Griffith College

Investigating The Current Challenges Involved In The Application of Process Analytical Technology (PAT) Methodologies In Pharmaceutical Industry.

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A dissertation submitted as a partial fulfilment for the requirements of Master of Science in Pharmaceutical Business and Technology

To Griffith College & Innopharma Education
Dublin, Ireland.

Innopharma education

Acknowledgements

I would like to express my heartfelt gratitude to my mother for her unwavering support throughout my academic journey. I am grateful for her sacrifices, patience, and understanding. I am also truly grateful to my supervisor, Martin Murphy, for his support and guidance throughout my dissertation.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

API	active pharmaceutical ingredient
cGMP	current Good Manufacturing Practice
CPP	critical process parameter
CQA	critical quality attribute
CQV	continuous quality verification
DOE	design of experiments
EMA	European Medicines Agency
FDA	Food and Drug Administration
GC	gas chromatography
GLP	good laboratory practice
GMP	good manufacturing practice
HR	NMR high - resolution NMR
HTS	high - throughput screening
ICH	International Conference on Harmonization
IOT	Internet of Things
IR	infrared
IRRAS	infrared reflection – absorption spectroscopy
LIF	laser- induced fluorescence
LIMS	Laboratory Information Management Systems
MS	mass spectrometry
MVDA	multivariate data analysis
NIR	near- infrared
NIR	CI near- infrared chemical imaging
NIRS	near- infrared spectroscopy
PA	process analytics
PAC	process analytical chemist/chemistry
PAT	process analytical technology
PCS	process control system
QA	quality assurance
QbD	quality by design
QC	quality control
QMS	quality management systems
RRS	resonance Raman spectroscopy
RTM	real - time monitoring
RTO	release - to - operations
RTR	real - time release
TPI	terahertz pulsed imaging
TPS	terahertz pulsed spectroscopy

Abstract

The application of Process Analytical Technology (PAT) methodologies in the pharmaceutical industry has gained significant attention due to its capability to enhance process control, improve product quality, and increase manufacturing efficiency. However, several challenges delay the widespread adoption and implementation of PAT in this industry. There are technological challenges, including the need for reliable and robust analytical instrumentation, suitable for real-time monitoring of critical process parameters and quality attributes. Additionally, the complexity and variability of pharmaceutical processes create challenges in developing efficient multivariate models for process control and optimization. Despite extensive research and investments involved in the implementation of PAT, the underlying challenges are yet fundamental and highly overlooked. These gaps prompted to understand the challenges involves in PAT implementation by conducting an extensive secondary research study with the current literature available. Once the possible gaps have been identified a draft from the current literature is made to plot the objectives and goals of the study. The study in this thesis seeks to analyse the challenges involved in the implementation of PAT technology in the pharmaceutical industry. For the primary research study, five members with industry experience not less than 2 years and suitable exposure to PAT implementations have been approached. The members were then initiated to participate in consent driven semi-structured interviews remotely using google meet. Gioia method of data analysis was used in the study to study and analyse the qualitative data obtained from the semi-structured interviews. The study results reveal that the challenges related to Product, Personnel and Funding are the primary challenges and Technical, Process Planning and Intellectual Property challenges were secondary cause for delay in adoption and deter the implementation of PAT technology across the industry. The challenges identified in the study are not only limiting the progress of PAT implementation but also affecting the industry by increased manufacturing costs and undue process quality tests. Through this study pharmaceutical industry to achieve success collectively PAT implementations must be considered as a vital innovative step towards Pharma 4.0 than a process enhancer. The present research study contribution will be beneficial for academic researchers, regulators, pharmaceutical companies, and consumers.

Keywords: Process Analytical Technology, Pharmaceutical Industry, Quality by Design, Process Analysis, Process Control, Process Monitoring, PAT tools

CHAPTER ONE

Introduction

1.1 Foundation of PAT Technology

In its fundamental form the field of process analysis (PA) is constantly developing and expanding across various industries, the adoption in the pharmaceutical sector as part of process analytical technology (PAT) is one of its derivations. Process Analysis involves the use of portable instrumentation with real-time analytics and chemometrics to monitor chemical or physical attributes or detect events that cannot be identified through conventional variables like temperature, pressure, or flow. While PA is typically associated with applying real-time analytics to production issues, it can also be applied to other fields. The instruments used in Process Analytics are applicable to a wide range of real-time challenges.(Read *et al.*, 2010) PAT is a broader field that includes process analysis, process automation and control, and is focused on improving manufacturing process understanding and control (PUC). Strategies based on PAT are used to mitigate manufacturing risks associated with product quality as part of the manufacturing quality by design (QbD) approach. Process analytical technology (PAT) is distinguished from off-line laboratory techniques by its real-time monitoring capabilities, which operate on the scale of seconds to minutes rather than hours or days.(Lopes *et al.*, 2004) Off-line approaches are usually insufficient for root cause analysis and identifying events within the process that lead to off-specification or poor product quality. PAT involves monitoring process trends or real-time monitoring (RTM) using data streams from process instruments, such as process spectral data.(Bakeev, 2010)

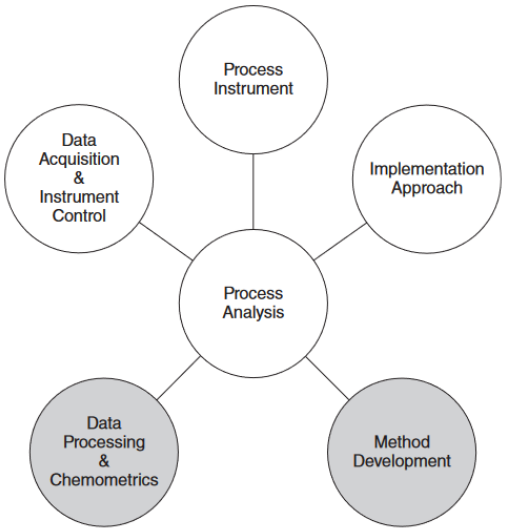


Figure 1 Elements of PA that form the Foundation of PAT – Source: (Bakeev, 2010)

Predictive models used in PAT enable real-time monitoring of critical quality attributes (CQAs) and their correlation to critical process parameters (CPPs). This level of knowledge of the process leads to a more accurate assessment of the control space, which helps with process control and variance management, or real-time assurance (RTA) of product quality.(Lopes *et al.*, 2004) The most advanced form of PAT is product parametric real-time release (RTR), in which process analysis (PA) data are used. All these levels of PAT provide a means to improve product quality, reduce product wastage and rework, facilitate cost reductions, increase production efficiency, reduce laboratory testing requirements, and identify opportunities for process improvement, ultimately resulting in reduced manufacturing costs and risks.

1.2 History of PA & PAT Technology

Process analytics has a history of almost 70 years within the chemical and petrochemical industries, with its roots in Germany where modern plants were highly instrumented after World War II. In the two decades following the war, many refineries, petrochemical plants, and nuclear plants worldwide adopted process analysers.(Bakeev, 2010)

Nowadays, process analysis is mainstream in several manufacturing industries and can be an integral part of process control. In addition to process analytics, phenomenological and soft sensing approaches are alternative methods that can be used for complex processes. Selection of approach relies on a number of things, such as the performance needed, the risks of implementation, the normal operations, and business concerns.(Kim *et al.*, 2021) Using a mix of techniques, such as PA and soft sensing, can give better PUC assurance for complex, high-risk operations as methods that work on their own start to converge.

In the last 20 years, process analytics (PA) has expanded steadily because all industries need to improve their manufacturing efficiency. This growth is partially driven by the pharmaceutical industry, which has only recently begun to adopt PAT practices. Regulatory initiatives, such as the FDA's "GMPs for the 21st century" and "PAT - A Framework for Innovative Pharmaceutical Manufacture and Quality Assurance," as well as the promotion of Quality by Design (QbD) through the CMC Pilot Program, have

contributed to the adoption of PA practices in the pharmaceutical industry.(Bakeev, 2010) QbD has been extensively implemented by other organizations around the world, in conjecture to ICH. For example, the ICH has released guidelines like ICH Q8 Pharmaceutical Development, ICH Q9 QRM, and ICH Q10 PQS that explain how to use QbD.

1.3 Process Analytical Technology (PAT)

The Food and Drug Administration (FDA) of the United States introduced a concept known as Process Analytical Technologies (PAT) to the pharmaceutical business in 2004. This was done with the goal of increasing industrial productivity and maintaining the quality of products. Instead of testing quality of a product, the PAT approach proposes that quality should be designed into it or built into it from the beginning.(Bakeev, 2010) PAT is a broad term that incorporates a variety of technologies that are not new; nonetheless, their application to the pharmaceutical industry might be perceived as unique.(Lopes *et al.*, 2004)

PAT is a subset concept that falls under the broader term Quality by Design (QbD). QbD is described as a systematic approach to manufacturing processes throughout the product development stage to achieve a predefined quality at the conclusion of the manufacturing process. The applications of QbD and PAT are not limited to the pharmaceutical industry but can be applied to any industry. The main goal of PAT is to reduce over-processing, minimize off-specification products, and ensure quality of products. (Simon *et al.*, 2015) PAT achieves this by combining real-time experimental measurements and mathematical tools to address downstream processes in large-scale bio-product purification using different unit operations.

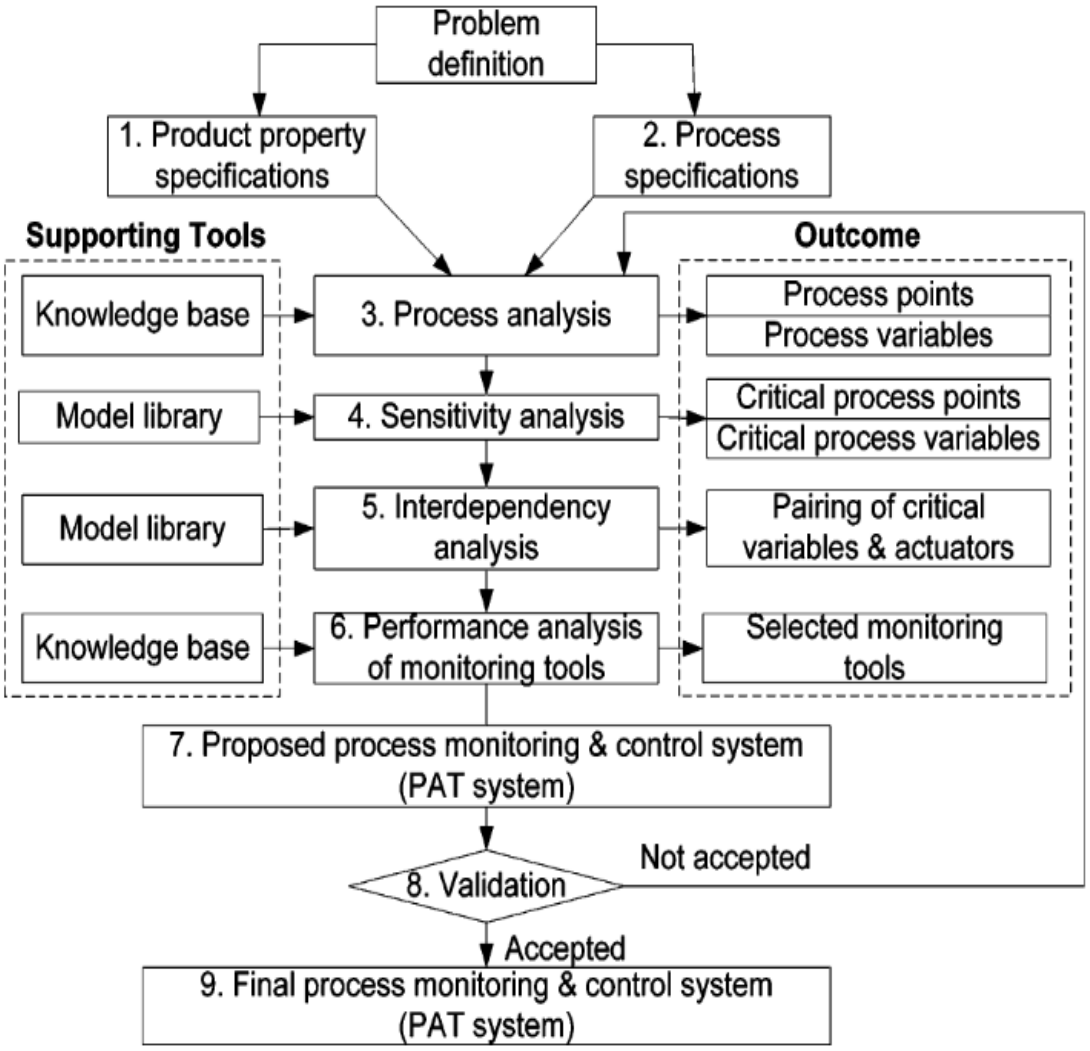


Figure 2 Overview of PAT Supporting Tools along with Design Methodology - Source: (Simon et al., 2015)

1.4 Problem Statement

Despite the challenges and costs associated with implementing PAT, the benefits can be significant.(Challa and Potumarthi, 2013) Real-time monitoring and control of processes can reduce variability and enable process optimization, leading to increased productivity and yield. The use of advanced data analytics and modelling tools can enable better process understanding and facilitate process improvements. PAT can also enhance process safety by detecting and preventing potential hazards in real-time. Hence it is vital to examine the current challenges that impede the adoption of PAT technology.

