effective way to reduce waste and defects that may result later on. The results of the interview also supported this finding that 5S and FMEA tools have shown to be beneficial within the validation process. It was highlighted that they are effective for optimising processes and reducing waste that result from defects and an unorganised process set up.

The Kanban tool was not one of the popular tools identified from the survey results, particularly for the validation process. In contrast, the participant of the interview highlighted this tool as one of the most beneficial tools. Used effectively it can increase task organisation and minimise time waste from specific tasks by ensuring all resources are readily available, and there is clear visibility on the status of each aspect.

Similarly, the analysis of the tools identified by the participants who have direct experience in implementing CI tools within their organisations indicated that tools such as Kanban, FMEA 5-Whys have the potential to benefit the validation process. VSM was another tool identified here, which was also emphasised by the interview participant as a helpful tool for process optimisation.

It is worth noting that a number of the common tools identified are related to investigation and deviation reporting, which can be a complicated aspect of the Validation process. These include

a number of RCA tools such as 5-Whys, Fishbone diagrams or C&E diagrams. This supports the observation that investment in CI initiatives can be driven by results of investigations and for future deviation prevention.

The tools that are considered more well-understood and easier to implement, including 5S, 5-Whys, VSM and Kanban are considerably more popular among all aspects of the data analysed. In comparison, tools such as SMED, Bottleneck analysis and Just-in-time are less popular, which are methodologies that are usually perceived as more complicated, and require a higher level of understanding and experience to implement efficiently. This observation may indicate that more simple initiatives tend to be embraced more often, which could be due to a lack of resource allocation and sufficient training in CI methodologies.

- Objective 3: Analyse the current challenges, both observed and potential, that could be associated with the implementation of Lean Validation.

Through the research process a number of challenges were identified to be associated with the implementation of CI initiatives, such as Lean and Six Sigma tools, to the Validation process, all of which vary in severity and impact. 'Time constraints' were highlighted across both research methods are a key challenge to the CI implementation. This can result from tight validation deadlines, balancing other priorities and not accounting for errors or rework in the CI project planning.

The participants of the survey were divided on whether they perceived hesitation or reluctance within their pharmaceutical organisation to implement CI methodologies and tools within Validation, with a majority of 57% answering 'Yes' that they did believe there was reluctance. This is interesting to note as while more of the participants believed there was hesitation, the survey data also revealed that all CI initiatives that had been implemented into the process previously were done so at least 'somewhat successfully', with no respondent indicating the initiative had been implemented 'not successfully'.

The main factors that were identified as challenges to CI implementation were insufficient 'time' and 'team engagement'. Both of these were discussed across many of the responses and were highlighted as factors that need to be effectively addressed to get the full benefit from the

CI initiatives. Interestingly, concerns for 'regulatory compliance' was not one of the key areas of apprehension for attempting to implement new initiatives into the process.

Critical Success Factors (CSF) that were identified during the interview also included a number of factors that relied on personnel skills and attitudes. The interviewee expressed that, in their experience, these factors were imperative for the successful implementation of CI projects within the Validation process. These included having 'adequate team engagement', 'members with sufficient CI experience & knowledge' and 'accountability for projects'. 'Effective project selection' & 'identification of problems' that can benefit from Lean tools are also important elements for ensuring success.

A number of Critical Failure Factors (CFFs) were also identified through the interview process. Again, a number of these relied on the attitude and culture from the personnel working within the project. This is included a 'fear of change', 'procrastination' and 'no team harmonisation on approach to solutions'. Comparably to the results of the survey, 'Lack of time' was also accounted for as a significant challenge for effective CI implementation.

- Objective 4: Assess the potential impact and benefits of optimising the validation process through Lean and other CI principles.

The main drivers and motivation behind implementing CI tools and initiatives were analysed through the survey results. Unsurprisingly, 'Maximising Efficiency of a Process' was identified as the main driver for incorporating CI. Saving 'time' and 'costs' were also highlighted as key drivers. The survey data also revealed that a large number of CI tools were used to either address a mistake that was previously made, or to prevent an error from occurring in the future. Errors and mistakes often lead to defects, waste and rework, all of which have negative consequences for the organisation. This can be a key motivator for organisations to invest in the implementation of these CI initiatives and tools, that have the potential to benefit the company down the line.