Overcoming these challenges may require companies to invest in specialized training for personnel, develop robust data management and analysis systems, and work closely with regulatory bodies to ensure compliance with regulations.(Mercier *et al.*, 2014) Standardization of the current PAT technologies is also a major concern uncovered in the literature review that needs to study further, similarly challenges related to integration of PAT into existing manufacturing processes needs to be studied for exploring ways to ease adoption.

In conclusion, while implementing PAT can be challenging, the benefits can outweigh the costs and enable companies to stay competitive in a rapidly evolving pharmaceutical industry. To fully leverage the benefits of PAT, it is crucial for companies to keep up with challenges that are a constant accordance with such complex technology. The purpose of this study is to investigate such challenges and provide conclusion on current major challenges that delay adoption of PAT technology.

1.5 Research Aims and Objectives

1. To analyse all the challenges that are currently affecting the implementation and/or adoption of PAT Tools in the pharmaceutical industry.
2. To analyse any internal downsides that deter the adoption of PAT tools within the pharmaceutical industry.

1.6 Research Questions

1. What are the current challenges for the implementation of PAT tools in the pharmaceutical industry?
2. Are there any possible downsides in the implementation of PAT tools that are delaying adoption?

1.7 Research Hypothesis

In the complex and highly regulated pharmaceutical business, it is hard to make high-quality pharmaceutical products in a way that is efficient and saves money. Process Analytical Technology (PAT) has become a potential way to make sure that products are of good quality and that processes work well. Even so, the adoption and integration of PAT in the pharmaceutical business face several challenges and problems. So, the goal of this study is to investigate the current challenges that come up when PAT methods are used in the pharmaceutical business.

Based on the review of the literature, it is thought that the problems with using PAT methods in the pharmaceutical business can be put into three main groups: technical, regulatory, and organizational. Technical challenges include the complexity of the technology, the need for specialized knowledge, and the need to integrate with existing production processes. Regulatory challenges include the need for regulatory approval, the fact that different regions have different regulatory standards, and worries about the privacy and security of data. Organizational problems include the need for specialized talent and financial implications.

It is also hypothesized that recent changes in the industry, such as the increasing use of artificial intelligence and machine learning, the adoption of continuous manufacturing, and the shift towards personalized medicine, may have a positive impact on the adoption of PAT methodologies. Nonetheless, the changes and adoption of PAT in the pharmaceutical industry may also give rise to new obstacles that need to be tackled effectively. The findings of this study will provide valuable insights into the challenges and opportunities associated with the application of PAT methodologies in the pharmaceutical industry and will help to inform future research and development efforts in this area.

CHAPTER TWO

Literature Review

2.1 Introduction

The following literature review is a critical analysis of prevalent existing literature on PAT technology and process analytics that covered various industries with focus on pharmaceutical implementation of PAT. The review involves finding, evaluating, and summarising relevant articles, and other sources of information to develop a comprehensive understanding of the topic for framing research hypothesis.

During this literature review, relevant databases were identified for sources of information and Google Scholar has been the primary search portal for gathering research papers and books on the topic. The sources have been carefully evaluated to pick relevant data for developing the interview questionnaire. The evaluation process involved the quality of the research by determining citations of the authors and the relevance of the findings to the research objectives. The synthesis process involved the organization of the information into segments to check for the strength of relevancy to the research objectives. Some of the data presented regarding the challenges in industries other than pharmaceutical related to PAT adoption have been critically evaluated to identify areas of agreement for the research objectives and conclusions were drawn based on the evidence.

2.2 Process Analytical Technology (PAT) from a Business Perspective

The literature review showed that the ideas behind Process Analytical Technology (PAT) come from Process Analytical Chemistry (PAC). The FDA changed the name of PAT from PAC so that it wouldn't just be about the science of processes.(Barrett *et al.*, 2005) PAT looks at getting information about the process in real time at a point on the production line where it can be used to control a key quality measure. The important component could be measured in a simple way, like with a thermocouple, or it could be measured in a more complicated way like the use of chemometric methods, multivariate

tools, process monitors, and process control tools, which aid in understanding the process better. (von Stosch *et al.*, 2014)

When PAT is integrated with methods like Quality Systems, Lean Manufacturing, or Quality-by-Design, the operational benefits are clearly seen upon implementation. The most important of these advantages is being able to direct the process while the manufacturing process is still going on. PAT saves time and the economic burden on the organisation since the QC lab doesn't have to prepare samples upon tool implementation. A risk analysis is needed to find out what could go wrong with the PAT so that the effect of the risk can be reduced or eliminated.(Glassey *et al.*, 2011) PAT often involves coming up with and using new ways to analyse data and makes changes in the production area by using new tools and methods, such as Near Infrared and Raman imaging.

Often, PAT implementation is based on the Quality-by-Design idea, and it involves trying out different ways to make sure that the process works as well as it can. There could be delays in putting these new ways of analysing data into place which involves a PAT-team with people from many different fields. They need to know about the manufacturing process, the analytical method for process tracking, chemometrics, data management, and the financial and production processes. Several PAT systems use near infrared spectroscopy, Raman spectroscopy, and multivariate data analysis to get information from the data they collect. Most of the methods used in the QC lab right now are based on simple data analysis, so usually training is needed to use these multivariate methods.

PAT projects also require a lot of investment to be spent on capital, and the investment needs to be justified by the economic effect. In the last ten years, some study has been done to back up this reason. In 2006, the economic viability of the by-product of putting PAT into place in the pharmaceutical business was looked at. Also, the cash gain from putting PAT and Lean Manufacturing into place has been looked at. At the same time, the framework of the business case for using PAT to identify and analyse raw materials was made.(Glassey *et al.*, 2011) The book reviews showed that the most common ways to evaluate an economic study are the NPV, IRR, and ROI. The Net Present Value (NPV) measures the investment made right now with the net cash flows that will be made in the future. The Internal Rate of Return (IRR) shows how profitable the project is and is generally linked to the net present value. The return on investment (ROI) measures the benefits gained to the amount of money invested to figure out how well the money was

spent. All of this helps structure a business case that looks at costs, rewards, and information and helps figure out how the PAT adoption in the pharmaceutical industry will affect the economy of the business unit. (Streefland *et al.*, 2013)

2.3 Quality by Design (QbD) approach for PAT Implementation

Pharmaceutical QbD is a method for developing drugs that starts with clear goals and focuses on knowing and controlling both the product and the process based on scientific data and quality risk management. (Barrett *et al.*, 2005)

Goals of quality-based drug development (QbD) involve the following:

1. To generate product quality standards based on clinical end performance.

2. To improve product and process design, knowledge, and control to improve process capability while minimizing product variation and defects.

3. To effectively increase the product design, development, and manufacturing efficiencies.

4. To improve the root cause analysis and change management after approval

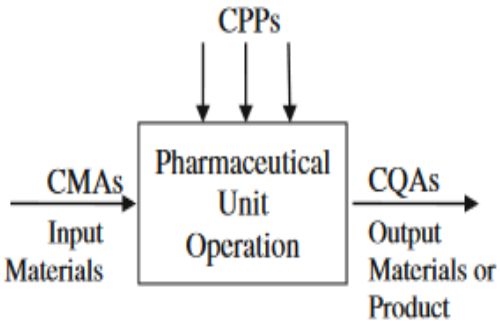


Figure 3 Link Flow Chart between CMAs, CPPs and CQAs – Source: (Yu et al., 2014)

Since its initiation, FDA has made a lot of work towards the first goal, which is performance-based quality standards. (Yu *et al.*, 2014)It can be seen in the FDA discussions about the assayed potency limits for drugs with a narrow therapeutic index and the physical properties of generic drug products. Still, it's important to note that ICH papers did not say that clinical performance-based specifications were a QbD goal, even though a recent scientific paper did say this. The second goal of QbD is to improve the ability of the process and reduce the variability of the product, which often leads to product flaws,

rejections, and recalls.(Yu *et al.*, 2004) Also, a better knowledge of the product and the process can make it easier to find and control factors that affect the quality of the drug product. After getting approval from the regulatory authority, the process should still be worked on to reduce product variation, defects, and rejections.

QbD takes a systematic method to designing and making products. In this way, it improves the speed, ability, and design of creation. Also, it moves resources from a remedial mode further downstream to a proactive mode further upstream. It makes it

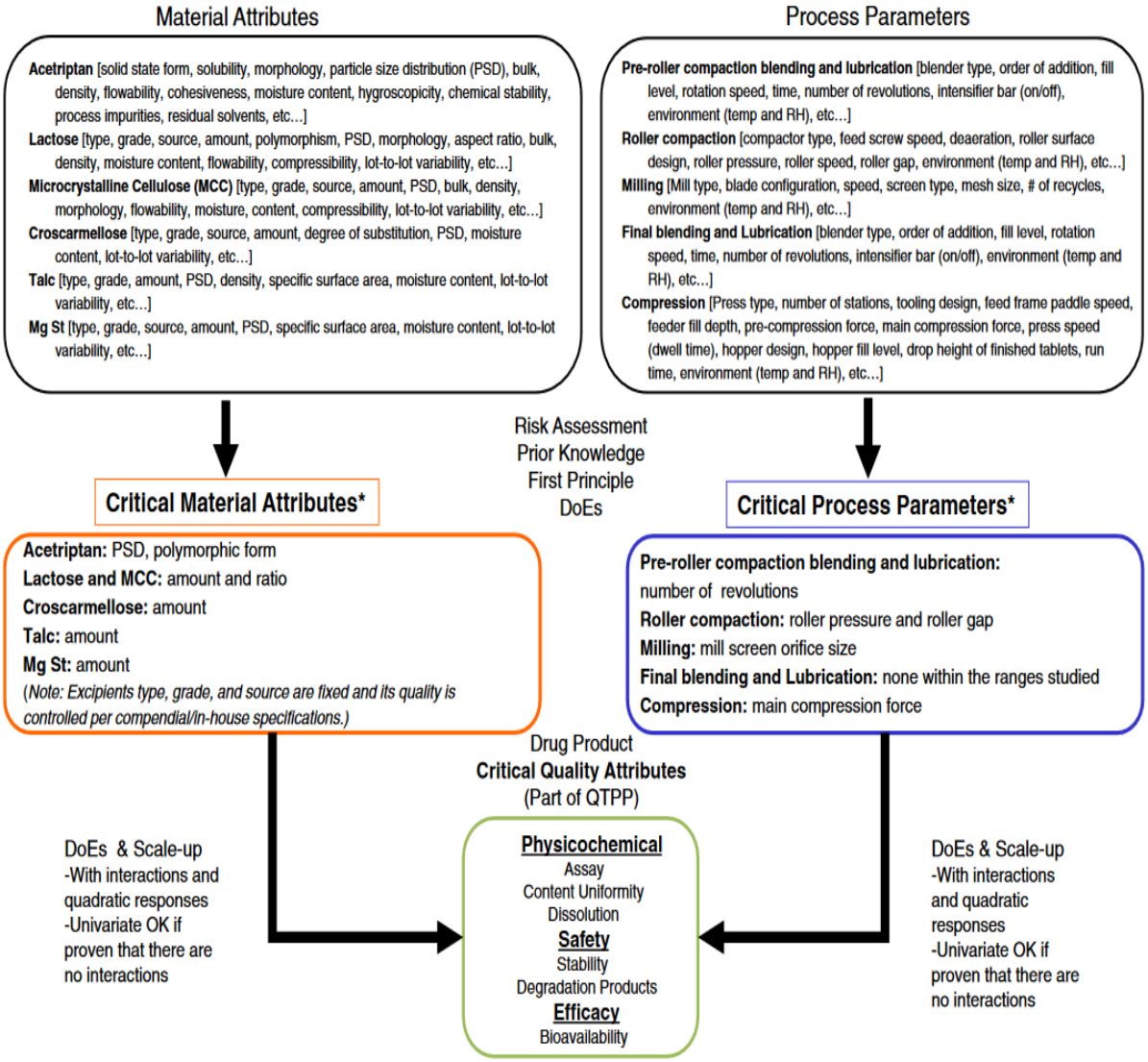


Figure 4 Process Understanding of QbD implementation: Immediate release dosage form - Source: (Yu et al., 2014)

easier for manufacturers to figure out why their products fail to perform. The last goal of QbD is to improve root cause analysis and change management after approval. Without a good understanding of the product and the process, it is hard to scale up and do root-

cause analysis efficiently, and the projected larger scale will require more data sets.(Barrett *et al.*, 2005) Change advice from the FDA also gives a plan for making changes after approval. The FDA recently put out a guideline to make it easier for certain low-risk chemistry, manufacturing, and control (CMC) post-approval production changes to not have to be reported.

2.4 Current PAT Tools in the Industry

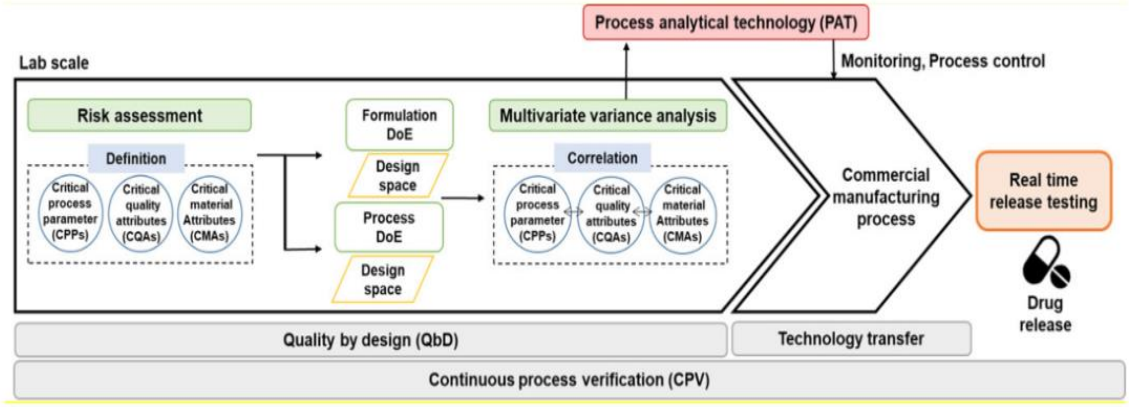


Figure 5 Overview of PAT application through QbD with continuous manufacturing - Source: (Kim et al., 2021)

2.4.1 Near-Infrared Spectroscopy (NIRS)

NIRS is a qualitative and quantitative study that uses light in the near-infrared range of 780–2800 nm to measure how molecules move and how much light they let through or reflect.(Moes *et al.*, 2008) Most of the time, it is used in the pharmaceutical business as a tool for real-time process monitoring to keep an eye on product quality and make sure it is good while it is being made.(Kim *et al.*, 2021) NIRS is directly linked to a fiber optic probe, which measures the transmission and reflections of NIRS by the sample to evaluate the quality of the product without affecting it which allows QC activities be done in real time. Inside the probe is an optical fiber, a lens, a mirror, and a data channel. It is linked by a sapphire window, so it can be used well even when process conditions aren't good. The light emitting from the probe is focused on the lens of the NIR spectrometer by reflecting a sample, the light that bounces off the mirror at the end of the probe is sent to the NIR range.

Through computer software linked to the NIR spectrometer, the signal being sent is turned into a spectrum.(Moes *et al.*, 2008) But one problem with NIRS is that it's harder to figure out what a signal means than with traditional research methods like chromatography, ultraviolet/visible (UV-VIS) light, and others. This is because the absorption bands overlap because the spectral complexity is so high. Also, because this is a relative approach, you need to use a reference method to make and check an accurate correction model to use it successfully.

Still, NIRS can measure the IQAs of a product quickly and without damaging it. Some literature from different pharmaceutical businesses shows that PAT is very useful for CPV through RTRT, which was done to monitor and evaluate product quality by using NIRS as a PAT tool.

2.4.2 Raman Spectroscopy

Raman spectroscopy is a non-contact analysis method that uses optical beams, just like NIRS. Most Raman laser sources have a wavelength of 785 nm, which is in the UV-VIS to near-infrared range. Visible light lasers are the most popular type.(De Beer *et al.*, 2008) In general, vibrations happen when chemical bonds are not stiff, and the frequencies of molecular vibrations can be used to describe materials. Raman spectroscopy is used a lot in the pharmaceutical industry because it gives detailed information about the vibrational transitions of a solid, liquid, gas, gel, or powder sample, which makes it easy to quickly figure out its chemical makeup and structure.(Read *et al.*, 2010) Raman spectroscopy is used to find out what kind of molecule is in a sample, and the strength of the molecules can be used to figure out how much drug is in a sample. Raman spectroscopy is a great choice for PAT systems because it can work both on-line and in-line. It also gives both quantitative and qualitative data, which makes it possible to watch and control real-time processes in an accurate and consistent way.(De Beer *et al.*, 2008) For each movement of the scattered photon energy, the Raman spectrum of a particular molecule is different depending on the compound. It can be used to keep track of quality information because it has a unique fingerprint. It can also be used to test liquids without moisture interruption getting in the way., like Fourier-transform infrared spectroscopy (FTIR) or NIRS, and it can measure things quickly.

Raman spectroscopy, like other types of spectroscopies, is often used to watch CPV in real time in different pharmaceutical unit processes, such as mixing, granulating, coating, and tableting. It can examine the IQAs and CQAs of the drug's composition throughout the blending process, the moisture content during the dehydrating and milling process, and the coating thickness and composition during the coating process.(De Beer *et al.*, 2008) It can also identify polymorphs in API preparation, analyse granule formulations, check the uniformity of the blending process, and measure particle size.

2.4.3 Terahertz Pulse Imaging (TPI)

TPI is a popular PAT instrument for real-time imaging. The 3D arrangement is linked to the terahertz absorption spectrum, which covers the range of 0.1–4.0 THz, which is between infrared and microwave frequencies. Far-infrared radiation is the name for the terahertz range because of this. Compared to infrared radiation, it has a longer wavelength, which makes it less likely to spread. Also, when it reacts with sample, it is less likely to be damaged by the lower radiation energy.(Gowen *et al.*, 2007a) TPI is also used a lot as a non-invasive way because it doesn't use ionizing radiation and is safe to use.

As was already said, TPI is mostly used in the process of treating pharmaceuticals. It is used to figure out how thick the coating is on sustained-release pills, where the thickness of the coating is directly linked to how much drug is released. If the drug is released through the coating instead of the tablet dissolving, it can be forecast by using TPI to look at how the coating is made.

2.4.4 Hyperspectral Imaging (HSI)

HSI is a non-destructive PAT tool that utilizes existing imaging and spectroscopy techniques to obtain spatial and spectroscopic information from the sample.(De Beer *et al.*, 2009) HSI can be used for a wide range of wavelengths, including the visible, the near-infrared, and the short-wave infrared (1000–2500 nm). The HSI tool takes a picture that has a spectrum of a certain place in each pixel. In each space of the image/pixel, a few hundred wavelength bands are present. This makes a lot of information because the spectrum is always being gathered from a big area.

In the blending, granulating, and tableting processes, HSI provides accurate chemical and spatial imaging data regarding the quantity and location of API and excipients. The pictures that were collected are put together and worked on in three dimensions (3D) to make the data cube. There are four main types of scanning: spatiotemporal scanning, spectral scanning, nonscan, and spatial scanning. As an online PAT tool, HIS has been used to check on the consistency of mixing and to look at how tablets vary.(De Beer *et al.*, 2008) In addition, it can analyze samples that need to be evaluated more quickly compared to spectral analysis, and it can be used to inspect packages to ensure that products are placed correctly, detect broken tablets, and locate empty slots. HIS device for checking the amount of drugs on the surface of microtablets. The PLSR and PCR chemometric models were used to look at the obtained multivariate data. The writers had a good sense of what would happen and suggested using HIS too quickly determine product quality in-line.(De Beer *et al.*, 2009)

2.4.5 Spatial Filter Velocimetry (SFV)

SFV is a method for measuring the length of a particle's cord as it moves. Therefore, it is utilized as a PAT instrument for real-time monitoring of particulate size, size distribution, and shape in various solid dosage manufacturing procedures including fluidized-bed granulation and spray-drying.(Gowen *et al.*, 2007b)

But, unlike FBRM, which uses backscattered laser light to figure out the length of the particle code, SFV uses a shadow. When the particles undergo an alternating laser beam, a shade is cast in the linear fiber-optic arrays, and an individual fiber sends out a secondary pulse wave. So, it is possible to measure the size and speed of each particle at the same time and figure out the particle's chord length by using the time of the pulse signal and the speed at which the particle is going.(Gowen *et al.*, 2007b) So, quality control can be done with SFV monitoring by looking at the properties of intermediate and finished products in a way that isn't invasive and doesn't require special sampling methods. Because of these things, SFV can be used in CPV through RTRT as a tracking tool.

Application	Process analyzer	Statistical tool	Observation
Rapid and accurate tablet identification	Acoustic resonance spectroscopy	Principle-components analysis (PCA)	A fast and non-destructive method for on-line analysis and label comparison before shipping, to avoid mislabeling of drug
Active determination of content of uncoated pharmaceutical pellets	NIR	Partial least-squares (PLS) analysis	NIR method was developed and validated for determination of active content ranging from 80-120% of the usual active content of the uncoated pharmaceutical pellets
Mechanical property determination of the drug tablet	Air-coupled excitation and laser interferometric detection	Iterative computational technique	Examination of the vibrational resonance frequencies can be directly correlated with the mechanical properties of the tablet providing a non- destructive technique for physical characterization of the tablet
Analysis of sustained-release tablet film coatings using terahertz pulsed imaging (TPI)	Terahertz pulsed spectroscopy (TPS)	–	Tablet coating thickness, coating reproducibility, distribution, and uniformity can be easily determined. The method was validated against optical microscopy imaging
Roller compaction process of dry granulation	Thermal effusivity measurement using the effusivity sensor	–	Effusivity measurement were used to monitor the roller compaction process
Evaluation of content uniformity for low-dose tablets	NIR	PCA	NIR/PCA was used to predict content uniformity of low-dose tablets manufactured by a direct compression process
Powder flow characterization	NIR	PLS	Real time information on the flowing cohesive powder mixture was used to avoid powder segregation or agglomeration and thus to maintain product quality
NIR measurement of the potency of an API	NIR	PLS	Potency of heparin active pharmaceutical ingredient was determined by this non-destructive method
Active drug identification and content determination	NIR	PLS	NIR method was used for qualitative and quantitative determination of ranitidine in granules for compression, cores, and final tablet
Monitoring capsule manufacturing at small-scale level	NIR	PLS	PAT was utilized for testing of identity and quality of raw materials, for blend uniformity analysis, and for final content analysis of busulfan pediatric capsules
Quantification of the active ingredient in pharmaceutical injectable formulations	NIR and UV–visible spectroscopy	PLS	More economical and less time-consuming method for quantification of the lysine clonixinate
Prediction of dissolution for a sustained-release dosage form	NIR	PLS	This method was used to identify differences in the composition of the coating polymer used for a tablet and thus assist with prediction of dissolution behavior
Analysis of liquid formulations containing sodium chloride	Laser-induced breakdown spectroscopy (LIBS)	–	Method does not need any sample preparation and is less time-consuming

Figure 6 Examples of PAT Tools applications in Pharmaceutical Industry - Source: (Rathore, Bhambure and Ghare, 2010)

2.4.6 Mass Spectrometry (MS)

MS is an extremely beneficial PAT tool for figuring out the quality of a drug, chemical, or other substance. Because it has a high resolution and accurate mass, it is also used to analyze the quality of small molecules. It is often chosen and used in biological processes, like studying biomolecules that are not the same. It also gives a quick study when a lot of samples can be prepared at once and data processing can be done automatically.(Read *et al.*, 2010) People often use the mass spectrum to find out what two compounds are or to figure out the structure of a new compound. It gives the correct molecular weight or molecular formula to show that a certain structural unit exists in a molecule. The main benefit of MS is that it can measure many kinds of molecules with great accuracy and in a very short amount of time. It is also used to figure out the structure and chemical properties of other molecules by figuring out how much of a known substance is in a sample or to find out what chemicals are in a sample that are unknown. For MS to work, there must be a vacuum, and the sample must be dissolved and ionized. So, one problem with MS is that a sample can't be looked at if it can't be broken up and dissolved. MS is usually used to direct the drying process in real time, especially to keep an eye on the small amounts of organic solvents that are used to make intermediate and finished products.

2.4.7 Acoustic Resonance Spectrometry (ARS)

ARS listens for and examines the sounds made during the process of making pharmaceuticals. It is generally used for processes that make noise, like checking a chemical reaction or mixing, pulverizing, or granulating drugs in a fluidized bed.(Medendorp and Lodder, 2017) As with most PAT tools, ARS does physically alter or intervene with the sample. Using sound emission, you can find out things like the size and shape of the particles and how much water is in them. Changes in the physical features of the powder, such as how it behaves when compressed and how it moves around, can be tracked. Tsujimoto et al. used ARS in the fluid bed granulator to track and describe how particles moved because of friction. They also used the connection between ARS and particle motion to track how particles behaved. At the bottom of the fluidized-bed granulator, ARS was put in place, and the sound it picked up was increased and the sensitivity was adjusted so that the frequency could be analysed. As the rotating speed of

the fluidized-bed granulator went up, the force of the particles hitting the room wall went up.(Medendorp and Lodder, 2017) This caused the AE amplitude to go up. ARS was also able to find out during the fluidized-bed granulation process that the increased amount of spray solution caused the powder to be unstable because it had more water in it.

2.5 Technical Challenges to PAT Implementation

Even though a lot of research has been done in both academia and industry to get a better understanding of the chemical and physical aspects of each process step from a first-principles perspective, there is still room for a better mechanistic understanding of how process parameters affect critical-to-quality attributes in pharmaceutical manufacturing.(Fonteyne *et al.*, 2015)

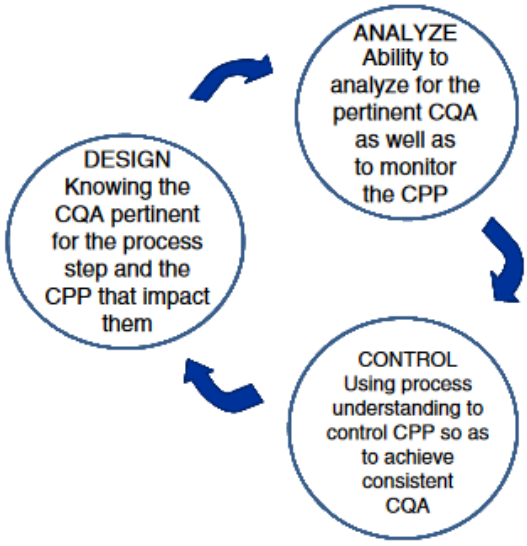


Figure 7 Three steps for designing PAT implementation objectives - Source: (Rathore, Bhambure and Ghare, 2010)

When it comes to using PAT Technology, the biggest technical problem is often the different kinds of materials used in the process. Method creation should pay special attention to sampling, especially when it comes to a representative sample size, how samples are given to analyzers, and how probes get dirty.(Read *et al.*, 2010) Another aspect of quality control that is unique to the pharmaceutical industry is both a technical challenge for the use of process analytics in the manufacturing process and a great opportunity: the elimination of the need to test the finished product to figure out how good it is. One of the most hopeful reasons to use process analytics is that PAT could be used to control the quality of the product during and not after processing. When the FDA PAT advice came out in 2004, almost no one had heard of this quality control method, which is also called "real-time release" (RTR)

(Yu *et al.,* 2004) Since then, a small number of listed and sold products have been evaluated in real time, and that number is growing. The change from traditional batch processing to continuous processing is another thing that makes process analytics a good idea and that didn't exist in the pharmaceutical business until recently.