A number of specific areas within the Validation process were identified through the survey that could potentially benefit from the implementation of CI initiatives. The most common area identified was for 'Instruments'. All instruments used must undergo validation and periodic requalification. This can often be a slow process, which can have a direct impact on other parts

of the process, such as manufacturing or analytical testing. To maximise the efficiency of the validation process in this area would minimise time waste. The interview participant shared this view that CI initiatives within this area have shown to be effective at reducing waste and subsequently improving efficiency.

Another area that was identified was ‘Documentation’ related to validation activities. The process of Validation requires specific protocol and report generation for each activity. This was highlighted through the survey and interview data. As a validation process must be based on documented evidence, there can be concern related that the documentation of a validation is thorough enough and contain enough information to justify all data to regulatory bodies. This can subsequently lead to excess information being collected, reviewed and stored which is not required. A more streamlined or risk-based approach to documentation, which can be achieved using Lean tools such as VSM and FMEA, can lead to a more efficient process that creates less waste as a result.

A more efficient validation process can free up resources and time to dedicate to other areas, and therefore each CI project that results in a reduction in waste contributes to this streamlined process. Addressing key areas that are identified as a bottleneck to the process is essential for improving overall efficiency for the company across the entire lifecycle of drug manufacture and release.

Chapter V

5. Conclusions & Recommendations

5.1. Discussion of Results

This research was conducted in order to explore the concept of 'Lean Validation' within the Pharmaceutical Industry in Ireland. The analysis of the data from the survey and interview conducted was used to draw conclusions on the research objectives discussed in outset of this study. The data has shown that there is an understanding of the importance and benefits of CI tools and initiatives within the Pharmaceutical industry, and specifically within Pharmaceutical Validation.

'Lean Validation' has been shown to be already in process and in implementation within the industry in Ireland. A variety of tools and principles, which range from Lean to Six Sigma methodologies have been successfully implemented into the Validation process. There were a number of tools and methodologies that have been highlighted as particularly beneficial for the validation process, which include FMEA and 5S.

A number of key drivers for CI implementation were also identified through this research process, as well as key areas within validation that could potentially benefit from more initiatives being introduced successfully. Some of the key factors that affect the success rate of implementation were also discussed, which can form the basis of focus points for future implementation projects.

While there is a clear effort evident from the data from these organisations to incorporate these tools, the results indicate that there is a level of hesitation or reluctance to attempt to implement new methodologies within the validation process, with the greatest concerns relating to lack of time and people's attitudes towards change. Addressing these concerns may be the solution to fully embracing these CI methodologies, such as Lean, and experiencing the full extent of benefits that they have to offer.

Objective 1 of the research which was to determine the extent to which CI initiatives have been implemented into the Validation process was met. The analysis concluded that CI initiatives have been incorporated into Validation to a certain extent, however there is potential for further

implementation within the process as the data suggests CI is not as prominent as it is within the organisations in general.

Objective 2 to identify specific CI tools from Lean and Six Sigma methodologies that have the potential to optimise the validation process was also met. The results highlighted a number of tools that have been successfully implemented as well as tools that can potentially streamline the validation process. These tools include FMEA, 5S, 5-Whys and Kanban, all of which aim to eliminate waste from the process and increase efficiency.

Similarly, objective 3 to assess the challenges associated with Lean Validation was successfully addressed and a number of factors were identified through the survey and interview process. Significant challenges that were highlighted included time constraints and a number of personnel factors, which were mostly focused on employees attitude to change and willingness to engage in CI projects.

Objective 4 explored the potential benefits that CI within Validation can have. There are a number of areas that can be improved through the use of these Lean tools, such as Training, Documentation and Equipment Validation, which have each shown to improve process efficiency within validation, which will consequently result in improvements in the overall process.

The Conceptual Framework detailed in Section in 3.6 explored the main areas that would present challenges and opportunities for CI implementation within the Validation sector. The key variables identified were Resources, People, Process and Regulatory Constraints. The findings from the research indicated that Regulatory Constraints was the least significant variable, with this not being a key consideration for drivers or challenges of CI implementation. People and Resources presented as the most prominent factors to consider, more specifically with ‘culture and attitude’ and ‘time’ emerging as the key elements for both, respectively.