Even though continuous processing isn't likely to be widely used in routine manufacturing for a few more years, most of the big pharmaceutical companies are already developing it in-house or with outside help so they can get the benefits of it, such as tighter quality control, less risk when scaling up, and more flexibility in responding to changes in demand. (Fonteyne *et al.,* 2015) The pharmaceutical industry will need to implement process analytics and feedback loops in the same way that other industries that have been employing continuous processing for a significant amount of time have done so to maintain control over these processes.

2.6 Regulatory Challenges to PAT Implementation

Current Good Manufacturing Practices (cGMPs), which are set out in the United States' Code of Federal Regulations (CFR) 11, are an important part of the rules for making drugs. Even though it's up to each organization to figure out how to interpret these rules in detail, the cGMP has made sure that high-quality products are made even though it doesn't directly encourage innovation in manufacturing. On the other hand, there have been a significant shift in the way that countries like the US and the remaining nations of the globe regulate the industrial and academic development of medications since 2004 The Food and Drug Administration (FDA) published a guideline in 2004 under the name "cGMPs for the 21st century" to offer a risk-based approach to the standards.(Glassey *et al.,* 2011) This was meant to remove the barriers to innovation. The next step was the release of the FDA PAT guidance, which was made with help from both business and academics.

Manufacturing units need to set up quality systems that describe in detail every step of the process used to make a product in order to follow the rules for compliance. The most important part of this kind of quality system is keeping detailed records of how the product is made and how it is tested. When developing or putting process analytics into place in the manufacturing units, documentation is a big part of the work

process.(Fonteyne *et al.*, 2015) This part is not meant to give a detailed explanation of these requirements or to be a guide for how to write good documentation. Instead, system qualification and change control, which are unique to the pharmaceutical business and have a lot to do with the way PAT is often used in process analytics.

Most of the time, the System life cycle document is made up of technical papers that describe the system. Before using PAT Tools in a pharmaceutical lab or manufacturing site, the SLC documentation set must usually be full. It must also be done before the system's data can be used in GMP.(Blanco *et al.*, 2006) Some of the ideas for qualifying instruments using the SLC model could slow down the start of process analytics. With the way process analytics uses changing technologies, information for some parts of a traditionally built SLC may not be made available until after the system has been used. It's possible that the creation of a process analytics approach will call for some feasibility studies, preferably with access to actual process equipment.(Fonteyne *et al.*, 2015) This is because the system or method requirements might be based on the capabilities of the process, which can only be measured with the process analytics system. On the other hand, the SLC idea has always required that these specifications be set before the experiments begin for laboratory analytical systems that use external standards instead of real process samples to test how well they work. When applying SLC requirements to process analytics analyzers, it will be important not to put the "cart before the horse" and instead do a thorough quality and business risk analysis for how the instrument will be used instead of blindly following what has been done in the past when applying the SLC idea to laboratory analyzer systems.

The pharmaceutical and chemical sectors both place a significant emphasis on the concept of change control. Change control can take on numerous forms, including change control of systems (carried out with the help of PAT), change control involving analytical methodologies, and change control of process. In the pharmaceutical business, change control means following rules. For all of these types of change control, it is important to keep an eye on the status of the system, method, or process in relation to the initial qualification or validation, and to take steps to make sure that the changes don't affect the GMP status of the system or the validity of the assumptions that were used to run the system, method, or process before the change.(Fonteyne *et al.*, 2015) One reason for change control is that it makes it easier for systems to work even if they don't belong to the same person. It also makes it less likely that non-expert will make changes to the

system that aren't needed. In the area of process analytics, where the efficiency of systems, techniques, and processes can be affected by a vast array of factors, formal documentation helps to identify and manage the risk that comes with a change. This risk can be caused by several different things. Most pharmaceutical businesses' quality systems deal with requests to change equipment, analytical methods, and processes. But, like the idea of process validation, it can make it hard to use principles of continuous improvement and make it expensive to make even necessary changes to the system. (Blanco *et al.*, 2006)

2.7 Conclusion

Today's PAT filings for the pharmaceutical industry are much more complicated than the first ones, which were mostly about QC processes or simple applications to certain production steps that used NIR to find the end point. Before pharmaceutical companies will be able to handle this workflow on their own, it will take a few years for the regulatory agencies to get used to and comfortable with many of the ideas used. Industry has moved on from the simple MVDA of processing old data. In the next few years, the regulatory authorities will have to work hard to catch up with many of the methods that are already being used, such as extracting and using complex PAT monitoring tools in a process development or production setting. Predictive PAT applications, which are based on correlating the performance of various elements of a process, are another area that will see an increase in the number of filings soon. This is an area where regulators might be proactive or slow down progress. This will require admitting the amount of variability, having a good understanding of how the processes work together, and taking a QbD approach to the whole process.

CHAPTER THREE

Methodology

3.1 Introduction

For this study, the research philosophy is social constructivism, the research methodology is descriptive, and the research method is qualitative. In the next few parts, I will explain why I chose the research philosophy, research design, and method I did for this study.

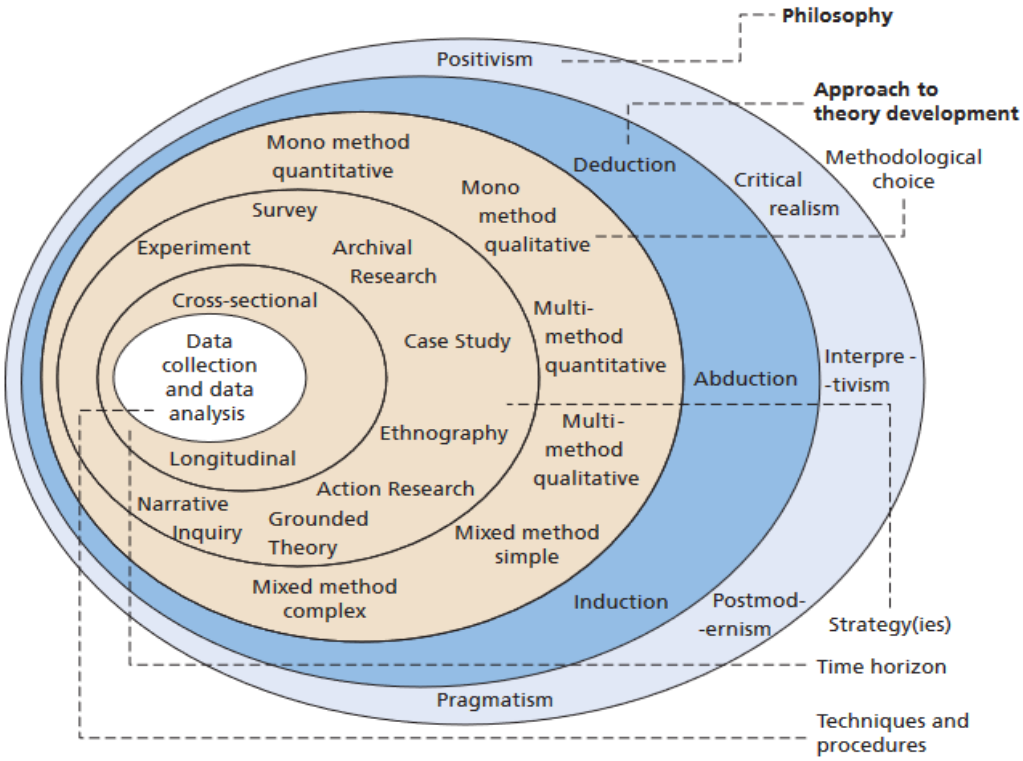


Figure 8 Framework to understand the research onion - Source: (Saunders et al., 2019)

3.2 Research Philosophy

The most suitable philosophy for this study is social constructivism because the researcher wants to get information from interviewees who have valuable knowledge about PAT implementation challenges in the pharmaceutical sector. The people being interviewed know what these challenges are because of their education and professional work experiences. They will talk about how their knowledge can be used to improve PAT implementation in pharmaceutical companies. The idea in constructionism that truth, reality, and information are all relative to the person who knows them is another reason

why this method is used.(Saunders *et al.*, 2019) So, by getting people involved, the views and answers they give will help the researcher find important themes to study, which will help them learn more about the topic. In this study, the researcher will make a promise to listen to the interviewees' thoughts and feelings and explain what they mean.

3.3 Research Design

The framework for the research is what research design is all about. It shows how the researcher will do the research, how they will deal with the research situation, and how they will answer the research questions. This plan, as a result, shows the research goal, research strategy, collecting and analysing data, time frame for the research to be done, social issues, research limitations, and reasons for the choices that were made. So, the study design shows the conceptual structure, which is made up of the choices made about how to collect, analyse, and make sense of the data. So, the idea of this study's research is one of exploration. The reason this design was chosen is to help the study learn more about the challenges of putting PAT into place, which haven't been studied much, and how it affects the pharmaceutical industry. This is the main reason why experimental research design is used. It gives researchers the chance to learn more about an issue or subject that hasn't been studied much before.(Saunders *et al.*, 2019)

3.4 Selection and Sampling of Participants

Wang and Gao (2020) defined that qualitative research has a purpose because it allows for the careful or meticulous selection of participants who the researcher thinks know a lot about the topic because they have certain qualifications. This means that their views and perspectives will be valuable and could help to build strong research results. Even though the sampling process in qualitative research design has been said to be non-probabilistic and could be biased, the benefit of using this method is that the data the researcher gets from the subjects is likely to be rich and well-informed. So, the current research will use semi-structured interviews, and respondents will be chosen through convenience sampling because they are easy to reach, willing to take part in the research, and expected to give good answers because of their knowledge and experience in the field of pharmaceuticals.(Saunders *et al.*, 2019) Five people who are experts in quality assurance, pharmacology, and the making of drugs have been chosen to take part in the semi-structured talks. They work with some of the largest pharmaceutical companies and

maintain global affiliates all over the world. The choice of five people to interview has been proven to be right because between the sixth and twelfth question, saturation sets in.

The details of participants are as follows:

Information	**Participant 1**	**Participant 2**	**Participant 3**	**Participant 4**	**Participant 5**
Gender	Male	Male	Male	Male	Male
Education	PhD, QP	Master's Degree, QP	PhD	Bachelor's Degree	Bachelor's Degree
Area of Work	Supplier Auditor	Quality Assurance Manager	Data Analytics Specialist	Lean Specialist	Production Operator
Position	Senior Manager	Manager	Data Analyst	Process Engineer	Production Technician
Experience	18 Years	12 Years	6 Years	1 Year	4 years

Table 1 Demographic Information of the Interview Participants - Source: (Researcher 2023)

3.5 Structure of Interviews

Research study adopted semi-structured interviews since they have a lot of added advantages and are beneficial. For example, the interviewer and participants can talk about whatever they want, and the interviews are interesting enough that participants can say whatever they want. (Saunders *et al.*, 2019) This method also helps people come up with interesting answers that show why the "what" is the way it is or explain "why" certain things are the way they are. A guide for interviews has been made to help focus and guide the conversations, which are meant to answer the research questions of this study.

3.6 Transcription of the Interviews

The semi-structured interviews took place online using either Google Meet or Zoom, based on what the participants wanted. All the researchers have said that they would like either one of these video platforms because they are easy to use and are used by many people. The researcher offers access to either of the two virtual meeting sites, if each

participant prefers the other one. During the interviews, notes will be taken to record what the interviewees have to say. But the interviews were not videotaped because the participants did not want to be recorded on video or audio. Instead, transcriptions were given to the participants after the interview so they could review them for any ethics concerns. During the interviews, important things that the people said were written down in a notebook. The researcher will be able to analyse the answers of the participants well by using both the transcripts and the notes in the notebook. The responses are going to be utilized for the data analysis.

3.7 Method for Data Analysis

Salamzadeh (2020) defines that there are five ways to analyze qualitative data. The Anthropological approach, the Gioia approach, the Long Data Excerpts approach, the Temporal Phases approach, and the Vignettes approach are the five ways to look at qualitative data. But, out of these five methods, the Gioia method has been shown to analyse qualitative data in a more scientific, methodical, and organized way, similar to how quantitative data is analyzed.(Saunders *et al.*, 2019)

3.8 The Gioia Approach

The Gioia method is a well-known way to analyze qualitative data that is applied in qualitative research. It is made up of the first-order code phase, the second-order code phase, and the third-order code phase.(Gioia, Corley and Hamilton, 2013) During the first-order code step, all of the answers from the participants are put into a first column. Then, these participants' answers are put into groups with identical themes in another column, which makes it easier to analyze.(Magnani and Gioia, 2023) During the third-order code stage, the second-order codes are purposefully broken down into specific ideas or concepts that stand for the codes. The result of this whole process is the "code map," which looks like a statistical analysis or a grouping of concepts into codes that show the average thoughts of the people who took the survey.(Gioia, Corley and Hamilton, 2013) This code map is what would be talked about in the next chapter.

3.9 Ethical Considerations

The supervisor in charge of this study made sure that the research tool was reliable by making sure that it was good enough to meet the research goals of this study. Before participants were asked to take part in the semi-structured interview, they gave their informed consent and were told about the purpose of the research. They were also told that their role was limited to giving answers to the questions in the interview guide. Participants were additionally informed that they could stop the answering questions at any time during the interview and nothing detrimental would happen to them. They were also told that they didn't have to answer any of those queries they didn't like if they didn't want to. They were also informed that the information they have provided in the responses is going to be utilized only for this study, and that any information they provided to the researcher would be kept confidential.

CHAPTER FOUR

Data Analysis and Interpretation

4.1 Introduction

In this chapter interview results obtained on the topic of PAT implementation challenges faced by the pharmaceutical industry is being disclosed and analysed. All the participants have attended the short interviews and gave their perspective on the knowledge of PAT implementation challenges faced by the industry. Participants are asked questions that are formulated from the research questions that are generated from the study: 1) What are the current challenges for the implementation of PAT tools in the pharmaceutical industry ?2) Are there any possible downsides in the implementation of PAT tools that are delaying adoption?

The socio-demographic participant information is discussed below, however considering the research ethics guidelines they have been coded to protect the identity and further shield their exposure. Instead of giving the name of the individuals participated in the interviews, identifiers were given such as: PRT-PAT1 for participant 1, PRT-PAT2 for participant 2, PRT-PAT3 for participant 3, PRT-PAT4 for participant 4 and PRT-PAT5 for participant 5.

4.2 Coding of Participants

Participant ID	Identifier of the Participant	Status of Interview
1	PRT-PAT1	Completed
2	PRT-PAT2	Completed
3	PRT-PAT3	Completed
4	PRT-PAT4	Completed
5	PRT-PAT5	Completed

Table 2 Identifier Codes of the Participants - Source: (Researcher 2023)

From Table 2, we can see that a total of five individuals have taken part in the interviews and have answered questions that have been derived from the research questions.

4.3 Analysis of Responses

The responses from the questions have been compiled in the below table 3 for better understanding with the related research objective.

Table 3 Responses of PRT-PAT1 for the Interview Questions - Source: (Researcher 2023)

Participant ID	Interview Question and Objective	Response of Participant
PRT-PAT1	Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology. Related to Research Objective 1 To determine and understand the experience of the participant and exposure to the PAT Tools.	I have around 18 years of experience in Supplier Auditing and Internal/External Auditing. Now I am working as a Senior Manager for the Principal Auditor office of a major Pharmaceutical MNC. During my tenure, I have audited a few sites that have implemented PAT in their manufacturing units.
PRT-PAT1	Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively? Related to Research Objective 1 To understand the current challenges involving the implementation of PAT methods from the perspective of the participant for further analysis.	From my experience of my earlier audits of the facilities that have implemented PAT tools, I would say that time constraints are a major challenge that industry is facing related to PAT implementation. Most of the PAT tools now are highly sophisticated and can capture wide range of data from the sample however it's the effective implementation with the existing instrumentation that causes delay in full scale production roll-out. It also takes significant amount of time to standardise the said tool for the production process and issue clearance based on CQA's

		captured. Major pharmaceutical company's invested millions in developing their own PAT processes but in these days of start-ups there have been uprising of many companies that have come up with superior isolated PAT tools that can be used for variety of monitoring purposes
PRT-PAT1	Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies? Related to Research Objective 2 To determine if there any downsides/disadvantages to the implementation of PAT that hinder the adoption in the industry.	In my earlier encounters with the team members within the unit, I believe the development and execution of the system is more complicated than any usual project development for a tool installation. The regulatory oversight on the overall project and the constant compliance checks before and after implementation make it quite intensive both during development and implementation. Overall, I haven't observed any downsides to the process other than the complicated execution which not every pharmaceutical company is capable of or wants to allocate funds to.
PRT-PAT1	Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes? Related to Research Objective 1 To examine any challenges that are related to existing manufacturing methods which delay adoption of PAT tools.	As I was telling you earlier, complicated execution is one of the reasons why not many pharmaceutical companies agree to get involved with this technology. The regulatory aspect after implementation trying to determine CQAs meet the requirements for line clearance is another challenge entirely. Not all pilot studies work a cent percent as they did when it comes to full scale production implementation.
PRT-PAT1	Interview Question 5	Companies that implement PAT within a production process needs

	Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them? Related to Research Objective 2 To determine if any ethical or privacy concerns exist that delay the adoption of PAT tools in the industry	to clear many audits and compliance regulations before ever standardized for the product. This is a cost cutting measure to avoid QC tests postproduction and have more real time control on production which makes it the Intellectual property of that company, unless its disclosed as open knowledge in any scientific articles published by the company. Having said that, there are many independent PAT tool consultants and start-ups that have specialized PAT tool implementations with many different clients that function on non-disclosure agreements.

Table 4 Responses of PRT-PAT2 for the Interview Questions - Source: (Researcher 2023)

Participant ID	**Interview Question and Objective**	**Response of Participant**
PRT-PAT2	Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology. Related to Research Objective 1 To determine and understand the experience of the participant and exposure to the PAT Tools.	I have worked on a project that involved filing compliance and regulatory documentation for a PAT tool implementation and worked closely for generating validation procedures for the implemented tool. Altogether, I worked on the project for around 1.5 years and have 12 years of total experience in the field.
PRT-PAT2	Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively? Related to Research Objective 1	I can give you a regulatory perspective on the question based on my experience. The process of PAT implementation heavily relies on the product lifecycle and the subsequent regulatory approvals, this shell out a lot of money form the budget allocated to the process

	To understand the current challenges involving the implementation of PAT methods from the perspective of the participant for further analysis.	development. The initial challenge would be to justify that the implementation would be able to make it through the regulatory approvals through lab studies. The later one and the most important one would be the budget justification to make sure that it pays off in a long run.
PRT-PAT2	Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies? Related to Research Objective 2 To determine if there any downsides/disadvantages to the implementation of PAT that hinder the adoption in the industry.	It's a novel and more efficient way to get IOT enabled in a production process, the question would be to what extent is it beneficial. Generally, if you are talking about a product that requires extensive QC tests that sometimes overlap the production safety measures already taken in-line, for example Biologics it makes sense to invest in PAT no matter the expense now. But if you ask me an API unit trying to use PAT for efficient manufacturing isn't something that makes sense form a business perspective.
PRT-PAT2	Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes? Related to Research Objective 1 To examine any challenges that are related to existing manufacturing methods which delay adoption of PAT tools.	I would say the type of product and the overall life cycle of the product in that plant would be a great concern that any instrumentation. Validation in these days isn't as time consuming as before since most of the LIMS systems are now integrated with PQS and CVS. It's the product that's vital in integration of PAT since the product life cycle might be short and certain changes must be made to ensure the longevity of the PAT tool even when the product changes making it easier to get approvals from EMA and any other regulatory bodies involved.
PRT-PAT2	Interview Question 5	Well, all the data that transpires within the project is strictly

	Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them? Related to Research Objective 2 To determine if any ethical or privacy concerns exist that delay the adoption of PAT tools in the industry	confidential and I haven't seen any instance that it caused any concerns in terms of patent clauses since it's a process rather than a product and it's very hard to replicate without right people.

Table 5 Responses of PRT-PAT3 for the Interview Questions - Source: (Researcher 2023)

Participant ID	**Interview Question and Objective**	**Response of Participant**
PRT-PAT3	Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology. Related to Research Objective 1 To determine and understand the experience of the participant and exposure to the PAT Tools.	I have done my PhD in the field of Data Analytics in collaboration with a pharmaceutical company that involved generating data gathering procedures and implementing statistical algorithms for PAT tools. I am currently working as a PAT Technologist/Manufacturing Data Analyst at one of major pharmaceutical companies with around 6 years of experience in this field
PRT-PAT3	Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively? Related to Research Objective 1 To understand the current challenges involving the implementation of PAT methods	The most understated and unknown activity of PAT tools is their data management and capture. PAT is one of the most data intensive processes which is superior to many technologies in the pharmaceutical industry. Any spectral data that has been captured is never discarded and always analysed to extreme lengths to predict any line errors. Due to its multivariate nature spectral data

	from the perspective of the participant for further analysis.	comes with its own challenges especially the storage aspect of it. Normally within a laboratory setting any of these challenges wouldn't seem much complicated since the isolated nature of it, but when you move to production with real-time analytics happening alongside enterprise software integration it can be quite a challenge to manage data with standard methods.
PRT-PAT3	Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies? Related to Research Objective 2 To determine if there any downsides/disadvantages to the implementation of PAT that hinder the adoption in the industry.	Once an organisation considers PAT tool implementation it essentially means that they have far more to gain in the future than they are losing in that moment. The downside aspect I would say is the process control aspect of it. I have delt with many PAT tools that are well integrated and provide excellent spectral data storage solutions within the tool implementation plans but never give any real time process control over the production. PAT that just measures CQAs isn't quite value providing anymore with companies looking for total enterprise automation. To provide better value and help in change control a PAT tool must be able to come with a process control measure/method which most of the modern PAT tools in the market lack.
PRT-PAT3	Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes? Related to Research Objective 1	Getting PAT tool implemented on-site is more than just one technical tool implementation. Unlike some other process changes the entire architecture of implementation must be mapped out to determine overall system management. Data integration & management and

	To examine any challenges that are related to existing manufacturing methods which delay adoption of PAT tools.	software modelling is the main challenge when it comes to cross instrumental implementations. Often cases I have seen technical teams reaching out to equipment manufactures to make changes in the systems for accommodating modelling software with a functional application programmable interface because most of the instrumentation in the sector are designed as standalone earlier and things have been moving to automation since past 5 years.
PRT-PAT3	Interview Question 5 Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them? Related to Research Objective 2 To determine if any ethical or privacy concerns exist that delay the adoption of PAT tools in the industry	Modelling software and most of the other software's in use aren't something that pharmaceutical companies essentially develop from scratch and own, they are often licensed from major tech companies like SAP & Emmerson who are major players in the industry. The ethical and privacy concerns are addressed by the licensing agreements per my understanding.

Table 6 Responses of PRT-PAT4 for the Interview Questions - Source: (Researcher 2023)

Participant ID	**Research Question and Objective**	**Response of Participant**
PRT-PAT4	Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the	I am a Lean Process specialist involved in a PAT project planning for a pharmaceutical company. It was essentially a contract that was being done for a span of 10 months. I primarily work with electronics manufacturing facilities with process development and lean

	years of experience with the technology. Related to Research Objective 1 To determine and understand the experience of the participant and exposure to the PAT Tools.	implementation being my main role.
PRT-PAT4	Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively? Related to Research Objective 1 To understand the current challenges involving the implementation of PAT methods from the perspective of the participant for further analysis.	From my exposure to the project, I would say that the available expertise on PAT tools internally within an organisation is very low. It adds quite significant burden to the project when it needs more external resources than internal. It is a complex model for a complete lean implementation hence there has been many instances there was internal resistance for push for PAT.
PRT-PAT4	Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies? Related to Research Objective 2 To determine if there any downsides/disadvantages to the implementation of PAT that hinder the adoption in the industry.	During the project implementation and regulatory submissions for the change reports that are going to occur there are many redundant processes that aren't required but necessary to get approvals. I would say that's the major downside form a project management angle.
PRT-PAT4	Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes? Related to Research Objective 1 To examine any challenges that are related to existing	Lean six sigma and any other waste elimination framework within pharmaceutical industry must meet the regulatory body approvals which makes it quite hard for getting it done on time. I would say that process change documentation and validation are the ones that take-up time and cause delays in the project within PAT

	manufacturing methods which delay adoption of PAT tools.	implementation when dealing with integration of different processes.
PRT-PAT4	Interview Question 5 Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them? Related to Research Objective 2 To determine if any ethical or privacy concerns exist that delay the adoption of PAT tools in the industry	I have no clue about this question, I haven't faced a situation where ethical concerns were involved within the project. I would say it's more of EHS related.

Table 7 Responses of PRT-PAT1 for the Interview Questions - Source: (Researcher 2023)

Participant ID	**Interview Question and Objective**	**Response of Participant**
PRT-PAT5	Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology. Related to Research Objective 1 To determine and understand the experience of the participant and exposure to the PAT Tools.	I have worked as a member of the team and have been trained on PAT Tool during its installation to the fluid bed granulator. I have been working as a Manufacturing Technologist for the past 2 years and have earlier experience as production operator with an API manufacturing unit for 2 years
PRT-PAT5	Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively? Related to Research Objective 1	I am not sure about all the industry, but I would say the training is very time consuming unlike any other standard instrument training and the calibration is quite complex as well between batches.

	To understand the current challenges involving the implementation of PAT methods from the perspective of the participant for further analysis.	
PRT-PAT5	Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies? Related to Research Objective 2 To determine if there any downsides/disadvantages to the implementation of PAT that hinder the adoption in the industry.	The PAT tool was used with the existing fluid bed granulator with minor changes made in the tank bed for the installation of probe, overall, I would say I didn't see any negative sides of it.
PRT-PAT5	Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes? Related to Research Objective 1 To examine any challenges that are related to existing manufacturing methods which delay adoption of PAT tools.	For the installation of the probe, they had to make custom changes to the fluid bed granulator and there were separate validation procedures involved after installation.
PRT-PAT5	Interview Question 5 Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them? Related to Research Objective 2 To determine if any ethical or privacy concerns exist that delay the adoption of PAT tools in the industry	I don't think I can answer this, I am unaware of anything related to privacy concerns.

4.4 First Order of Codes for Interview Questions

From the responses of the participants, the first order codes will be drawn. The first order codes are summarised points that are generated from the responses.