5.2. Research Conclusion & Recommendations

In conclusion, there are a number of CI initiatives, including Lean and Six Sigma tools, that have been shown through this research to be beneficial within the Validation process for Pharmaceutical organisations. There are a number of benefits to implementing these which are

in line with Lean and Six Sigma principles to improve process efficiency and remove any waste or non-value added activities. It was highlighted that there are some concerns and challenges associated with CI implementation within Validation, and these areas can potentially be a focus for organisations to address if they wish to further embrace a culture of CI and incorporate more beneficial changes into their processes.

A suggestion for a Pharmaceutical organisation looking improve their Validation process could be to start by implementing CI initiatives into the areas that were highlighted through this research, which have been shown to have a good success rate and improve the validation process. This will include areas such as training, documentation and equipment qualification. Another recommendation would be to begin with the tools that have been shown be beneficial specifically in the Validation process throughout this research, which include 5S, FMEA, 5-Whys and Kanban. These tools can be relatively straight-forward and have a high success rate when implemented in a suitable project.

A final suggestion would be to focus on addressing some of the CFFs and CSFs that were identified through this research, such as effective project planning prior to starting the CI implementation. This can be achieved by ensuring that there is sufficient time and resources invested in the project to maximise the chances of success and to have the most impact on the process. Investment in education and training for employees involved in the projects on CI tools and methodologies is also a key factor for this. Addressing the culture of the organisation and aligning all employees on the attitude to embracing change and engaging in the CI projects is essential for any project to be successfully implemented and sustained for a significant amount of time.

5.3. Limitations of Study

This scope of this study included employees of the pharmaceutical industry in Ireland only. While Ireland does have a decent representation of global pharmaceutical organisations approach to CI implementation, this narrowed scope does not account for different cultural approaches that could be observed in other nations in Europe or worldwide. The sample size for the survey was also small relative to the number of people employed in the Pharmaceutical industry in Ireland, which can be considered a limiting factor of the results.

5.4. Suggestions for Further Research

This research could be repeated with a larger sample population in Ireland, in order to capture a broader perspective. Further research could also include a wider scope for the sample population, which is not limited to Ireland. This could be performed to compare findings across a more diverse sample population, with potential to examine differences in cultural approaches. The sample population could be expanded to a broader range of countries or could be expanded to include other closely related industries that involve Validation, such as the Medical Device industry.

Another approach to further research could focus specifically on the more popular Lean tools that were identified through this research, and explore the benefits and challenges associated with a number of these tools within Validation in more detail, and analyse the strengths and weaknesses of each tool specifically for the Validation process.

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Appendix

Appendix 1 – Interview Questions

1. Do you understand your rights to participate in this research, as agreed in Informed Consent Form that you signed prior to this interview?

2. Do you have experience in the field of Pharmaceutical validation and/or the implementation of Continuous Improvement (CI) tools, such as Lean? What is your role?

3. What is your current understanding of 'Lean Validation'?

4. In your experience, have efforts been made to incorporate Lean tools or principles for the validation process where you have worked in the Pharmaceutical Industry? If yes, what are they?

5. What would you consider the 'Critical Success Factors' for successful implementation for CI initiatives? (i.e. what is needed to ensure implementation will be successful)

6. What would you consider the 'Critical Failure Factors'? (i.e. the key areas where things are incorrect or things that must happen in order for plan to fail)

7. Are there any elements of the validation process that you think could benefit from Lean or CI tools? If so, what elements?

8. Do you think there are difficulties or challenges associated with the implementation of these? If so, what do you think they are?

9. If you work with CI, Operational Excellence or Lean principles – have you worked to implement these tools in the validation sector?

10. What areas within validation have you seen that have benefitted from the implementation of Lean or CI tools?

11. What Lean tools do you believe could be used to benefit the validation process?

Appendix 2 – Survey Questions

Lean Validation in the Pharmaceutical Industry

'Lean Validation' is a concept that aims to maximise efficiency and remove waste from the Validation process. The can be achieved by incorporating a variety of Continuous Improvement {CI) initiatives, such as Lean or Six Sigma methodologies, into the Validation Process. This research is being conducted to determine the extent to which CI initiatives have been implemented into the Validation process in the Pharmaceutical Industry in Ireland.