Table 8 First Order Codes Generated from Interview Data - Source: (Researcher 2023)

Interview Question	First Order Codes
Interview Question 1 Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology.	1. Participant has 18 years of experience in Supplier Auditing and Internal/External Auditing and has audited a few sites that have implemented PAT in their manufacturing units. 2. Participant worked on a project that involved filing compliance and regulatory documentation for a PAT tool implementation with around 1.5 years on the project and have 12 years of total experience in the field. 3. Participant has a PhD in the field of Data Analytics in collaboration and has experience implementing statistical algorithms for PAT tools with around 6 years of experience in this field. 4. Participant is a Lean Process specialist involved in a PAT project planning for a pharmaceutical company with exposure to the technology for a period of 10 months. 5. Participant has been trained on PAT Tool during its installation to the fluid bed granulator and has 4 years of total experience in the industry.
Interview Question 2 What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively?	1. Time constraints are a major challenge that industry is facing related to PAT implementation. 2. Significant amount of time to standardise the said tool for the production process and issue clearance based on CQA's captured. 3. Superior isolated PAT tools that can be used for variety of monitoring purposes are available now from start-ups. 4. PAT implementation heavily relies on the product lifecycle and the subsequent regulatory approvals which is economically costly. 5. It's hard to reach justification that PAT implementation would be able to make it through the regulatory approvals through lab studies and the budget justification to make sure that its economically viable in long run.

	6. PAT is one of the most data intensive processes which is superior to many technologies in the pharmaceutical industry. 7. Multivariate nature spectral data makes its challenging to store. 8. Real-time analytics happening alongside enterprise software integration can be quite a challenge to manage data with standard methods. 9. Available expertise on PAT tools internally within an organisation is very low. 10. PAT is a complex model for a complete lean implementation hence there has been many instances there was internal resistance for push for PAT. 11. Training on PAT is very time consuming unlike any other standard instrument training and the calibration is quite complex as well between batches.
Interview Question 3 Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies?	1. The development and execution of the system is more complicated than any usual project development for a too installation. 2. The regulatory oversight on the overall project and the constant compliance checks. 3. Questionable on the extent of benefits. 4. PAT that just measures CQAs isn't quite value providing anymore with companies looking for total enterprise automation which most of the modern PAT tools in the market lack. 5. Many redundant processes are present that aren't required but necessary to get approvals.
Interview Question 4 What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes?	1. Not all pilot studies in laboratory work as they did when it comes to full scale production implementation. 2. Type of product and the overall life cycle of the product in that plant would be a great concern that any instrumentation since most of the LIMS systems are now integrated with PQS and CVS. 3. Entire architecture of implementation must be mapped out to determine overall system management. 4. Data integration, management and software modelling is the main challenge when it comes to cross instrumental implementations. 5. Instrumentation in the sector is designed as standalone earlier and things have been moving to automation since past 5 years. 6. Process change documentation and validation take-up time and cause delays in the project within PAT implementation.

Interview Question 5 Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them?	1. Unless its disclosed as open knowledge in any scientific articles published by the company, PAT tool implementation process knowledge is intellectual property. 2. Independent PAT tool consultants' function on non-disclosure agreements. 3. Data that transpires within the project is strictly confidential. 4. The ethical and privacy concerns are addressed by the licensing agreements.

4.5 Second Order Codes for Interview Questions

Further distillation of common opinions from the first order codes has been done and interpreted in the below table as second order codes.

Table 9 Second order codes generated from Interview Data - Source: (Researcher 2023)

Interview Question	**Second Order of Codes**
Are you involved in the implementation of Process Analytical Technology (PAT) methodologies in your organization? If yes, can you briefly describe your role and the years of experience with the technology.	1. Auditing Experience 2. Compliance and Regulatory Filing Experience 3. Data Analytics and Software Modelling Experience 4. Process Planning Experience 5. Manufacturing Experience
What are the current challenges in implementing PAT methodologies in the industry and your organisation comparatively?	1. Time Constraints 2. Economic Burden and Budget Constraints 3. Data Intensive Process 4. Specialized Personnel with Expertise
Have you observed any downsides in product quality, process efficiency, or cost savings after implementing PAT methodologies?	1. Complicated System 2. High Regulatory Oversight 3. Questionable on the extent of benefits. 4. Lack of Process Control
What are the challenges you have observed that obstruct the integration of PAT into your organization's existing manufacturing processes?	1. Failure of Pilot Studies 2. Product Life Cycle 3. Independent Instrumentation
Are there any ethical or privacy concerns associated with implementing PAT methodologies in the pharmaceutical industry? If yes, can you describe them?	1. Intellectual property. 2. Non-disclosure agreements. 3. Licensing agreements.

4.6 Second Order Codes with Respect to Research Questions

In the below table the interview questions have been linked to the research questions based on corresponding objectives mentioned in table 9. The second order of codes are then matched to the relevant research questions.

Table 10 Second Order Codes generated in relation to research questions - Source: (Researcher 2023)

Research Question	Second Order of Codes
Do the Participants have relevant experience?	Relevant Experience has been established
What are the current challenges for the implementation of PAT tools in the pharmaceutical industry?	Time Constraints Economic Burden and Budget Constraints Specialized Personnel with Expertise High Regulatory Oversight Questionable on the extent of benefits. Product Life Cycle Failure of Pilot Studies
Are there any possible downsides in the implementation of PAT tools that are delaying adoption?	Data Intensive Process Lack of Process Control Complicated System Independent Instrumentation Intellectual Property Challenges

4.7 Third Order Codes with Respect to Research Questions

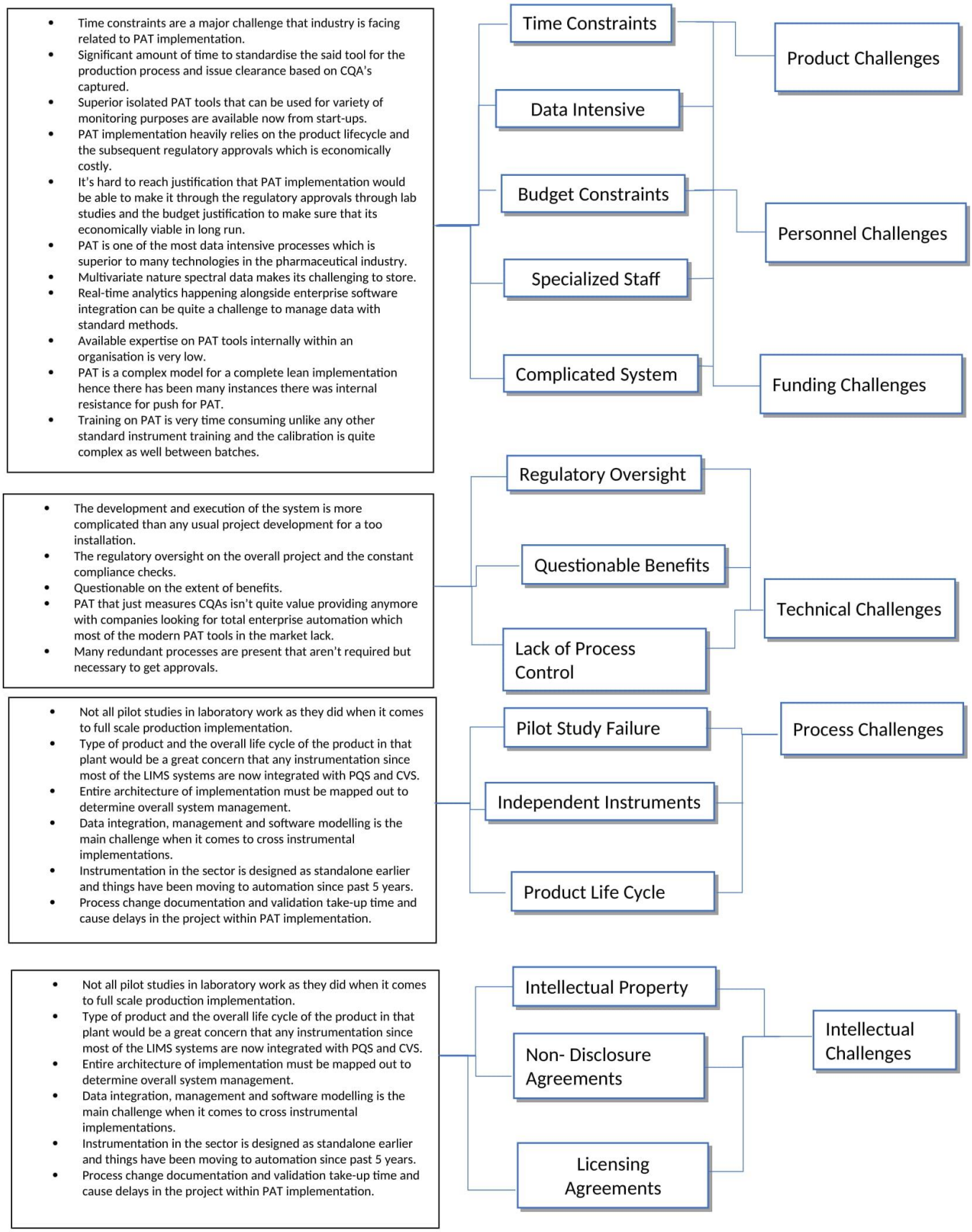
The third order of codes are generated by rendering the second order codes into thematic singular ideas. These third order codes give a wider outlook into the second order codes from table 10.

Table 11 Third order codes generated in relation to research questions - Source: (Researcher 2023)

Research Question	Third Order of Codes
What are the current challenges for the implementation of PAT tools in the pharmaceutical industry?	Product Challenges Personnel Challenges Funding Challenges
Are there any possible downsides in the implementation of PAT tools that are delaying adoption?	Technical Challenges Process Planning Challenges Intellectual Property Challenges

4.8 Results

Figure 9 Gioia Method is used to create mapping of the study conducted - Source: (Researcher 2023)



4.9 Interpretation of Results

After the research questions have been plotted against the third order of codes a clear understanding of thematic challenges faced by the industry in relation to PAT implementation has been identified.

4.9.1 Interpretation of Research Question 1

Research Question 1: What are the current challenges for the implementation of PAT tools in the pharmaceutical industry? In relation to this question the generated third order codes were Product, Personnel and Funding Challenges.

4.9.2 Product Challenges

Most of the participants have raised a concern about the type of the product that's being used greatly affects the implementation of the PAT tools and caused delay in implementation in many cases due to the underlying regulatory challenges. PRT-PAT1 said that *"The regulatory oversight on the overall project and the constant compliance checks before and after implementation make it quite intensive both during development and implementation".* PRT-PAT2 also pointed out saying "*the question would be to what extent is it beneficial. Generally, if you are talking about a product that requires extensive QC tests that sometimes overlap the production safety measures already taken in-line, for example Biologics it makes sense to invest in PAT no matter the expense now. But if you ask me an API unit trying to use PAT for efficient manufacturing isn't something that makes sense form a business perspective".* Both the statements clearly indicate the importance of product selection for PAT implementation, and it isn't standardized now. PRT-PAT2 also states that *"I would say the type of product and the overall life cycle of the product in that plant would be a great concern that any instrumentation. Validation in these days isn't as time consuming as before since most of the LIMS systems are now integrated with PQS and CVS. It's the product that's vital in integration of PAT".*

4.9.3 Personnel Challenges

Considering the complex nature of PAT tools and their time-consuming implementation, the expertise required by the staff handling the implementation is also a limiting factor for its delayed adoption. It can be seen in the statements made by PRT-PAT4 *"I would say that the available expertise on PAT tools internally within an organisation is very low. It adds quite significant burden to the project when it needs more external resources than internal."* The same can deduced from the comments made by PRT-PAT5 *"I would say the training is very time consuming unlike any other standard instrument training".*

4.9.4 Funding Challenges

From a business perspective funding and budget constraints are one of the main challenges for the delayed adoption of PAT Tools within the industry. It can be clearly seen from the statement of PRT-PAT1 *"Major pharmaceutical company's invested millions in developing their own PAT processes but in these days of start-ups there have been uprising of many companies that have come up with superior isolated PAT tools that can be used for variety of monitoring purposes".* And from the statement "*the complicated execution which not every pharmaceutical company is capable of or wants to allocate funds to".* Similarly, PRT-PAT2 also stated that *"and the subsequent regulatory approvals, this shell out a lot of money form the budget allocated to the process development. The initial challenge would be to justify that the implementation would be able to make it through the regulatory approvals through lab studies". And reaffirmed again later with a comment saying "if you are talking about a product that requires extensive QC tests that sometimes overlap the production safety measures already taken in-line, for example Biologics it makes sense to invest in PAT no matter the expense now. But if you ask me an API unit trying to use PAT for efficient manufacturing isn't something that makes sense form a business perspective".* PRT-PAT1 in the Interview question 5 pointed out clearly that PAT implementation is essentially a cost measure from a business perspective *"This is a cost cutting measure to avoid QC tests postproduction and have more real time control on production which makes it the Intellectual property of that company".*

4.9.5 Interpretation of Research Question 2

Research Question 2: Are there any possible downsides in the implementation of PAT tools that are delaying adoption? In relation to this question the generated third order codes were Technical, Process Planning and Intellectual Property Challenges.

4.9.6 Technical Challenges

Integration, Implementation, and deployment ends are the major technical areas where challenges were observed form the statements made by the participants. PRT-PAT1 stated in the opening that *"Most of the PAT tools now are highly sophisticated and can capture wide range of data from the sample however it's the effective implementation with the existing instrumentation that causes delay in full scale production roll-out. It also takes significant amount of time to standardise the said tool for the production process and issue clearance based on CQA's captured".* PRT-PAT3 clearly identified the data handling aspect of the issues by pointing out the challenges involved in rendering the spectral data obtained from the PAT tools. PRT-PAT3 states that *"The most understated and unknown activity of PAT tools is their data management and capture. Due to its multivariate nature spectral data comes with its own challenges especially the storage aspect of it. Normally within a laboratory setting any of these challenges wouldn't seem much complicated since the isolated nature of it, but when you move to production with real-time analytics happening alongside enterprise software integration it can be quite a challenge to manage data with standard methods".* PRT-PAT3 again reaffirms that by stating *"Getting PAT tool implemented on-site is more than just one technical tool implementation. Unlike some other process changes the entire architecture of implementation must be mapped out to determine overall system management. Data integration & management and software modelling is the main challenge when it comes to cross instrumental implementations".*

4.9.7 Process Planning Challenges

Implementation of PAT tools involve integration of existing manufacturing processes with the new tool that often is either partially compatible or requires some level of process change occurrence. This was stated by many participants at different instances. It was

clearly indicated in statements made by PRT-PAT1 *"I believe the development and execution of the system is more complicated than any usual project development for a tool installation".* PRT-PAT2 also stated the same by pointing *"It's the product that's vital in integration of PAT since the product life cycle might be short and certain changes must be made to ensure the longevity of the PAT tool".* PRT-PAT3 also indicates the challenge of process planning aspect in implementation *"PAT that just measures CQAs isn't quite value providing anymore with companies looking for total enterprise automation. To provide better value and help in change control a PAT tool must be able to come with a process control measure/method which most of the modern PAT tools in the market lack".* PRT-PAT4 also stated that *"I would say that process change documentation and validation are the ones that take-up time and cause delays in the project within PAT implementation when dealing with integration of different processes".*

4.9.8 Intellectual Property Challenges

Access to knowledge of implementation is not a challenge to mid-cap pharmaceutical companied but also for large-cap since cross organisational knowledge shared on the topic of PAT implementation process is quite low due to the patent rights, this can be seen in the statements made by PRT-PAT1 *"It the Intellectual property of that company, unless its disclosed as open knowledge in any scientific articles published by the company. Having said that, there are many independent PAT tool consultants and start-ups that have specialized PAT tool implementations with many different clients that function on non-disclosure agreements".* PRT-PAT2 also indicates the same by saying *"Well, all the data that transpires within the project is strictly confidential and I haven't seen any instance that it caused any concerns in terms of patent clauses since it's a process rather than a product and it's very hard to replicate without right people".* This is again reinforced by the statement made by PRT-PAT3 *"The ethical and privacy concerns are addressed by the licensing agreements per my understanding".*

In the next chapter further discussion of the results is concluded and summarised

CHAPTER FIVE

Discussion

5.1 Introduction

This research study looks at the challenges involved in the implementation of PAT technology pharmaceutical industry. It does this by using the Gioia qualitative data analysis to code, classify, evaluate, and interpret the qualitative data that was acquired through semi-structured interviews. This last part talks about what was learned via the semi-structured interviews and gives an effective closing to the whole study. In this last part, a summary of the results or findings will be written, and the results and findings will be talked about considering evidence from other works. The study's limits, its potential for future research, the theoretical as well as practical significance of the results, and the conclusion will also be talked about in this chapter.

5.2 Summary of Findings

All the conducted interviews of the five participants were semi-structured interviews. All the participant population were males. Only three of the participants have filled and signed the participant consent forms before the interview the other two participants have requested to remain on anonymous status. They have been very cooperative during the entire interview process and shared their industry knowledge and experience by responding to questionnaire.

Participants are college educated and majority of them have their bachelor’s degree in the field of chemistry and engineering. Two of the participants PRT-PAT2 and PRT-PAT4 are master’s degree holders while the other two participants have PhD in their respective fields. All the participants range between the age groups 35 and 51 respectively. Two of the participants PRT-PAT1 and PRT-PAT2 are in senior managerial and managerial roles respectively with QP accreditation and extensive background in quality assurance.

The order codes generated through the Gioia qualitative data analysis have given rise to themes and conclusions that correspond to the research questions raised and address the research objectives from the study conducted.

Conclusion 1: The challenges related to Product, Personnel and Funding are the primary challenges that have been identified which cause delay in adoption and deter the implementation of PAT technology across the industry.

Conclusion 2: The internal challenges that were identified form the study which delay the implementation of PAT technology are Technical, Process Planning and Intellectual Property related.

5.3 Discussion with Respect to Extant Literature

In the current discussion, findings are extensively discussed and compared to the earlier literature.

5.3.1 Time Constraints

Pharmaceutical industry operates on very thing margins which depend on the time bound deadlines that involve drug discovery, trails, and approval. In the study conducted we can see from the qualitative data that the time bound deadlines related to product delivery is a core bottleneck for the implementation of PAT tools. It is also well known from (Moes *et al.*, 2008) that the implementation of PAT tools even when the product line is as fundamental as tablet/powders take up a time. It can also be seen in the (Fonteyne *et al.*, 2015) where PAT tools were implemented in a continuous manufacturing process with very less intervention in terms of process disruption but was time exhaustive. Hence, as indicated by the participants and from the research findings time bound PAT implementations with specific deadlines for process is necessary to overcome this downside.

5.3.2 Economic Burden and Budget Constraints

Investments has risen for the implementation of PAT technology in the entire industry which is evident from (Rathore, Bhambure and Ghare, 2010). However, the technology involved in the deployment with the existing manufacturing facilities is still highly complex and involves changing many existing processes. This proves to impact the plant operations in a much larger scale than the investments itself which is quite an economic burden on the business unit. It can also be seen from the statements made by

the participants that the finical aspect of these implementations is always looked like risk vs reward rather than novel innovations for automation. Independent PAT tool consultants are more widely available now than the past decade. But the use of these consultants comes with integration of teams and contractors that puts a steep price on the process. From the research study and the earlier literature, internal investments within organisations yield more value rather than external consultations.

5.3.3 Data Intensive Process and Lack of Process Control

(Wasalathanthri *et al.,* 2020) in many instances mentioned that the implementation of PAT tools involves analysing massive amount of spectral data and store it to further investigate using statistical models. One of the participants PRT-PAT3 has also pointed out the complications involved in the gathering and screening of spectral data from the PAT tools. The multivariate nature of the data makes it extremely difficult to analyse and store for further computation.

The challenges in terms of data handling are constantly changing and are being addressed by the ever-evolving field of data computation. However, it is important for the pharmaceutical companies to invest in the fundamental research initiatives in the field of computation for leaving their use in the pharmaceutical industry.

Pharmaceutical modelling at one point is going to replace all primary compound testing in drug discovery(Mercier *et al.,* 2014). The same is going to be seen in the field of process automation for manufacturing units. This change as pointed out by the PRT-PAT3 can only be seen if PAT tools can provide process control and automation based on the spectral data gathered. The challenge of the current market involves the development of tools with enterprise integration to enable IOT In the process. PRT-PAT3 indicates that a tool without any real-time process control doesn’t provide any value to the end user. For the industry to move complete automation it is vital to realize the importance of process control integration in PAT tools.

5.3.4 Regulatory Oversight

Many participants have commented on the regulatory constraints involved in the approval of process changes after the implementation of PAT tools. The cGMP in terms of PAT implementation is to guide good practice than to standardise the use of tools. The risk based that was employed in cGMP for PAT implementations doesn't provide any clear road map for implementation approvals. (Glassey *et al.*, 2011) This leads to manufacturing units having to spend more resources on external equipment and experts to meet the overall regulatory compliance for the product. The extensive oversight without any clarity on the CQA's employed the industry makes it extremely difficult to minimize the efforts on regulatory aspect than to focus on implementation itself. Both PRT-PAT1 and PRT-PAT2 described the implementation process as highly exhaustive regulatory expenditure and requires more standardisation of the process employed for meeting compliance. Industry is slowly moving towards standardizing certain types of tools; however, the change needs to happen form the regulatory bodies to have a meaningful impact.

5.4 Synthesis of Research Findings

The research involved the investigation and analysis of PAT implementation challenges in the current pharmaceutical industry. The results obtained from the study show that the challenges involved in the implementation of PAT have both internal and external roots in terms of where the challenge is detected. Internal challenges are the ones that are post-PAT implementation that cause delay in adoption by discouraging companies, as they look at the troubles caused during implementation. External challenges involve the core challenges that affect the industry for adoption of PAT. The internal being mostly process change and data handling related which delay the adoption through complexion of deployment. Another major challenge detected internally was the absence of transparent knowledge pool on the Process implementation of successful PAT tools by the industry leaders. The external challenges identified were related to product which is broad and covers the broader aspect of need for PAT vs product justification. Another major challenge identified in the external ones is the lack of funding or the lack of push for investment in the PAT technology. The discussion done on the study projects the view of the current challenges in the industry compared to earlier literature findings. The tested

hypothesis clearly indicate the challenges identified are relevant to the current industry trends which still project slow adoption of PAT in the coming years unless there is a significant change in Intellectual property pooling and regulatory constraints.

5.6 Conclusion

Globally PAT driven implementations although have significantly risen they are yet to catch-up with many other industries that have already moved to complete automation and have enabled IOT in most of their process. Logistics and Automotive industries are one of the few examples that are leading the AI driven automation integrated industry solutions. PAT tools now are still in their infancy with development focused only on quality control and assurance. Most of the pharmaceutical industry is now in need of process control solutions than ever before due to the impact of Covid-19. Automation not only involves monitoring but also complete process control with free of any human intervention unless necessary. Sadly, industry right now is far from implementing any such level of automation in terms of PAT applications. However, there are many companies that are leading the way in terms of PAT integrated solutions, but adoption of these solutions are based on product, process, and funding available for implementation. Standardisation of PAT tools for process is yet to be done which also significantly affects the overall applicability. Industry is yet to be transparent in terms of knowledge pooling on the data of PAT implementations to achieve success collectively which is again bottlenecked by privacy and intellectual rights clauses. The challenges identified are not only limiting the progress of PAT implementation but also affecting the industry by increased manufacturing costs and unnecessary process quality tests. All these changes finally affect the end consumer by medicines being more expensive.

5.7 Recommendation

Pharmaceutical industry is a highly competitive and functions on a first come basis in terms of revenue generated from NDA approvals. This competitive edge not only makes knowledge pooling difficult but also causes the ineffective usage on investments on research that has already been accomplished by some other entity. From the study, It is evident that the challenges involved in the delayed adoption of PAT are both internal and external in nature. Investing in new technologies is often discouraged due to the overlying complications that than affect current production. To enhance the adoption of PAT

partnerships essentially between organizations rather than academia is much needed. There is always a move for pushing inter-organizational partnerships for drug discovery and submission rather than PAT related which is much recommended and needed.

Technical challenges identified are ever changing due to the rapid progression in data storage and analytics which might not cause much resistance for implementation, however it is essential to maintain the balance of right talent related to technological aspect of industry. Since, the goal is to move slowly towards achieving complete automation and Pharma 4.0 enabled units, the personnel involved in the development of software planning, execution and architecture play a major role in progression.

5.8 Limitations

The following study done has its limitations since data gathered is qualitative in nature which in turn is generated from a small population. Even though, the exposure of the population involved in the study to the subject is very high, all the participants have different field experiences from varied segments of PAT implementation. To narrow the challenges involved it would be highly beneficial if the study focused on the participants which have similar field experiences to the subject which is one of the major limiting factors of the study. The second limiting factor would be to have a higher population of participants for achieving and analysing common themes form the responses obtained.

5.9 Future Research

As indicated in the limiting factor, the scope of the study can be narrowed down to perform focused study on challenges involved in one of the segments of PAT implementation. The qualitative study can also be expanded to include quantitative studies which can investigate the opinion of population pertaining to the challenges involved in the PAT implementation. The challenges obtained from the current study are quite broad and cover the entire industry perspective. Further study can be done by examining the individual challenges and expanding on the same. Studies can also be performed by narrowing down particular industries such as Medical Devices and Biopharmaceuticals for further research.

References

Bakeev, K.A. (2010) Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries. John Wiley & Sons.

Barrett, P. et al. (2005) 'A Review of the Use of Process Analytical Technology for the Understanding and Optimization of Production Batch Crystallization Processes', Organic Process Research & Development, 9(3), pp. 348–355. Available at: https://doi.org/10.1021/op049783p.

Blanco, M. et al. (2006) 'A process analytical technology approach based on near infrared spectroscopy: Tablet hardness, content uniformity, and dissolution test measurements of intact tablets', Journal of Pharmaceutical Sciences, 95(10), pp. 2137–2144. Available at: https://doi.org/10.1002/jps.20653.

Challa, S. and Potumarthi, R. (2013) 'Chemometrics-Based Process Analytical Technology (PAT) Tools: Applications and Adaptation in Pharmaceutical and Biopharmaceutical Industries', Applied Biochemistry and Biotechnology, 169(1), pp. 66–76. Available at: https://doi.org/10.1007/s12010-012-9950-y.

De Beer, T.R.M. et al. (2008) 'Raman spectroscopy as a process analytical technology (PAT) tool for the in-line monitoring and understanding of a powder blending process', Journal of Pharmaceutical and Biomedical Analysis, 48(3), pp. 772–779. Available at: https://doi.org/10.1016/j.jpba.2008.07.023.

De Beer, T.R.M. et al. (2009) 'In-line and real-time process monitoring of a freeze drying process using Raman and NIR spectroscopy as complementary process analytical technology (PAT) tools', Journal of Pharmaceutical Sciences, 98(9), pp. 3430–3446. Available at: https://doi.org/10.1002/jps.21633.