This research is being performed as part of MSc in Pharmaceutical Business & Technology with Griffith College and Innopharma.

* Inrlif'::::atoc_ron11irorl_n11octinn

1. Do you consent to participate in this research, knowing that you have the right to withdraw consent at anytime? *

   Mark only one oval.

   Oves
   QNo

2. Do you have experience working in the Pharmaceutical industry in Ireland? *

   Mark only one oval.

   Oves
   QNo

3. In your experience, have you seen the implementation of Continuous Improvement (CI) initiatives, such as Lean or Six Sigma tools and methodologies, within your pharmaceutical organisation?

   Mark only one oval.

   0 Yes *Skip to question 4*
   0 No *Skip to question 7*

Continuous Improvement in the Pharmaceutical Industry

4. Which CI tools or initiatives have been used or implemented in your organisation? Select all that apply.

Tick all that apply.

☐ SS
D **Kanban**
D **Value Stream Map (VSM)**
D **Kaizen**
D **Cause & Effect (C&E) analysis**
D **Failure Mode and Effects Analysis (FMEA)**
0 **5-Whys**
D **Fishbone (Ishikawa) diagram**
D **Gemba**
D **Bottleneck analysis**
D **Just-in-time**
D **Single-Minute Exchange of Dies (SMED)**
D **Error-proofing (Poka yoke)**
D **Other:** _____

5. What would you consider the main drivers for the implementation of these CI initiatives?

_____

_____

_____

_____

_____

6. What are the main challenges associated with the implementation of these CI initiatives?

_____

_____

_____

_____

Skip to question 7

Experience in Pharmaceutical Validation

7. Do you have experience in the field of Pharmaceutical Validation?

Mark only one oval.

- Oves *Skip to question 8*
- QNo *Skip to question 12*

CI in Pharmaceutical Validation

8. In your experience, have you seen the use of Lean or CI tools specifically in the Pharmaceutical Validation process?

Mark only one oval.

- Oves *Skip to question 9*
- QNo *Skip to question 12*

Implementation in Validation

9. In what specific areas of the Validation process have you seen CI initiatives implemented in?

_____

_____

_____

_____

10. In your experience, which CI tools have been attempted to be implemented into the validation process? Select all that apply.

Tick all that apply.

- ☐ SS
- D Kanban
- D Value Stream Map {VSM)
- D Kaizen
- D Cause & Effect {C&E) analysis
- D Failure Mode and Effects Analysis {FMEA)
- 0 5-Whys
- D Fishbone (Ishikawa) diagram
- D Gemba
- D Bottleneck analysis
- D Just-in-time
- D Single-Minute Exchange of Dies {SMED)
- D Error-proofing {Poka yoke)
- D Other: _____

11. How successful has the attempt to implement these CI initiatives and tools been within the validation process?

Mark only one oval.

- 0 Not at all successful
- 0 Not very successful
- 0 Somewhat successful
- 0 Quite successful
- 0 Very successful

Openness to embrace CI

12. Do you think there is hesitation or reluctance to implement Lean or CI tools in the validation process?

Mark only one oval.

- Oves *Skip to question 13*
- LJNo *Skip to question 14*

13. What factors contribute to this hesitation, in your opinion?

Areas for CI in Validation

14. Do you think there are areas of validation that could benefit from a more Lean approach?

Mark only one oval.

- Oves *Skip to question 15*
- LJNo *Skip to question 16*

15. What areas within validation do you think could benefit from the implementation of CI tools, such as Lean?

_____

_____

_____

_____

_____

Skip to question 17

16. Why do you think that Lean or CI initiatives would not be beneficial for the validation process?

Experience with CI Implementation

17. Do you personally have experience in implementing Continuous Improvement initiatives within the pharmaceutical industry, including experience with Lean principles and tools?

Mark only one oval.

Oves *Skip to question 1B*
QNo

Tools to benefit Validation

18. In your experience, have CI initiatives been attempted to be implemented into the Validation process?

Mark only one oval.

Oves
QNo

19. What Lean or CI tools do you think have potential to be beneficial within the validation sector?