Fonteyne, M. et al. (2015) 'Process Analytical Technology for continuous manufacturing of solid-dosage forms', TrAC Trends in Analytical Chemistry, 67, pp. 159–166. Available at: https://doi.org/10.1016/j.trac.2015.01.011.

Gioia, D.A., Corley, K.G. and Hamilton, A.L. (2013) 'Seeking Qualitative Rigor in Inductive Research: Notes on the Gioia Methodology', Organizational Research Methods, 16(1), pp. 15–31. Available at: https://doi.org/10.1177/1094428112452151.

Glassey, J. et al. (2011) 'Process analytical technology (PAT) for biopharmaceuticals', Biotechnology Journal, 6(4), pp. 369–377. Available at: https://doi.org/10.1002/biot.201000356.

Gowen, A.A. et al. (2007a) 'Hyperspectral imaging – an emerging process analytical tool for food quality and safety control', Trends in Food Science & Technology, 18(12), pp. 590–598. Available at: https://doi.org/10.1016/j.tifs.2007.06.001.

Gowen, A.A. et al. (2007b) 'Hyperspectral imaging – an emerging process analytical tool for food quality and safety control', Trends in Food Science & Technology, 18(12), pp. 590–598. Available at: https://doi.org/10.1016/j.tifs.2007.06.001.

Kim, E.J. et al. (2021) 'Process Analytical Technology Tools for Monitoring Pharmaceutical Unit Operations: A Control Strategy for Continuous Process Verification', Pharmaceutics, 13(6). Available at: https://doi.org/10.3390/pharmaceutics13060919.

Lopes, J.A. et al. (2004) 'Chemometrics in bioprocess engineering: process analytical technology (PAT) applications', Chimiometrie 2003, 74(2), pp. 269–275. Available at: https://doi.org/10.1016/j.chemolab.2004.07.006.

Magnani, G. and Gioia, D. (2023) 'Using the Gioia Methodology in international business and entrepreneurship research', International Business Review, 32(2), p. 102097. Available at: https://doi.org/10.1016/j.ibusrev.2022.102097.

Medendorp, J. and Lodder, R.A. (2017) ‘Acoustic-resonance spectrometry as a process analytical technology for rapid and accurate tablet identification’, AAPS PharmSciTech, 7(1), p. 25. Available at: https://doi.org/10.1208/pt070125.

Mercier, S.M. et al. (2014) ‘Multivariate PAT solutions for biopharmaceutical cultivation: current progress and limitations’, Trends in Biotechnology, 32(6), pp. 329–336. Available at: https://doi.org/10.1016/j.tibtech.2014.03.008.

Moes, J.J. et al. (2008) ‘Application of process analytical technology in tablet process development using NIR spectroscopy: Blend uniformity, content uniformity and coating thickness measurements’, International Journal of Pharmaceutics, 357(1), pp. 108–118. Available at: https://doi.org/10.1016/j.ijpharm.2008.01.062.

Rathore, A., Bhambure, R. and Ghare, V. (2010) ‘Process analytical technology (PAT) for biopharmaceutical products’, Analytical and bioanalytical chemistry, 398, pp. 137–54. Available at: https://doi.org/10.1007/s00216-010-3781-x.

Read, E.K. et al. (2010) ‘Process analytical technology (PAT) for biopharmaceutical products: Part II. Concepts and applications’, Biotechnology and Bioengineering, 105(2), pp. 285–295. Available at: https://doi.org/10.1002/bit.22529.

Saunders, M. et al. (2019) ‘“Research Methods for Business Students” Chapter 4: Understanding research philosophy and approaches to theory development’, in, pp. 128–171.

Simon, L.L. et al. (2015) ‘Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review’, Organic Process Research & Development, 19(1), pp. 3–62. Available at: https://doi.org/10.1021/op500261y.

von Stosch, M. et al. (2014) ‘Hybrid modeling for quality by design and PAT-benefits and challenges of applications in biopharmaceutical industry’,

Biotechnology Journal, 9(6), pp. 719–726. Available at: https://doi.org/10.1002/biot.201300385.

Streefland, M. et al. (2013) ‘Process analytical technology (PAT) tools for the cultivation step in biopharmaceutical production’, Engineering in Life Sciences, 13(3), pp. 212–223. Available at: https://doi.org/10.1002/elsc.201200025.

Wasalathanthri, D.P. et al. (2020) ‘Technology outlook for real-time quality attribute and process parameter monitoring in biopharmaceutical development—A review’, Biotechnology and Bioengineering, 117(10), pp. 3182–3198. Available at: https://doi.org/10.1002/bit.27461.

Yu, L.X. et al. (2004) ‘Applications of process analytical technology to crystallization processes’, Pharmaceutical solid polymorphism in drug development and regulation, 56(3), pp. 349–369. Available at: https://doi.org/10.1016/j.addr.2003.10.012.

Yu, L.X. et al. (2014) ‘Understanding pharmaceutical quality by design’, The AAPS journal, 16(4), pp. 771–783. Available at: https://doi.org/10.1208/s12248-014-9598-3.

Innopharma education

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Appendix

Ethics Application & Declaration Form

DISSERTATION TITLE: Investigating the current challenges involved in application of process analytical technology (PAT) methodologies in pharmaceutical industry.

RESEARCHER'S NAME: Santosh Kumar Dugginapalli

PROGRAMME OF STUDY: M.Sc. Pharmaceutical Business and Technology

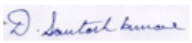
SUPERVISOR'S NAME: Martin Murphy

DECLARATION:

The information in this application form is accurate to the best of my knowledge. I undertake to abide by the principles outlined by Innopharma/Griffith College ethics policy in my research dissertation. I confirm that I have completed a full ethics assessment for my research dissertation as per the college guidelines. I will not begin my primary research until such approval from my supervisor and/or ethics Committee has been obtained.

I pledge to carry out my research according to the Innopharma/Griffith College academic integrity standards. Any results presented in my dissertation will be from my own, original research, I will reference and/or acknowledge any material or sources used in its preparation and I will not plagiarise the work of anyone else.

For Student:

STUDENT SIGNATURE: 

DATE: 10/Apr/2023

The research contained within this research dissertation proposal has been approved.

For Supervisor:

Ethics Committee Approval Required: Yes ☐ No ☒

SUPERVISOR SIGNATURE: 

DATE:10/04/23

NOTE: Supervisors are responsible for ensuring their students fill in this form correctly and that all ethical areas have been considered.

SECTION 1: DESCRIPTION OF RESEARCH STUDY

1.1 Purpose and objectives of research

Performing secondary research and analyse the current literature on PAT tools implementation challenges in the pharmaceutical industry. To apply the knowledge gained from the secondary research for developing a questionnaire and interview subject experts in the current industry and gather primary research data and assess and summarize the findings from the primary research data and provide a report on comparison to secondary and primary research data.

1.2 Research methodology:

The collection of data from the secondary research material is done by extensively evaluating the material from all available sources both form the pharmaceutical companies, PAT tools developing institutions and relevant Drug regulatory agencies. Upon the conclusions derived from the secondary research a questionnaire is generated to understand the scope of challenges in the current industry along with implications for future R&D.

The questionnaire will involve both open and close end questions covering technical, regulatory, and cost measures involved in the implementation of the PAT Tools. Any earlier interviews given by the subject matter experts in the recent times within the timeframe of 6 months before the initiation of the primary research will also be taken into consideration to develop the questionnaire.

SECTION 2: POSSIBLE ETHICAL ISSUES

Answer 'yes' or 'no' to the following questions.

SUBJECT MATTER

Does the research proposal involve:

Research into specific company activities that would be deemed sensitive or confidential	No
Research into politically and/or racially/ethnically and/or commercially sensitive areas	No
Sensitive, personal, professional, or corporate issues	No

RESEARCH PROCEDURES

Does the research proposal involve:

Research that might damage the reputation of companies or participants	No
Research that may negatively affect the reputation of Griffith College/Innopharma	No
Use of personal records without consent	No
Use of company data without consent	No
The offer of any inducements to participate	No
Audio or visual recording without consent	No
Using a language other than English	No

PARTICIPANTS

Does the research proposal involve:

People who are not competent and/or fluent in English	No
Does your research group include any of the following vulnerable groups	No

(Adults with psychological impairments; Adults with learning difficulties; Adults under the protection/control /influence of others (e.g. in care/prison); Relatives of ill people (e.g. parents of sick children); Hospital or GP participants recruited in a medical facility; persons under the age of 18)

If you have answered NO to ALL questions, please go straight to Section 4.

If you have answered YES to ANY question in SECTION 2, you must fill in SECTION 3.

SECTION 3: STEPS TAKEN TO AVOID ETHICAL ISSUES

[Only fill in this section if you answered YES to ANY of the questions in Section 3. For example, if you answered yes to including participants who are not fluent in English, you might put forward a plan that offers your survey in two languages to take this into account. Another example could be a study where the researcher wants to include information about the care received by children with a long-term condition but it would not be ethical to approach the children directly but it might be acceptable to instead ask parents questions about their child's care. If these plans are acceptable to your supervisor, you may not need to apply for ethical approval from the Ethics Committee].

3.1. If your ethics relates to ***Subject Matter***, outline your action plan to work around any sensitive issues.
3.2. If your ethics relates to ***Research Procedures***, outline your action plan to deal with possible ethical issues in your research procedures.
3.3. If your ethics relates to ***Participants***, outline how you will protect vulnerable persons or those that do not have English as their first language.

SECTION 4: ABOUT YOUR PARTICIPANTS

4.1. Outline your participant profile and why you have chosen them for this study – Last Name Omitted
Participant 1 : Prasad.S – QP – Experience in auditing a site with PAT implementation
Participant 2 : Devi.P– QP – Experience in PAT Tool Compliance for implementation at a site
Participant 3 : Ramesh.N - Manufacturing Data Analytics Specialist – PAT Data Analytics Experience
Participant 4 : Anonymous – Operational Excellence Lead – Experience in Process Development for a PAT project
Participant 5 : Anonymous – Manufacturing Technologist - Experience in PAT Tool implementation for FB-Granulator

4.2 How do you plan to gain access to/contact/approach your participant(s).

SECTION 5: INFORMATION, CONSENT AND CONFIDENTIALITY

5.1 **Participant Information Letter (PIL) for participants**

[You must submit an information letter for participants with this application, as part of your appendices document. For online surveys, it is sufficient to include a paragraph summarising and explaining the purpose of the research at the beginning of the survey. In all other research e.g. interviews, phonecalls, a PIL should be provided to each participant before they are asked for their consent to take part. A template PIL is available in Moodle].

Please confirm below that your information letter covers:

Description of the research topic and method	Yes
Details of what participation will involve	Yes
Rights to anonymity	Yes
Confidentiality	Yes

Rights to withdraw from the research	Yes
The contact details of the researcher and supervisor (if necessary)	Yes

5.2 **Informed Consent Form (ICF) for participants**

[Informed consent is required for most research. For online surveys, it is sufficient to get the participant to tick two boxes at the beginning of the survey – one to state they understand the research and one to give consent. In all other research e.g. interviews, phonecalls, a signed consent form is required. If the data is gathered online e.g. zoom, a signed consent form can be scanned and sent to the researcher. A template ICF is available in Moodle. The signed ICFs, along with the surveys, audio files or interview notes etc. must be stored in the primary data folder on moodle and can be accessed by Innopharma staff for the purposes of verifying the authenticity of the research carried out and the data collected].

Please indicate below if your research requires a signed consent form by selecting the relevant option only:

Yes: My research requires signed consent and I have attached an ICF in the appendices of my application.

SECTION 6: STORAGE OF DATA

[Please ensure that you are abiding by GDPR and the national Data protection laws https://www.hrb.ie/funding/gdpr-guidance-for-researchers/gdpr-and-health-research/).

*The student is responsible for storage of data and this will be handed over to the college in an electronic format as part of the thesis submission i.e. primary data and completed ICFs where applicable will be added to the primary data folder on moodle. The rationale is to keep data **as long as it is still useful** and there is an intention to use it further **for research** so if this is not the case then this can be stipulated here and a shorter retention period given.]*

6.1. How will you store the research data and for how long? How will you manage data protection issues?

SECTION 7: NON-DISCLOSURE AGREEMENT & STUDENT CONSENT

7.1 **Non-Disclosure Agreement (NDA)**
Will the final dissertation contain any information pertaining to any source what would warrant the use of a Non-Disclosure Agreement (NDA) e.g. industry-based research?

No

7.2 **Student consent**
If a Non-Disclosure Agreement (NDA) is not required, does the Student consent to allow their completed dissertation to be held/published by Innopharma/Griffith College?

Yes

SECTION 8: RECORDING AND RETENTION OF DISSERTATION VIVA

8.1 **Viva Recording**
The Dissertation viva will be recorded. This recording may be used to facilitate assessment by Innopharma staff, a third reader if necessary and/or if requested by the external examiner for the Programme. The recording will be held in line with current GDPR guidelines and will not be made publicly available.

SECTION 9: DOCUMENT CHECKLIST

NOTE: Applicants must attach the following documents in electronic format to the appendix.

Which documents are added to the appendix? Please tick N/A if not applicable:

9.1 Participant Information Letter (PIL) for participant	Yes
9.2 Informed Consent Form (ICF) for participant	Yes
9.3 Questions/survey for interviewees/focus groups etc *(can be in draft form)*	Yes
9.4 Any other documents e.g. Non-Disclosure Agreement	N/A

I confirm that this application is complete, and all required documents are included in the appendix.

For Student:

STUDENT SIGNATURE: