Griffith College

The Role and Impact of Process Analytical Technology (PAT) on Solid Dose Manufacturing in Nigeria

By

CHINEDU NNADOZIE CHUKWU

3015454

A thesis submitted in partial fulfilment of the requirements for MSc in Pharmaceutical Business & Technology

Innopharma Labs Faculty of Science

Griffith College Dublin

June 2021

Declaration

PROJECT TITLE: THE ROLE AND IMPACT OF PROCESS ANALYTICAL TECHNOLOGY (PAT) ON SOLID DOSE MANUFACTURING IN NIGERIA
RESEARCHER'S NAME: CHINEDU NNADOZIE CHUKWU
PROGRAMME OF STUDY: MSc. PHARMACEUTICAL BUSINESS AND TECHNOLOGY
SUPERVISOR'S NAME: PAUL BLUNNIE

DECLARATION: The information in application form is accurate to the best of my knowledge. I undertake to abide by the ethical principles outlined by Innopharma/Griffith College ethics policy in my research project. I confirm that I have completed a full ethics assessment for my research project as per the college guidelines.

I confirm that the research contained within my research project does not require Ethical review and/or subsequent approval by the GEC/Innopharma Ethics Committee.

Student signature:

Date: 02/04/2021

Supervisor signature:

Date:

Acknowledgement

Firstly, my utmost thanks is to God who made all things possible through his infinite grace and guidance throughout the research.

Secondly, I am taking this opportunity to appreciate my able research supervisor, Paul Blunnie for making out time through his busy schedule to lead and mentor me making this dissertation a smooth and worthwhile process. His dedication for my success is unmatched. I humbly appreciate his numerous mentorship and guidance. I also want to use this medium to appreciate all the lecturers that taught me throughout the master's programme, you all are indeed helpful despite all the hassles the world had to face due to the pandemic.

Lastly, I am grateful to my family for providing this opportunity for a brighter future for me. To my siblings, your immense support cannot be waved bye. A special thanks to my colleagues back home, I am pleased to have you all as your contributions made this thesis a success.

Dedication

I dedicate this work to the Almighty God.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

PAT	Process Analytical Technology
QbD	Quality by Design
QbT	Quality by Testing
WHO	World Health Organization
COVID-19	Coronavirus Disease 2019
SPSS	Statistical Package for Social Sciences
FDA	Food and Drug Administration
NAFDAC	Nigeria's National Agency for Food and Drug Administration and Control
cGMP	current Good Manufacturing Practice
PMG/MAN Nigeria	Pharmaceutical Manufacturers Group/Manufacturers Association of
GDP	Gross Domestic Product
RTR	Real Time Release

Abstract

This research investigated the role and impact of Process Analytical Technology (PAT) on solid dose manufacturing in the Nigerian pharmaceutical industry. PAT has been generally adjudged to be a promising technology that can significantly improve manufacturing efficiency and reduce the cost of production. There is evidence to back this point of view based on the automotive industry and other industries that have successfully implemented PAT. However, regardless of the demonstrated benefits of PAT, manufacturers in the pharmaceutical industry seem too slow to implement it in their manufacturing process. Realising this, the United States Food and Drug Administration (FDA) enacted a series of initiatives to drive a regulatory framework that could motivate manufacturers in the pharmaceutical industry to implement PAT. Nigeria represents one of the biggest pharmaceutical market in the world by virtue of its population which is estimated to be the biggest in Africa where PAT could help deliver quality medication at affordable rates. To investigate the role and impact of PAT in the Nigerian pharmaceutical industry, this research adopted a quantitative approach whereby self-administered questionnaires were sent to manufacturers through an online Google Form. The list of registered pharmaceutical manufacturers was obtained from NAFDAC, the regulator of the industry in Nigeria. Out of about 130 established manufacturers, 62 responses were obtained. Based on inferential statistics, the results show that indeed PAT plays a role in the Nigerian pharmaceutical industry albeit an insignificant one. Out of about twenty-one (21) identified challenges, eleven (11) were statistically significant. The most significant challenges that the respondents agreed the strongest to relate to the cost of implementing PAT. Although the hypotheses tested revealed that PAT has a significant effect on the price, quality and effectiveness of solid dosage forms, the general experience of health practitioners could not justify PAT adoption. Therefore, it is recommended that manufacturers in the Nigerian pharmaceutical industry must think long term in order to overcome the hurdle of the initial cost of implementing PAT. The regulator of the industry must find strategies of making pharmaceutical manufacturing attractive so as to drive innovation from the manufacturers.

Keywords: *PAT, Solid dose, Pharmaceutical Manufacturing, Nigeria*

CHAPTER ONE

INTRODUCTION

1.1 Background

For decades, the pharmaceutical industry has relied on conventional batch processing for manufacturing purposes. Although batch processing has been able to deliver some quality drugs for all these years, the world is now being faced with challenges that are too complex for batch processes and techniques. These challenges are of scales that threaten the existence of the entire human race. Consider for example, the ongoing COVID-19 pandemic; the speed with which vaccines needed to be produced for the entire population of the world is a testament that a new era of challenges is upon humanity. A typical batch manufacturing process for solid dosages consists of a series of separate start and stop steps with several intermediate handling processes which have been known to lead to issues such as drug recalls and drug shortages due to poor quality drugs and longer cycle time for drug releases. Continuous manufacturing has thus been successfully applied in other industries e.g. the automobile industry, to eliminate these challenges, thereby increasing the efficiency of manufacturing and reducing production costs.

Apart from associated financial loss, a poor quality drug poses several health risks to the user. Quality control is instrumental to minimizing drug risks to consumers. It is pivotal to identifying excessive variability at the production stage. According to Momeni, Pincus and Libien (2018), the continuous and real-time measurement, analysis and interpretation of quality metrics is requirement to achieving the goal of quality control; which is to minimize variability and maximize accuracy and precision of drug development. This can be difficult to implement manually. For example, in the formulation of nano products, the product characteristics can be influenced by a large number of the process and product variables. Considering each and every variable during the manufacturing process is usually a time consuming task that requires huge investment (Mittal et al., 2019). However, this must be done to ensure product quality.

Without some form of automatic implementation, effective quality control will be practically impossible especially with new industry dynamics and challenges such as those posed by pandemics. The pharmaceutical industry which has longed been

associated with batch processing is currently undergoing a paradigm shift into continuous processing (Ostergaard et al., 2020). As a result, the development and manufacturing of drugs in a continuous process cannot be sustained by the traditional end-point testing of batch processing. Therefore, the concept of Quality by Design (QbD), which is not new, is now a topic of central discussion in the pharmaceutical industry. Quality by Design has been defined as a "systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (FDA, 2009). QbD is driven by process understanding and the application of Design of Experiment (DoE) framework for a broader coverage of operating space at the design stage (Szilagyi et al., 2020). The operating space is defined by the design space whereby the ultimate product reaches the target specification or quality.

The QbD approach represents a significant improvement when compared with the traditional system of Quality by Testing (QbT) where products are tested at the endpoint of the batch process. Although QbT has succeeded in producing some quality drugs over the years, there are many risks associated with the process including high number of rejected batches which represents considerable financial risk. QbD has the potential of eliminating the risks associated with QbT. In so many ways, Process Analytical Technology (PAT) is considered to be a key enabler of QbD (Nagy, Fujiwara and Braatz, 2019) (Lundsberg-Nielsen, Schlindwein and Berghaus, 2018) (Undey, 2012) (Baradez et al., 2018). It has been defined as 'a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality' (FDA, 2004). The QbD – PAT initiative is now the regulatory framework being advocated in most countries' regulators including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

The continuous collection of these timely measurements in real-time through PAT is a Big Data opportunity that can be harnessed for exerting control over the critical production processes that are typical of the pharmaceutical industry. In this way, PAT is essentially an application of Big Data to the pharmaceutical industry. Big Data has

been defined as a large volume of data in the range of an Exabyte incorporating velocity and variety that is difficult to process using traditional analytical tools (Tiwari, Wee and Daryanto, 2018) (Sasubilli, Kumar and Dutt, 2020) (Anderson, 2020). The application of Big Data in all industries is a developing field of study because it is generally analogized as the 'new oil' due to immense benefits that can be generated from its applications across multiple industries (Hirsch, 2014). Therefore, the area under the consideration of this proposal represents an active and developing subject that is at the fore of the pharmaceutical industry. The subject is also well-documented in literature. The purpose of this section is to review pertinent and current literature on PAT with the aim of identifying how gaps and debates relate to this proposal.

1.2   The Concept of Process Analytical Technology (PAT)

The concept of PAT was introduced to the pharmaceutical industry by the United States Food and Drug Administration (FDA) in a 2004 paper titled Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance; based on the bedrock that 'quality cannot be tested into a product; it should be built-in or should be by design' (FDA, 2004) (Ishihara et al., 2020) (Kozma, Salgó and Gergely, 2018) (Tucker et al., 2016) (Raw, 2004). However, PAT is an umbrella term that relates to technologies which are not really new by virtue of existence. The application of those technologies to the pharmaceutical industry can be regarded as innovative initiatives, given that the pharmaceutical industry presents entirely new areas of application.

According to Read et al. (2010), the concept of PAT is an aspect of the larger umbrella term Quality by Design (QbD); overlapping in meaning with other subset concepts of risk management principles, process design spaces, and creation of manufacturing knowledge base. Quality by design has been defined as 'designing and developing manufacturing processes during the product development stage to consistently ensure a predefined quality at the end of the manufacturing process' (Henck and Byrn, 2007). The applications of QbD or PAT transcend any one particular industry. In the pharmaceutical industry, QbD is defined as 'a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and

process understanding and process control, based on sound science and quality risk management' (FDA, 2012).

The concept of PAT was introduced to eliminate over-processing, reduce off-specification products and ensure quality of products (Bowler, Bakalis and Watson, 2020). The foundation of PAT is built on the idea that a combination of real-time experimental measurements and mathematical tools is capable of addressing most of the difficulties of downstream processes; by which bio-products are separated and purified in large scales using a number of unit operations (Misra, Sullivan and Cullen, 2015). The components of PAT include knowledge management tools, endpoint monitoring and process control tools, modern process analyzers or process analytical chemistry tools and multivariate data acquisition and analysis tools (Yu et al., 2004). Some or all of these components may be applied to a single unit operation or to an entire manufacturing process.

1.3   Benefits of PAT to the Nigerian Pharmaceutical Industry

According to Merkus (2018), the benefits of PAT (and by extension QbD) include increased manufacturing efficiency due to reduced cycle time, high and stable quality products, greater process understanding with the ability to identify variations, reduced cost of manufacturing and improved regulatory framework that is driven by scientific knowledge and risk management. According to Obukohwo et al. (2019), the pharmaceutical industry in Nigeria plays a significant role in providing the nationwide citizens all the health facilities and services along with enhancement of welfare of the economy in the country. In addition to that, the pharmaceutical sector in Nigeria has several complexities as there has been an involvement of medicine manufacturers, national regulators, ministries of the government, retailers, wholesalers and other stakeholders. According to Jaiyeoba, Abdullah and Dzuljastri (2019), the Nigerian pharmaceutical industry is marred by fallen standards of production. Based on the rating provided by the World Health Organisation (WHO) as of 2010, the health sector of Nigeria got 187th rank out of 191 members (Azoma, 2010). According to Akamatsu et al. (1975), the pharmaceutical Industry of Nigeria persists in intense competition where the market witnesses a monopolistic environment resulting in very low profits for industry players.

1.4   Challenges to PAT Adoption in the Nigerian Pharmaceutical Industry

Although PAT is generally advocated for widespread industry adoption due to immense benefits (and indeed overall adoption has significantly increased), a vast majority of application is in Research and Development processes in lab-based pilot facilities rather than in actual production processes (Reid et al., 2012). Therefore, the real-time application of PAT in commercial production is very limited (Simon et al., 2015). According to O'donnell, Fagan and Cullen (2014), this may be attributed to the high regulation of the pharmaceutical industry which creates a culture of risk averseness among manufacturers. Bakeev (2007), also asserted that the benefits inherent is PAT adoption are balanced by extensive cost and risk of subsequent validation and regulatory validation of process change. According to Ekeigwe (2019), there have been several challenges in the manufacturing process of medicines in Nigeria. The main challenge is due to lack of effective infrastructure relating to communication, transportation networks and the constant supply of powers. In addition to that, the healthcare sector of Nigeria has also been heavily dependent on the importing medical products such as drugs, vaccines, medical devices and diagnostic equipment especially from countries like India and China (Ekeigwe, 2019).

According to Akande-Sholabi et al. (2020), Nigeria is a country that has been highly dependent on importation of more than 70% of active pharmaceutical ingredients from China and India. A study conducted by Muritala, Kabiru B. and Adewole, Jimoh K. (2019), has revealed that the pharmaceutical industries in Nigeria used to face several technical challenges which include emulsion stability, metals impurity, hydration, thickening and air bubbles which increase the cost of productions through increased wastage of time, energy and raw materials and ingredients necessary for drug manufacturing. Besides that, there has also been a lack of viability in the pharmaceutical manufacturing of local and low-income countries like Nigeria due to inadequate technical expertise (Fatokun, 2020). As depicted by Garuba et al. (2009), the manufacturing process of pharmaceutical products in Nigeria has witnessed challenges due to inadequate legislation, ineffective execution of existing manufacturing laws of the country, inclusion of professionals from non-health background in the pharmaceutical sectors and inadequate control systems. The aforementioned factors

create loopholes that impede the implementation of process analytical technology in the Nigerian context.

1.5   Research Aims and Objectives

The aims and objectives of this research include the following:

- To determine the level of Process Analytical Technology (PAT) adoption for solid dose manufacturing in the Nigerian pharmaceutical industry.

- To determine the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry.

- To determine the impact of PAT adoption by pharmaceutical manufacturers on solid dose forms.

1.6   Research Questions

The research questions are as follows:

- What is the level of adoption of Process Analytical Technology (PAT) for solid dose manufacturing in the Nigerian pharmaceutical industry?

- What are the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry?

- What is the impact of PAT on solid dosage forms with regards to the experience of health professionals in Nigeria?

1.7   Research Hypothesis

It is generally agreed in literature that PAT adoption by manufacturers improves the quality, affordability and effectiveness of medication. However, medication quality, price and effectiveness are not the only factors that determines the satisfaction that consumers derive from a particular medication. There are other factors that may be equally strong or stronger such as cultural factors and level of literacy of consumers. Ordinarily, PAT adoption should have a significant positive relationship with consumers' satisfaction in respect of quality, affordability and effectiveness that it brings to medications. However, it is also possible that medication quality is not as

strong a factor as these other factors (cultural factors, illiteracy of consumers for example) that determine medication satisfaction in the Nigerian context. If these other factors are significantly stronger, then there may not be a significant positive relationship between PAT adoption by manufacturers and consumers' satisfaction with medication in terms of quality, price and effectiveness. If this is the case, then there is actually no consumer incentive for adopting PAT in the Nigerian context. Therefore, the hypotheses of this research are postulated as follows:

H1$_1$: There is a significant difference in the mean effect of PAT adoption on price of solid drugs.

H2$_1$: There is no significant difference in the mean effect of PAT adoption on effectiveness of solid drugs.

H3$_1$: There is a significant difference in the mean effect of PAT adoption on quality of solid drugs.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

A literature review is a selection of available documents, whether published or not, with a commentary that is characterised by appropriate depth, breadth, consistency, rigour, brevity, clarity, synthesis and effective analysis on a particular topic (Lawal, 2009). Literature review is used in the justification of an approach to research and for demonstrating gaps in literature in order to show where new knowledge is to be contributed. In this way, an appropriate literature review will reveal potential duplication of research efforts as regards the proposed research. The literature review is not a mere summary. It must express a critical evaluation of available literature. According to Salman Ben Zayed et al. (2021), the three steps involved in performing a literature review include planning, execution, and reporting findings. The purpose of this chapter is to review pertinent literature on the role and impact of Process Analytical Technology. In doing so, the focus will relate categorically to solid dose manufacturing and geographically to Nigeria. Nigeria is a very unique context. Naturally, because the country is still developing, there will be much opportunities for improvement. Moreover, with an estimated population of over 200 million people (World Bank, 2017) and a unique set of challenges, Nigeria represents an important pharmaceutical backdrop with global ramifications.

In the execution of this literature review, the themes that form the subjects of discussion in subsequent sections and subsections are generated from the main topic of this research and objectives of this research. From the research topic, these themes include Process Analytical Technology (PAT) and solid dose manufacturing with special focus on Nigeria. From the aim and objectives of this research, these themes include the level of PAT adoption for solid dose manufacturing, the Nigerian pharmaceutical industry, the challenges to PAT and consumers'' satisfaction with medication. In order to prevent publication bias and evidence selection bias, both published and unpublished literature will be considered with repeated and comprehensive search results that demonstrate transparency such that similar results can be reproduced by other researchers elsewhere. Literature search will cover multiple databases with consideration for grey literature also. Google Scholar will serve as the primary search data. However, the school library

will also serve as an important search database. Moreover, other online repositories will also be considered. Although priority will be given to the most recent works because they present the most updated information, older works will not be neglected especially when considering information that is static in nature.

2.2 Background to Process Analytical Technology (PAT)

The pharmaceutical industry is a heavily regulated industry. The process of discovery, development and production of drug products are subjects of regulation across the globe. Without an intrusive regulatory framework, quality control may not be the central theme of the industry as it is today. However, this regulatory nature of the pharmaceutical industry has made drug manufacturers to be risk averse. As a result, manufacturers are hesitant to introduced new technologies which stand the risk of being impacted negatively by regulation, especially during production scale-up. Realizing this in 2002, the United States Food and Drug Administration (FDA) launched the initiative to develop risk-based current Good Manufacturing Practice (cGMP) for the Twenty-first Century (Doherty and Kettler, 2005). PAT was part of that advocacy. In 2003, the first draft of PAT guidance was issued by the FDA. Essentially, PAT was conceptualized by the United States Food and Drug Administration (FDA) in order to encourage the pharmaceutical industry to introduce and develop online methods for process quality monitoring and control (Gupta, O'Brien and Ruiyao Gao, 2013). According to Doherty and Kettler (2005), both cGMP and PAT are posed to impact the development of online spectroscopic tools in pharmaceutical development and manufacturing control for several decades to come. PAT is projected to drive the implementation of QbD (Yu, 2008).

2.3 Quality by Design (QbD)

The underlying theme of PAT framework for the pharmaceutical industry produced by the FDA is based on the assertion that "quality cannot be tested into a product; it should be built-in or should be by design" (FDA, 2004). The encapsulated idea behind the theme is the concept of Quality by Design (QbD). Achouri et al., (2021) agrees that PAT is a subset of QbD. The concept of QbD is not new (Berridge, 2009). The origins or QbD can be traced back to the 1920s when Sir Ronald A. Fisher founded the field of statistical Design of Experiments while working on agricultural and biological research

studies in Rothamstead Experiment station in England (Snee, 2016). However, QbD and its family of terms have recently gained popularity largely due to the advocacy of the FDA, becoming the central theme for the pharmaceutical industry and regulators (Snee, 2016) (Hickey and Smyth, 2020). QbD has been defined as a "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (FDA, 2009). A simplified QbD framework for generic drugs is shown in Figure 2.1 below.
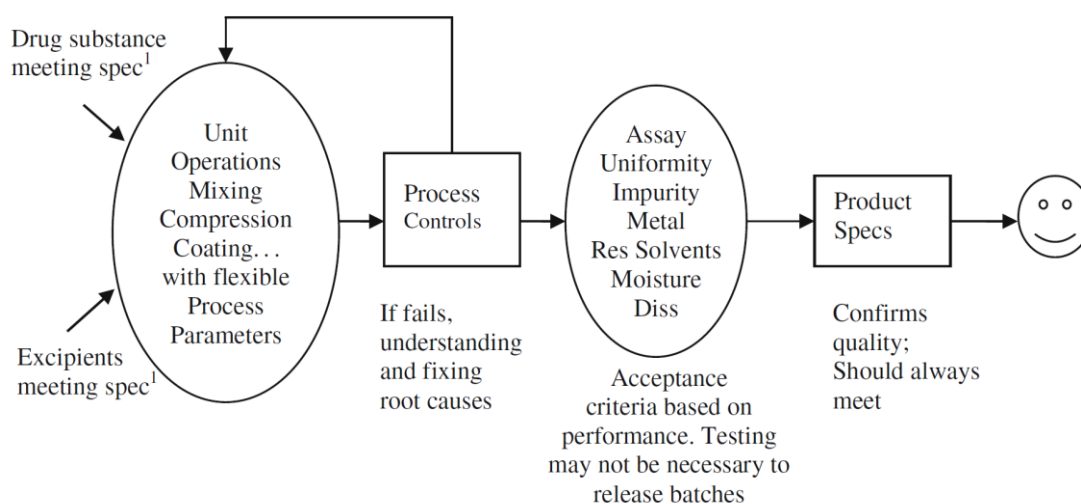
Note 1: "Drug substance and excipient specifications only contain critical attributes that will impact performance and processing of the final product"

Figure 2.1: A simplified QbD framework for generic drugs [source: (Yu, 2008)]

QbD is a systematic and scientific method of product and process design and development that involves multivariate data acquisition and modelling for understanding the critical sources of variability, process control techniques to ensure product quality, product and process design space for conditions to enable risk management and control space for formulation and other process factors that are critical to product performance (Snee, 2016). PAT is primarily focused on the process aspects of QbD. Under the older Quality by Testing regulatory framework, product quality is implemented by testing raw materials, drug substance manufacturing, fixed-process drug manufacturing, in-process material testing and end product testing (Yu, 2008). Since there is a possibility of contamination during the manufacturing process, the drug manufacturing process is usually controlled by regulation. Any change in the

manufacturing process may be done with approval from the regulators. Finish products are then tested to ensure that they meet up with regulatory specifications. When products do not meet standards at any stage as shown in Figure 2.2 below, they are usually discarded. The disadvantages involved with QbT include inability to fully understand the root cause drug failure, risk of incurring losses by drug manufacturers until cause of failure is identified, product recalls, and an overwhelming number of Chemistry Manufacturing and Control (CMC) supplementary requests filed at various regulatory offices (Yu, 2008). QbD has the potential of eliminating all these issues.
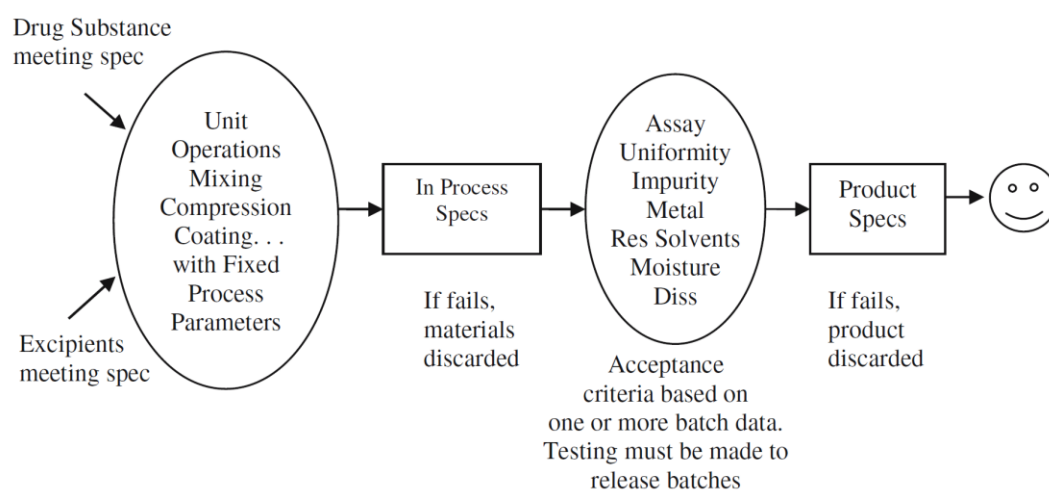
Figure 2.2: A simplified QbT framework for generic drugs [source: (Yu, 2008)]

2.4 The Concept of Process Analytical Technology (PAT)

The concept of PAT was introduced in the pharmaceutical industry by the United States Food and Drug Administration (FDA) (Burggraeve et al., 2010). The FDA describes PAT as a "system for designing, analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" (FDA, 2004). The concept of PAT can be seen, in many ways, as an enabler for the broader concept of QbD (Fisher et al., 2019). The analytical aspect of PAT is a comprehensive term that integrates chemical, physical, microbiological, mathematical, and risk analyses. The goal of PAT is to ensure that pharmaceutical drug manufacturers have a full understanding and control of the manufacturing process. This can be said to have occurred when prediction of product quality attributes is reliable

and accurate over the design space established for materials used, process parameters, manufacturing, environmental and other conditions; when the process is able to manage variability; and when all critical sources of variability can be identified and explained (FDA, 2004). In order to achieve this, critical product attributes must be measured in real-time either online, inline or at-line or near at-line (in-situ measurements) before a decision point. This is described by a new approach referred to as real-time release (RTR). RTR is a system for ensuring that final product meets quality standards while eliminating or reducing end-product testing (Cogdill et al., 2005). RTR results from PAT implementation and is set for a paradigm shift in replacing conventional quality control methods for product release.

According to Kessler and Kessler (2020), PAT tools will serve as an avenue for Big Data analytics, cloud architecture, manufacturing intelligence and in-process control to be integrated into the same workflow for manufacturing purposes. These have long been fundamentally desirable for pharmaceutical manufacturing, especially given that modern pharmaceutical manufacturing is now oriented in favour of continuous processing which integrates all unit operations into one system. Continuous manufacturing requires the high level of data analytics which Big Data offers, with the promise of faster development process, elimination of scale-up procedures and intermediate storage, improved product knowledge and RTR. Big analytical data will result from PAT in that frequent, continuous and automated measurements will be created. The resulting Big Data can then be used to accurately build qualitative and quantitative models such as process trajectories or process signatures which are useful for characterizing process variability and highlighting unusual process behaviours. According to Cogdill et al. (2005), the advancement of analytical technology creates the opportunity to develop a total quality management system (TQMS) for PAT implementation in a working manufacturing environment. TQMS is a cross-industry term that is defined as a "holistic management philosophy that strives for continuous improvement in all functions of an organisation" (Kaynak, 2003, page 406). The statistical confidence in decisions regarding product quality will be improved because as more samples of data are analysed, the statistical power of decisions will also improve. In this regard, the analytical aspect of PAT has created an expanded role for the concept through Big Data.

2.5   PAT Tools and Technologies

An effective manufacturing and optimization process is required to be able to produce quality drugs consistently (Dave, Wu and Contractor, 2011). For example, the process of granulation, which is important for solid dose manufacturing especially tablets and capsules, could be improved in terms of quality by in-line monitoring which can also avoid need for irregular shutdown and loss resulting from number of recycled or bad batches. The endpoint of granulation can be described as the point at which the granule properties such as granule size distribution are optimal. In order to achieve optimal point, the analytical tools required must be online and the process must be real-time (Gupta, O'Brien and Ruiyao Gao, 2013). These tools are essentially Process Analytical Technologies. Traditionally, the end point of granulation could be determined through indirect measurement of torque or power consumption; the current practice for determining end point of granulation is through the use of massing time or total processing time (Yu et al., 2019). However, power consumption or torque could still be monitored as reference to prevent the risk of over-granulation during process development. Although there are many traditional methods of determining end point of granulation, they are limited in terms of accuracy and reproducibility (Dave, Wu and Contractor, 2011). Real-time monitoring and characterization through the application of PAT can provide much more reliable information than end point monitoring that is traditionally employed in granulation and tabletting (Rathbone, Hadgraft and Roberts, 2003).

The implementation of PAT in any industry is an interdisciplinary task. Focussing on this interdisciplinary aspect is vital for harnessing the progress to be made in hardware and software and requires the joint effort of scientists, process experts and data scientists (Kessler and Kessler, 2020). Although there are myriad PAT technologies that have been developed in recent years, they can be categorized as either direct or indirect measurement techniques (Gupta, O'Brien and Ruiyao Gao, 2013). Direct measurement tools allow direct online measures of Critical Quality and Performance Attributes (CQPAs), Critical Process Parameters (CPPs) or directly lined parameters such as online High Performance Liquid Chromatography (HPLC). According to Streefland et al. (2013), the implementation of PAT involves the selection of the right online or offline sensors for measuring CQPAs and CPPs. The Table 2.1 below shows

some commonly used PAT tools. PAT tools can also be classified as either online or offline. Online PAT tools provide multivariate data that can be interpreted with chemometric processing, an example include spectroscopic tools such as Near Infrared Spectroscopy (NIRS). Off-line tools do not offer direct process control but can provide detailed information about variables, an example include Deoxyribonucleic Acid (DNA) microarrays used for measuring the expression levels of large numbers of genes. The FDA generally classified PAT tools into four categories namely Multivariate tools (for design, data acquisition and analysis); process analyzers; process control tools; and continuous improvement and knowledge management tools (FDA, 2004). This classification shows that PAT is much more than process analyzers or process control. These tools can be used in conjunction on a single unit operation or an entire process of manufacturing and quality assurance.

PAT tool	Measured attribute	On/at/off-line[a]
Optical spectroscopic tools		
Near infrared spectroscopy	Many biologically important bonds (aliphatic C–H, aromatic or alkene C–H, amine N–H and O–H), physical properties (particle size, morphology, optical density)	On-line
Infrared and RAMAN spectroscopy	Detailed chemical information of compounds	On/at-line
Photoacoustic spectroscopy	Off gas analysis	On-line
2D fluorescence spectroscopy	Many biomolecules and cofactors with fluorescent properties	At/off-line
UV spectroscopy	Measures absorption of biomolecules in the UV spectral range	On/off-line
Real-time imaging	On-line microscopic analysis of the cultured organism	On-line
Other spectrometric tools		
Mass spectrometry	Analysis of metabolome or proteome of the cultivated organism, to get information on the metabolic and physiologic state, expression of recombinant proteins, growth characteristics, and harvest point determination	Off-line
Dielectric spectrometry	Analysis of membrane potential to assess the viability of the culture	On-line
Biomolecular tools		
Biosensors/biochips	Sensors that are activated upon binding of a molecule to a receptor. Highly sensitive for specific compounds	At/off-line
Transcriptome or proteome measurements (microarray)	Analysis of the transcriptome of the cultivated organism, which gives information on the metabolic and physiologic state, expression of recombinant genes and determination of optimal harvest point	Off-line
Other tools		
Bio calorimetry	Analysis of heat generated by metabolic activity of the cell to estimate biomass concentration	On-line
Flow cytometry	Analysis of cell morphology and expression of surface proteins and isolating sub-populations of cells	At/off-line
On-line HPLC	Analysis of a cell-free sample stream, giving information about nutrient and metabolite concentrations during cultivation	On-line
Soft sensors	Mathematical algorithms that perform calculations on one or more on-line available parameters to calculate or predict a parameter that is not on-line measurable	On-line
Dynamic modeling and prediction	Statistical process models that incorporate a wide range of process data from PAT tools to describe the process and make predictions on product formation and quality	On-line

[a]On-line: real-time measurements of the process; at-line: off-line measurements that are fast enough to be used to control the process; off-line: off-line measurements that cannot be used to control the bioreactor process.

Table 2.1: Some PAT tools and their area of application [source: Streefland et al. (2013, page 215)

2.6   Challenges to PAT Implementation

Implementing any new technology that is worthy of a paradigm shift is bound to be fraught with challenges. At the very minimum, although some of these challenges may not lead to a halt of manufacturing process, they can cause wastage of effort, resources and time. One of the key challenges to PAT implementation relates to the challenges associated with the resulting Big Data. Data mining involving the chemical compounds used in making drugs usually results in a highly heterogeneous data (Mante et al., 2019). The fact that the data needs to continuously collected over a long period of time from different projects and product lines also results in a very voluminous data. This heterogeneous nature of the data and the volume involved does not only contribute to create a wealth of information to be generated, it also contributes to the challenges of analysing such data. Although there are great benefits to harnessed, handling such data requires a certain level of expertise, capital investment and technicalities that may not be available to some manufacturers in the pharmaceutical industry.

According to Brearley and Foulk (2010), some of the most serious challenges to PAT implementation are not technical in nature. These include large initial investment requirement and steep learning curve. Some other challenges listed by Tripathi and Shrivastava (2018), include small production skids, disposable units, different raw materials, and lack of real-time online measurement devices. Another challenge pertains to high complexity of the products, process and substances used in the manufacturing of pharmaceutical products, (Rathore, 2011). According to Richard and Tweedie (2015), the aforementioned challenges can generally be categorized under the following themes: technological and implementation diversity challenges, frequent and high cost of maintenance, knowledge deficit, conservatism and resistance to change, treating online as lab in a pipe, high cost of process analyzers, and cost associated with system failures. The solution to these challenges can either be technical or commercial in nature (Richard and Tweedie, 2015). Technical solutions include improved measurement equipment, separation of data and knowledge, improve data presentation techniques, and integrated approach to process control and analytical instrumentation; while commercial solutions include vertical product integration, standardization, regulatory encouragement, and new business models that can address challenges.

2.7 Solid Dose Manufacturing and PAT

The most commonly used route of drug administration is through the oral route with dosages either in liquid (solutions and suspensions) or solid forms (powders, tablets and capsules). However, of all the drugs taken through the oral route, tablets and capsules are the most common forms (Pazhayattil et al., 2018). Most drugs are usually absorbed in the gastrointestinal tract. However, the active pharmaceutical ingredients are usually unsuitable for direct ingestion for reasons which may include low quantity (sometimes fraction of a milligram), unpleasant taste, poor stability, poor solubility etc. Therefore, drugs are usually manufactured in dosage form by combining the active pharmaceutical ingredient with an inactive ingredient so that drugs may be delivered to the desired site before absorption. The discussion under this section will primarily focus on tablets because according to Pazhayattil et al. (2018), tablets are the most popular form of solid dosage, forming more than 70 percent of pharmaceutical product in the market. Generally, the process of solid dose manufacturing include screening the active and excipients with a Comil fitted with 0.032R screen; using a suitable sized blender to blend the milled materials, using a compactor to compact the blended materials while evaluating the process through compaction study; adding screen material and over-blending while evaluating the process through blend time analysis and then finally compressing the granulation into tablets and evaluating the process through Compression Specification Range Determination studies (Pazhayattil et al., 2018). The Figure 2.3 below show a continuous solid dose manufacturing framework. According to Pazhayattil et al. (2018), continuous solid dose manufacturing utilizes PAT and process modelling to enhance the process. A multitude of electro-mechanical process sensors can be connected to the entire process to continuously generate data throughout the duration of operation.
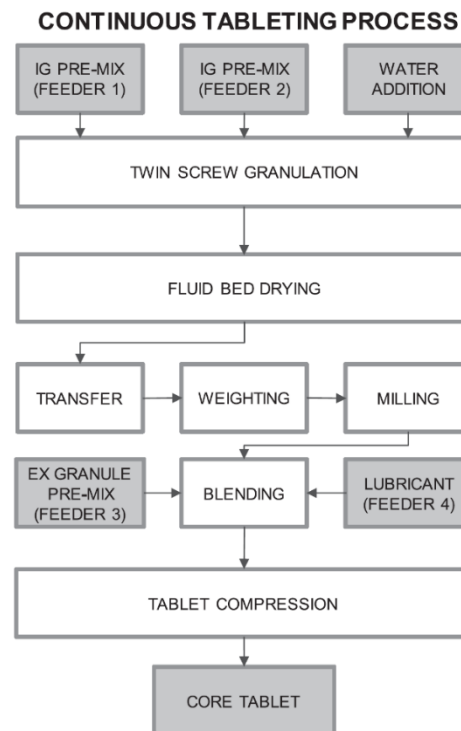
Figure 2.3: Continuous solid dose manufacturing process [source: (Zomer et al., 2018)]

2.8 The Nigerian Pharmaceutical Industry

The Nigerian Pharmaceutical Industry has a history which dates back to the pre-independence period with the distribution of imported drugs by the representatives of different foreign manufacturers such as May and Baker, Pfizer, Beecham, Glaxo and J.I Morrison were involved in the pharmaceutical sector (Ugbam and Okoro, 2017). However, since the 1990s, the practice of pharmacy in Nigeria has changed considerably. The Nigerian professional fabric has since undergone a series of changes that have directly impacted the practice and education of the profession. Due to the population of Nigeria, the commercial incentive makes Nigeria to currently be one of the most important and most developed pharmaceutical market. As at 2017, there were 130 pharmaceutical firms operating in the Nigerian pharmaceutical industry (Ugbam and Okoro, 2017). The industry was valued at $9.4bn in 2016 and $13.2bn in 2020. However, available performance indicators suggest that the performance of the Nigerian pharmaceutical industry is poor. Capacity utilization for local drugs is 40 percent, only about 25 percent of local drugs demand is being met by the Nigerian pharmaceutical industry; the remaining 75 percent is being mainly met through imports from Asia: majorly India and China. Pharmaceutical imports were estimated at $789

million in 2018 (Chiejina, 2014). Although the global pharmaceutical industry is projected to be valued at more than $1.3 trillion, Nigeria is not among the 17 identified growth markets in the industry. The contribution of the industry to the Gross Domestic Product (GDP) was US$7.396 billion or 2 percent in 2012 (Ogada, 2019) (Ugbam and Okoro, 2017).

Through the exploitation of the Nigerian patent system, brand-name manufacturers usually engage in systemic monopolistic competition and also demonstrate a high level of awareness regarding the healthcare needs of consumers (Peterson, 2014). The core competencies of pharmaceutical manufacturers in Nigeria is centred around identifying success factors which are critical for remaining successful and relevant in the market which is constantly changing. The pharmaceutical industry in Nigeria can be categorized into two group of players: the manufacturers and the importers. The high percentage of production raw materials processed and imported from abroad is indicative of the fact that the Nigerian pharmaceutical industry is secondary based with little or no primary base. Most of the heavy machines and equipment used by pharmaceutical manufacturers in Nigeria are imported from overseas. A survey by Ikoni Ogaji and Alawode (2014), shows that about 100 percent of the equipment used in solid dose manufacturing are imported. The industry is also characterized by cheap labour. Due to the high population of Nigeria, the market for drugs is naturally vast. The situation regarding availability of skilled labour in the industry has witnessed improvement given that unlike in the past, local professionals and experts are now being consulted for technical services. Some of the drugs that are commonly produced locally in Nigeria include anti-malaria drugs, vaccines, and antibiotics. The National Agency for Food and Drug Administration and Control (NAFDAC) serves as the main regulator of the Nigerian pharmaceutical industry.

2.9 Consumer Drug Satisfaction in the Nigerian Pharmaceutical Industry

The Nigerian pharmaceutical industry has since been acting as the source of drugs for the country. The importance of this role cannot be over-emphasized. With the population of the country, the fulfilment of this role will curb the importation of spurious and substandard drugs while meeting consumers' needs and supporting the growth of the economy (Joshua, Anthony and Titus, 2014). Correspondingly, good and

quality drugs have a crucial role to play in the wellbeing of Nigerians. The importance of these drugs transcend curing diseases and alleviating pain. Their availability and efficacy give patients a sense of confidence in the healthcare system. Therefore, consumers' satisfaction with drugs is critical for the health sector and the economy at large. However, the situation with drugs in Nigeria is generally characterized by non-availability of drugs and availability of drugs that are usually expensive and bear no relation with the health needs of Nigerians (Salako, 1991). Although there is improvement in more recent times, the situation is largely the same. Public health institutions are affected the most by drug shortages, leaving patients to go to private pharmacies outside of hospitals to purchase drugs that are not affordable. Therefore, patient confidence in the healthcare system is low. Moreover, the pharmaceutical market in Nigeria is constantly being infiltrated by people that lack the requisite knowledge and qualification to run the affairs of things. This is particularly due to high drug prices of drugs available outside the public health system. This has also resulted in the prevalence of counterfeited and substandard drugs, cheap generics that are not effective, as well as fake drugs in the country (Salako, 1991). The poor health indicators of Nigeria are also indicative of consumers' poor satisfaction with drugs in the country.

2.10 Challenges of the Nigerian Pharmaceutical Industry

The Nigerian pharmaceutical industry is made up of both private and public drug manufacturers who are daily facing challenges that impact the development of drugs. The industry has long been dominated by foreign manufacturers. The situation with indigenous manufacturers is epileptic. The growth of the industry has been at an average of 10 -15 percent for the last five years. The industry is also characterized by the prevalent issue of double taxation issues and a tax regime that is aggressive (Onyali and Okafor, 2018; Uadiale, and Fagbemi, Ogunleye, 2010). Drug production is Nigeria is mainly driven towards essential medicines such as antimalarial, with a number of challenges. Because of the high cost of maintaining manufacturing infrastructure in Nigeria, drugs that are manufactured locally are usually more expensive than imported drugs. Other challenges of drug manufacturing in Nigeria include high cost of production due to correspondingly high costs associated with importation of pharmaceutical ingredients and machinery, weak financial base of manufacturers, problems with infrastructure, lack of updated technology and weak supply chains

(WHO, 2014). Moreover, manufacturers usually rely on foreign expertise usually from Europe and Asia for bioequivalence studies and laboratory testing because of lack of contract research organisations in West African that have international repute. There are also challenges that relate to lack of capacity to comply with international regulatory standards such as speedy registration of drugs. Furthermore, there are also challenges that relate to the lack of effective guidance in manufacturing practices in line with international community, the need for financial incentives to keep companies progressing.

2.11 PAT Regulatory Environment and the Future of Nigerian Pharmaceutical Industry

The regulatory environment of the Nigerian pharmaceutical industry is made up of the National Agency for Food and Drug Administration and Control (NAFDAC) as the regulator. NAFDAC is the agency of the federal government that was established in October 1992 and mandated by an act of parliament to "regulate and control the manufacture, importation, exportation, distribution, advertisement, sale and use of Food, Drugs, Cosmetics, Medical Devices, Packaged Water, Chemicals and Detergents (collectively known as regulated products)" (NAFDAC, 2017). More recently, the agency has been involved in numerous enforcement activities geared towards combating substandard and counterfeit drugs. The WHO (World Health Organization) has been a strong partner of the agency. Together, they have worked to strengthen the quality control and post-marketing monitoring of pharmaceuticals in Nigeria. The regulation of the pharmaceutical industry in any country is a function of the government where drugs are produced and used. NAFDAC's role in actively monitoring the progress of manufacturers and verifying corrective actions has been very vital towards performing this regulatory function of the government. As a result, there is effective communication between industry and regulators in the Nigerian pharmaceutical industry (WHO, 2014).

There are also other non-regulatory bodies involved in the Nigerian pharmaceutical industry. These include the Pharmaceutical Council of Nigeria, the Nigerian Association of Industrial Pharmacists, the Nigeria Association of General Practice Pharmacists and the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG/MAN). These organisations have all organised

symposiums and seminars on counterfeited drugs in the recent years. In relation to the drug situation in the Nigerian pharmaceutical industry, the issue may be indicative of the most pressing challenge that the industry faces. The practice of pharmacists in Nigeria is regulated by the Pharmacists Council of Nigeria (PCN), through the registration and issuance of annual license to individuals and organisations. This responsibility was supported by a new drug policy which states that "only duly licensed pharmacists shall have the authority to supply, sell and dispense drugs to the public" (Federal Ministry of Health, 2003). The regulatory body is also responsible for the renewal of annual licence for continuous provision of healthcare services by pharmacists (Okafor et al., 2021). Summarily, the pharmaceutical industry in Nigeria comprises the academia, regulatory, administrative, community (retail), industry and hospital practice areas that are regulated by the Pharmacists Council of Nigeria (PCN).

2.12 Conclusion

To the best of knowledge, there has been no study on the role or impact of PAT on the Nigerian pharmaceutical industry. Therefore, this research excludes an empirical review of literature. This research also represents an innovative attempt to study how PAT can revolutionize pharmaceutical manufacturing in one of the biggest and important pharmaceutical industry in the world. The concept of PAT is still a developing subject around the world. It is very promising and set to cause a huge paradigm shift for the pharmaceutical industry. The fusion of Big Data with PAT further expands the impact that the technology is likely to have. These concepts will give industrial analytics at molecular level a bright and promising future. They possess the potential for establishing global standardization in process analysis that will lead to small scale continuous manufacturing with the flexibility to meet the market need for personalized products. The interdisciplinary nature of PAT will require cooperation across industries in order to leverage any progress key knowledge across industries. Focusing on this interdisciplinary aspect is very important for the future. PAT, like other key concepts such as QbD, DoE etc., cut across industries and rely on the joint effort of scientists, process experts and data scientists for harnessing inherent benefits. At the industrial level, the trend now lies in building new production systems for smart personalized products. Sensor manufacturing is also seeing a trend in using context sensitive information for manufacturing sensors for use at the molecular level. PAT has

a vital role to play integrating these trends and harnessing the benefits for pharmaceutical manufacturing demanded by critical markets such as Nigeria.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

The purpose of this chapter is to set out the methodology that is used in investigating and answering the questions of this research to fulfil the corresponding research objectives. The general aim of this research is to investigate the role and impact of Process Analytical Technology (PAT) in solid dose manufacturing in Nigeria. The application of PAT to the pharmaceutical industry appears to be very promising from the literary perspective. The general question here is whether, in the practical sense, PAT is currently having an impact in the Nigerian pharmaceutical industry. With particular respect to Nigerian, this research seeks to determine the level of PAT adoption, the challenges to PAT adoption and the impact of PAT on the quality, price and effectiveness of solid dosage forms. The purpose of a research methodology is to outline the steps that need to be taken in order to achieve the research objectives and answer the questions of the research (Newing, 2011).

The methodology of this research is designed with the mind-set that the strength of the subsequent analysis and interpretation of data is hinged on the quality of data collection instrument. In this case, the quantitative methodology is adopted, and the questionnaire is chosen as the instrument of data collection. The questionnaire survey is chosen because it is particularly useful for collecting data from a large number of participants where the right of participants to remain anonymous is highly desired (Wood, 2001). Anonymity is required in this case because the questionnaire data will be sensitive. The next sections discuss the process of undertaking a questionnaire survey: defining the research objectives, identifying the population and sample, deciding how to collect replies, designing the questionnaire, testing the questionnaire with a pilot survey, carrying out the main survey and analysing the data (Burgess, 2001).

3.2 Defining the Research Objectives

This research seeks to answer three main questions. The first question seeks to know the level of Process Analytical Technology (PAT) adoption for solid dose manufacturing in the Nigerian pharmaceutical industry. The research answer to this question will be in the form of a quantitative summary that describes either low level

of adoption, moderate level of adoption, and high level of adoption. The quantitative summary will be based on the responses to a question in the questionnaire that will be sent to manufacturers in the Nigerian pharmaceutical industry. The question will take the form of yes or no answers and will basically ask whether or not the manufacturer is employing PAT with regards to their manufacturing process of any solid dosage form in Nigeria. The review of literature has shown that there are about 130 pharmaceutical firms operating in the Nigerian pharmaceutical industry (Ugbam and Okoro, 2017). The list of manufacturers in the Nigerian pharmaceutical industry is obtainable from the office of the National Agency for Food and Drug Administration and Control (NAFDAC). NAFDAC is the sole government agency established by act of parliament and tasked with the role of regulating and controlling the manufacturing of drugs, among other things (NAFDAC, 2017).

The second research question seeks to investigate the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry. The reason for this question is based on the fact that in literature, PAT has been widely adjudged to be highly beneficial to pharmaceutical industry. However, it can be concluded from literature that the implementation of PAT in practice is generally slow, poor and limited (Vanhoorne and Vervaet, 2020) (Simon et al., 2015). Consequently, there must be challenges that are hampering the widespread introduction of continuous manufacturing of drug products and PAT. A predefined list of challenges has been identified from literature review, consultations and based on experience in such a way that a comprehensive list is achieved. Manufacturers will then be asked, through the questionnaire, to rank the challenges using a 5-point Likert styled questions. An overall summary of the responses will indicate which challenges are most pertinent for the Nigerian pharmaceutical industry. The result will be a list of challenges to PAT implementation, ranked in an order of importance that is peculiar to the Nigerian Pharmaceutical industry.

The third research objective of this research is to determine the impact of PAT adoption by manufacturers on solid dose medication. In other words, those manufacturers that have implemented PAT in their manufacturing process, do their medications perform better than the medications of those that have not implemented PAT? This comparison will be based on price, quality and the efficacy of the drugs in questions. The link between PAT, quality of manufactured drugs, affordability of drugs and the efficacy of

manufactured drugs have been established in literature (Low and Chrisman, 2012) (Vanhoorne and Vervaet, 2020) (Simon et al., 2015). In order to achieve this, this research is employing two sets of questionnaires. The first set of questionnaires is sent to the manufacturers in the Nigerian pharmaceutical industry who would indicate whether or not they employ PAT in the manufacturing process of any of their solid dosage medications. When this first of questionnaires is received, the second set of questionnaire is designed for health practitioners to assess the quality, efficacy and affordability of the list of drugs based on their experience in the medical field. The quality, price and efficacy of a drug are benefits that have been associated with PAT in literature. Using a Likert-typed scaled questions these professionals will rate the drugs based on those qualities. Inferential statistics will then be used to reveal any pattern that may exist using linear regression.

3.3   Research Population and Sample

The population of a research consists of the members of the group of interest; the sample is a subset that comprises members of the population that are accessible and chosen for participation (Burgess, 2001). This research is based on the Nigerian pharmaceutical industry. The population of the study consists of registered manufacturers in the Nigerian pharmaceutical industry who have been previously revealed to be about 130 in number. The research sample consists of all members of this population based on the fact that the population is not inexhaustible. A minimum of 100 questionnaires will be considered for the third research objective based on the health professionals in Nigerian. Nigeria is located in West Africa with a total area of 923,768 km2 (356,669 sq mi). The countries that share border with Nigeria include Benin, Niger, Chad, and Cameroon. Nigeria is a rich cultural milieu that lies between latitudes 4° and 14°N, and longitudes 2° and 15°E. The country has an abundance of more than 250 different ethnic groups. In terms of climate, the dry season and the rainy season are applicable to Nigeria. The vegetation spread of the country and the climatic condition have a strong connection. From the southern part of the country to the northern part of the country, the names of the vegetation include the following: Mangrove Swamp and Coastal Vegetation, Freshwater Swamp Forest, Lowland Rain Forest, Derived Savanna, Guinea Savanna, Sudan Savanna, and Sahel Savanna. The

agricultural sector of Nigerian is known to be the main employer of labour despite the country's high dependency on crude oil.

3.4   Data Collection Instrument

Data collection has been described as a way through which the data is collected from the sample of the research population (Cresswell, 2013). This research will involve the collection and analysis of primary data. In this case, a self-administered questionnaire is used as the instrument of primary data collection which represent first-hand information obtained from the distribution of questionnaires. Generally speaking, the design of the questionnaire is based on secondary data from literature review as well as personal observations and experience of the researcher who has come in contact with the study area. A questionnaire has been defined as an instrument of research that is made up of questions and other indicators to obtain information from respondents with a focus on a research objective (Mugenda and Mugenda, 2013). It has also been noted that a self-administered questionnaire can be sufficiently utilised to objectively collect data because of the researcher's interference and manipulation is minimal (Zikmund, 2013). It can also be considered as a cheap means of collecting data that requires less time to administer. The structured questionnaire in this case will be administered using Google Form by sending online invitation to pharmaceutical manufacturers in Nigeria through their email addresses. The second questionnaire will also be administered through the same channel to health practitioners. The ongoing COVID-19 pandemic makes this method of data collection the most probable.

The questionnaire is generally divided into two sections, the background information section which collects demographic information and the main research questions section. The research questions section consists of questions that are designed to address the research objectives. The research questions section mainly employs a five-point Likert type interval scale. The questions for each of this parts are tailored to measure a specific characteristic. Each characteristic has a minimum of three questions to get data to evaluate the aim of the research which is to evaluate the impact of PAT on the manufacturing of solid dosage forms. Each question uses a five-point Likert type interval scale that respondents can use in rating a particular measure based on their experience and knowledge. The demographic data section employs the ratio scale for

questions. The nominal scale was also employed and used to obtain information with a level of precision. This research employs the descriptive survey because the survey style helps in focusing the data on the desired characteristics that research question is designed to collect. The use of a sample drawn from the main population is useful for providing clearer insights to the issue under examination which further ensures that the representative sample from the population can be used to generalize the results to a wider population (Osuala, 2002).

3.5 Research Design

A descriptive research survey is employed in this research in order to ensure a comprehensive study of the topic of research. This research design is preferred because data collection can be used to answer questions concerning the objectives of the research. According to Mugenda and Mugenda (2013), descriptive research determines and reports the way things are done by helping a researcher to describe a phenomenon in terms of attitude, values and characteristics. Furthermore, the descriptive survey is a method of collecting information through the use interviews or by employing a questionnaire to a sample of the population. This method is used in studies where it is useful in portraying the accuracy of people's profile, the situations and the events in question (Orodho, 2003). The research aim which tends to investigate the impact of PAT on solid dose manufacturing in Nigeria would be achieved by administering a questionnaire that targets manufacturers in the industry. By asking the right questions, the degree of accuracy in the analysis is maintained to a high standard. The Likert scale employed in this research is based on a symmetrical scale construct in which the neutral position is located between two extremes of strongly disagree (SD) to strongly agree (SA). This ensures that there is independence given to each respondent in choosing any reply in a balanced way based on either direction of consideration. The Likert type scale enables access to the opinions, attitudes, or behaviours of the research participants in regard to the question and objectives of a research. The Likert type scale also makes it possible for the researcher to easily operationalise opinions and perceptions. The statements used in the Likert scales allow a continuum of possible responses that range in five gradations in the case of this research. For the data to be analyzed quantitatively, each level of gradation is given a numerical score so that the data. The first grade

quantitatively represents a case of strong agreement from a respondent while five (5) represents the case of strong disagreement from the research respondents.

3.6 Sampling Technique

As mentioned previously, there are two sets of questionnaires that are designed to address the third objective of this research. The first set of questionnaires for this research will utilize simple random sampling since all members of the population are known and accessible through online means. This research also employs purposive sampling in the administering of the second set of questionnaires targeted at specific health professionals that are in close contact with patients. Using the purposive sampling technique, all the drugs listed by their manufacturers in the first questionnaire will be addressed. Sample size as previously defined is a subset of the population drawn in a representative manner. It can also be regarded as any combination of sampling units that do not include the entire set of sampling units that make up the population (Garson, 2012). The use of the right sample size for any research is a critical factor to the outcome of the research because there are several factors that affect what the size becomes. These factors include the population of the study, the allowed sampling error and the aim of research. Over the years, researchers have used new technologies for improving the level of research precision, the level of confidence with regard to the degree of variability of sample size. A simplified formula postulated by Yamane (1967) has often been used to determine the sample size of research studies. For the purpose of the second set of questionnaires for this research, a minimum sample size of 100 health professionals will be considered based on rule of thumb. This number is sufficient to give the level of clarity and precision needed in the data analysis (Bryman and Bell, 2007).

3.7 Data Analysis

Data analysis is undertaken to make sense out of research respondents' views and opinions of situations. It involves the process of recognizing corresponding patterns, themes, categories and regular similarities (Cohen *et al.*, 2007). According to Gibbs (2007), data analysis is the process of converting data using analytic procedures, into a clear, understandable, insightful, trustworthy and authentic information. The process of data analysis begins with cross-checking to ensure that data is accurate, consistent,

uniformly entered, complete and well arranged to facilitate coding and tabulation. Descriptive and inferential statistical analysis will be employed in the analysis of the questionnaire data using Statistical Package for Social Sciences (SPSS)**. SPSS is a computer software for facilitating data analysis.** Descriptive statistics will be use in summarizing and presenting data in the form of percentages and frequencies to show how many times a measured variable occurs and also the probability of occurrence. Therefore, frequency distribution will be used. Additionally, means and standard deviations will be computed to show the average response of the variable items. Inferential statistics will also be involved in addressing the third objective of this research which seeks to determine the impact of PAT adoption by pharmaceutical manufacturers on solid dosage forms.

3.8 Validity of Research Instrument

Both construct validity and content validity will be applied to this research. The questionnaire instruments used in this research will be divided into sections in order to ensure that each section is used in assessing information for a specific objective. As a result, construct validity will be achieved. It will also be ensured that each section of the questionnaire is tied to the conceptual framework of this study. For content validity, the questionnaires will be subjected to thorough examination through pilot study. This will involve testing the questionnaire for relevance with few of the potential participants and getting their assessment as to whether the research instrument is meaningful, clear and offensive. Based evaluation through pilot study, the research instrument will be adjusted accordingly before subjecting it to the final data collection exercise. In this way, the comments of participants from the pilot study will be used to ensure that content validity was enhanced.

3.9 Ethical Consideration

To ensure that due consideration is given to ethics, informed consent will be required from participants and in order to make sure that all participation is voluntarily. Participants will be allowed cancel their participation in the study at any time without prior notice to the researcher. The respondents will not be required to indicate personal information that could expose them to risk on the questionnaire, so that anonymity can easily be achieved. However, in the case of the two questionnaires used in this research,

email addresses will be required for monitoring questionnaire entries since information is collected electronically collected. The email will also facilitate any potential communication from respondents. However, the emails will not be shared to any third party and will not feature in the actual research report. Generally, the following informed consent will be observed: confidentiality of participants' information; integrity, care and honesty in the survey research process; objectivity; protection of participants; and ensuring social responsibility and non-discrimination.

CHAPTER FOUR

DATA ANALYSIS AND INTERPRETATION

4.1 Introduction

The general aim of this research is to investigate the role and impact of Process Analytical Technology (PAT) adoption for solid dose manufacturing in the Nigerian pharmaceutical industry. To achieve foregoing, this chapter will present the analysis of data, the corresponding findings and the interpretation of results. The discussions will be presented in the next chapter so as to provide more context to the findings. The following analyses and interpretation of the data will be based on the research questions and the hypotheses presented in the introductory chapter of this research. This chapter will answer questions that seek to know the general level of PAT adoption for solid dose manufacturing in the Nigerian context and the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry. Moreover, this research also investigated hypotheses that test whether there is any significant relationship between the adoption of PAT by manufacturers in the Nigerian pharmaceutical industry and the corresponding price, quality and effectiveness of their drugs.

As a matter of methodology, this research employed two sets of questionnaires. Before going into the nitty-gritty of inferential analysis, descriptive statistics will first be used to present summary of the data from the two questionnaires. Descriptive summary of data using charts and tables are important for contextualizing inferential analysis and as such it is not ignored here. Moreover, all the questions answered in the questionnaires are specifically chosen to aid the reader in providing context so that the findings are not overblown out of scope. Afterwards, the specific objectives of this research will be evaluated to ensure that they have been sufficiently addressed. The evaluation will be followed by the establishing of the significance of the link between the independent variable (PAT adoption) and the dependent variables (price, effectiveness, and quality of selected drugs). The techniques used in achieving this was largely influenced by the data structure. Moreover, visual representations will also be used wherever possible to aid better understanding of the information presented.

4.2   Descriptive Statistics

4.2.1 Manufacturers Questionnaire

The Table 4.1 below shows that all the participants provided consent for their data to be used in the analysis of this research. In all, there were 62 respondents to the questionnaire. This number represents less than half of the total population of certified solid dose manufacturers in the Nigerian pharmaceutical industry, which from literature review has been established to be around 130 in number (Ugbam and Okoro, 2017).

Table 4.1: Consent from participants

Consent	Participants	Percent
Yes	62	100
No	0	0
Total	62	100

The Table 4.2 below describes the organisational rank of the staff that responded to the questionnaires on behalf of the manufacturers. This information is also depicted in Figure 4.1 below. Most of the respondents were junior-level staff. This might be due to the fact that senior level staff are always busy and unavailable to fill questionnaires from a student. However, it is also noteworthy that some senior level staff representing about 16% of the respondents also participated in the research.

Table 4.2: How would you describe your organizational rank?

Organizational Rank	Frequency	Percent
Junior Level	30	48.4
Mid-Level	22	35.5
Senior Level	10	16.1
Total	62	100.0

Figure 4.1: How would you describe your organisational rank?

The Table 4.3 and Figure 4.2 below shows the age of the manufacturing companies in Nigeria. Generally, companies that are less than 5 years may not have sufficient experience considering the level of technology required for PAT. It is important that these companies do not form the bulk of these respondents.

Table 4.3: How old is your company in Nigeria?

	Frequency	Percent
1 - 5 Years	16	25.8
6 - 30 Years	35	56.5
31+ Years	11	17.7
Total	62	100.0
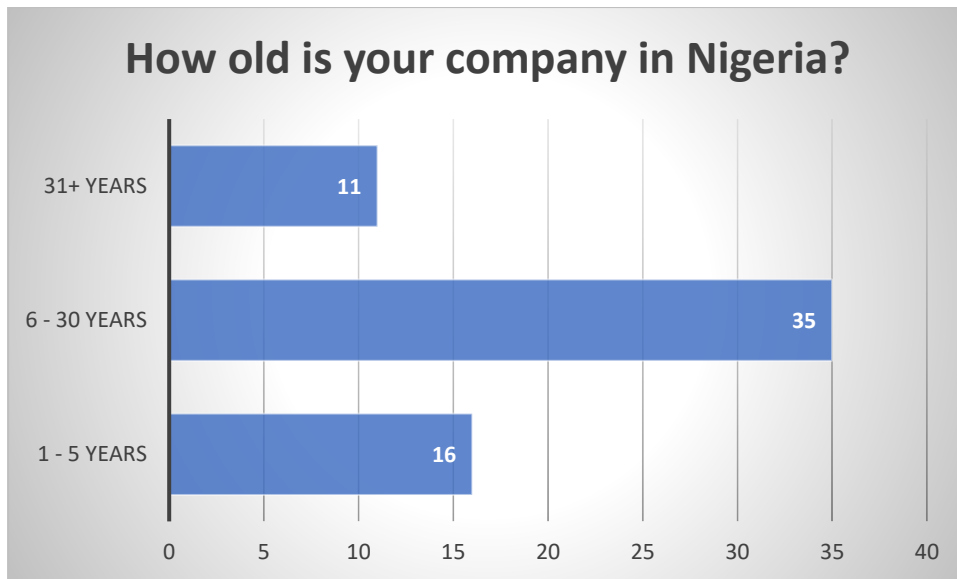
Figure 4.2: How old is your company in Nigeria?

The Table 4.4 and Figure 4.3 shows that most of the respondent companies have staff strengths that are greater than 50. This again goes to bolster the quality of the respondent companies.

Table 4.4: How many employees does your company have?

	Frequency	Percent
1 - 10	2	3.2
11 - 50	31	50.0
51+	29	46.8
Total	62	100.0
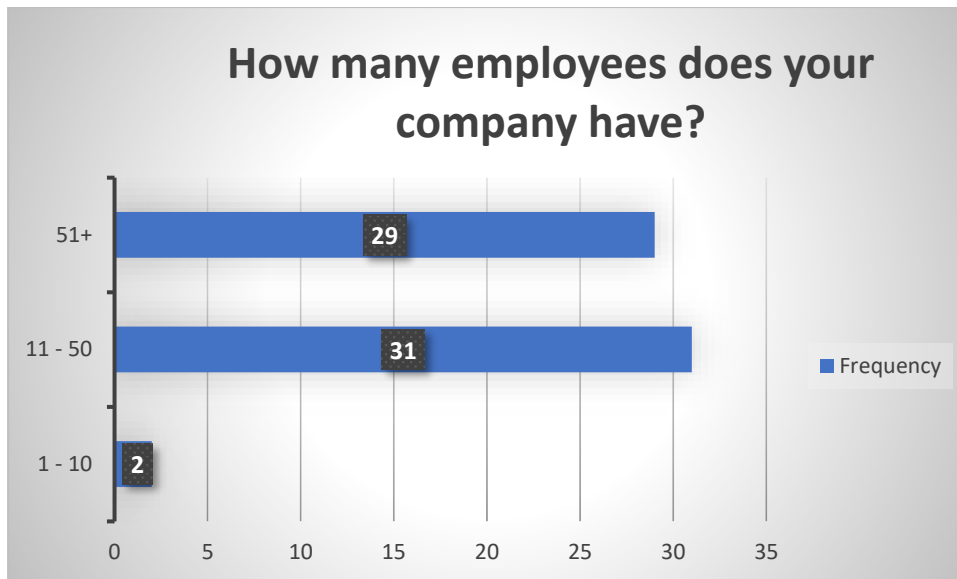
Figure 4.3: How many employees does your company have?

Table 4.5 and Figure 4.4 below present a key information that answers the first objective of this research, to find out the level of PAT adoption. The data shows that the level of PAT adoption in the Nigerian pharmaceutical industry is generally low with over 80% of the manufacturers saying they do not employ PAT.

Table 4.5: Do you employ PAT in the manufacturing of any solid dose drug?

	Frequency	Percent
No	51	82.3
Yes	11	17.7
Total	62	100.0
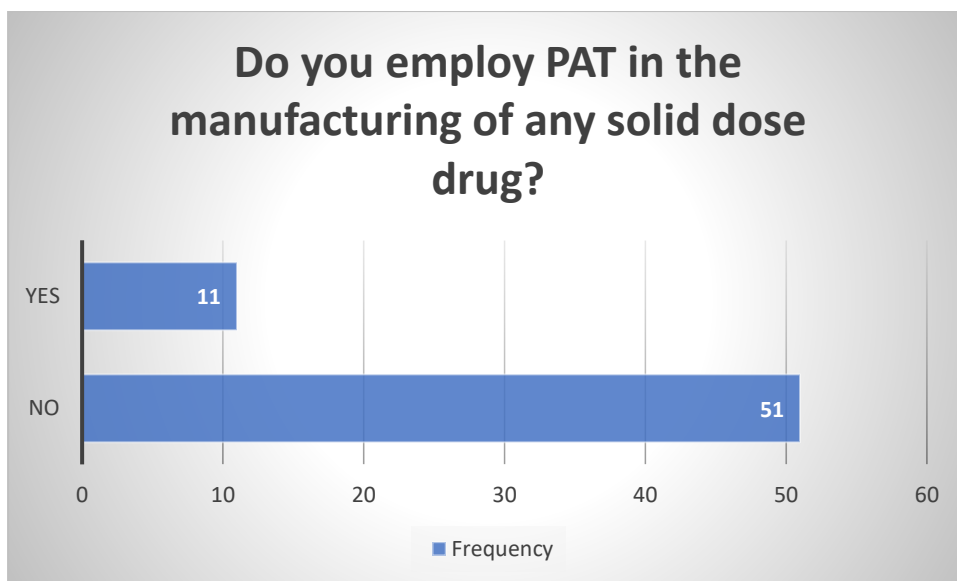
Figure 4.4: Do you employ PAT in the manufacturing of any solid dose drug?

Table 4.6 and Figure 4.5 shows that Tablets are the most common form of solid dosage produced in Nigeria with 71% share, followed by capsules with 23% and powder with 7%.

Table 4.6: What is the form of the drug in Table 4.5 above?

	Frequency	Percent
Tablets	44	71.0
Capsules	14	22.6
Powder	4	6.5
Total	62	100.0
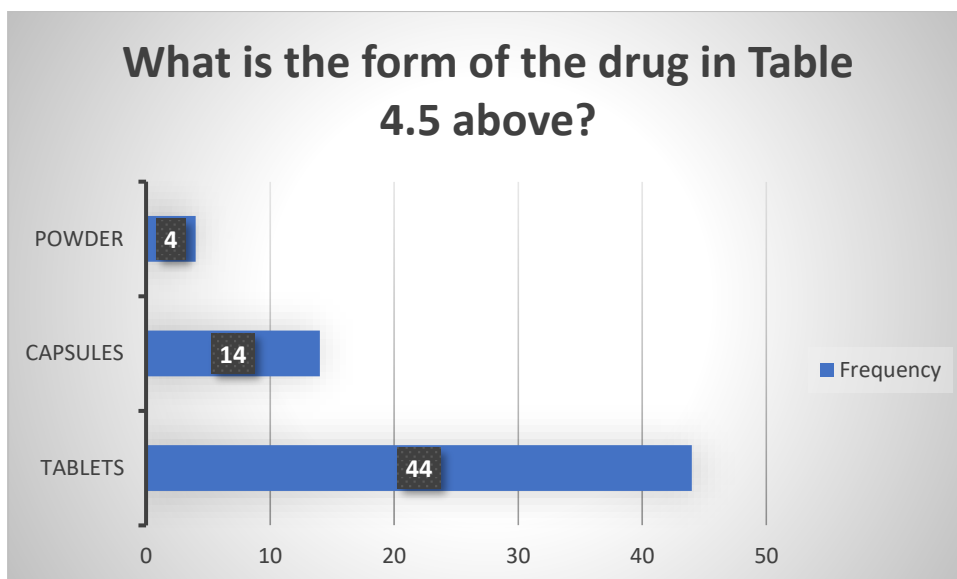
Figure 4.5: What is the form of the drug in Table 4.5 above?

As seen from Table 4.7 and Figure 4.6 below, about 90% of the respondents feel that

PAT implementation in the Nigerian pharmaceutical industry is desirable.

Table 4.7: What is your general view about employing PAT to manufacture drugs in Nigeria?

	Frequency	Percent
Neither good nor bad	6	9.7
Good	56	90.3
Total	62	100.0
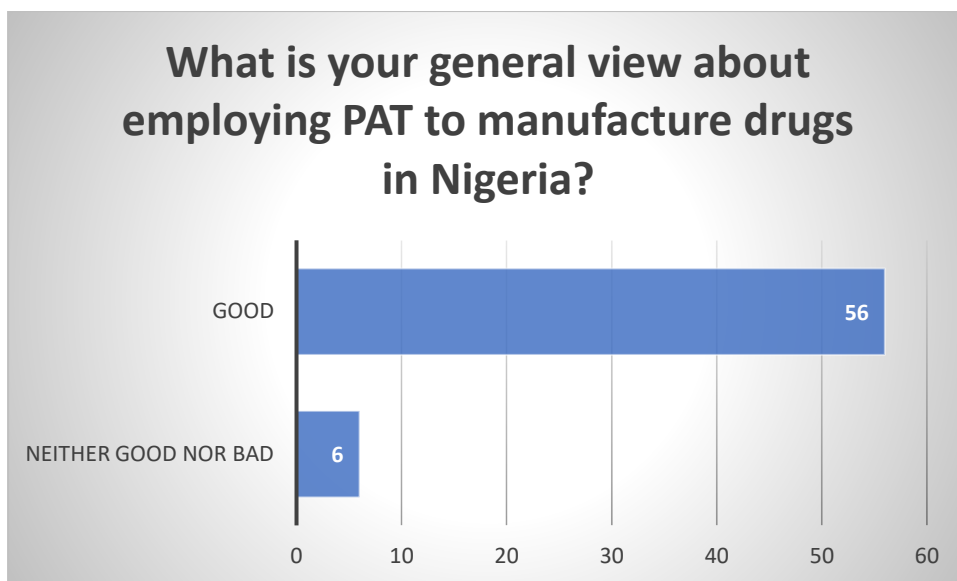
Figure 4.6: What is your general view about employing PAT to manufacture drugs in Nigeria?

The next sets of tables and charts present data that was generated from the Likert-typed questions in the B section of the questionnaire send to the manufacturers. The Table 4.8 and Figure 4.7 below shows that most of the respondents (50%) agree that producing a variety of drugs from the same production line represents an impediment to PAT implementation.

Table 4.8: Producing varieties of drugs is an impediment to Process Analytical Technology (PAT) Implementation

	Frequency	Percent
Disagree	14	22.6
Neither Agree nor Disagree	10	16.1
Agree	31	50.0
Strongly Agree	7	11.3
Total	62	100.0
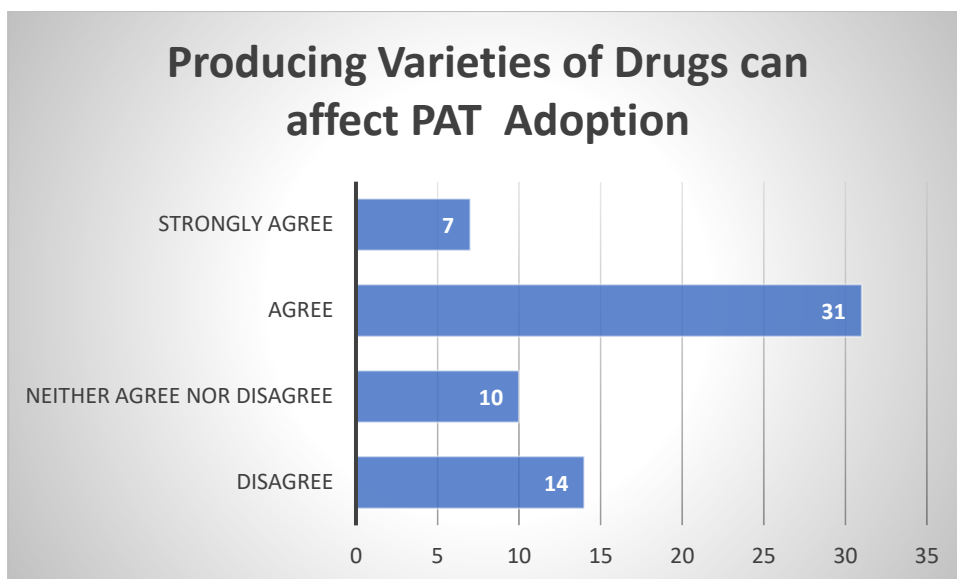
Figure 4.7: Producing varieties of drugs can affect PAT adoption

Most of the manufacturer's respondents (53%) also believe that the technology required to implement PAT is too advanced. This is shown in Table 4.9 and Figure 4.8 below.

Table 4.9: The technology level required to implement PAT is too advanced.

	Frequency	Percent
Disagree	15	24.2
Neither Agree nor Disagree	8	12.9
Agree	33	53.2
Strongly Agree	6	9.7
Total	62	100.0
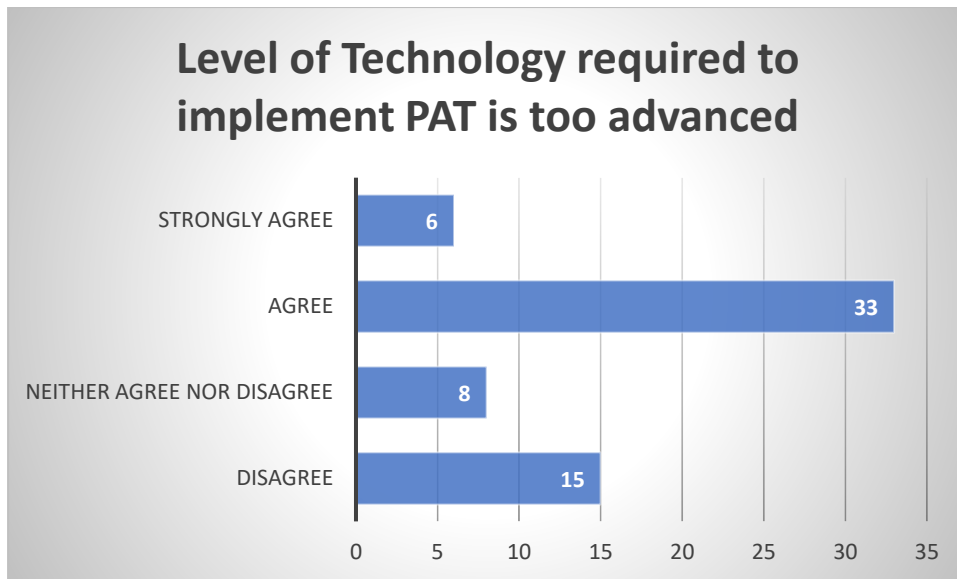
Figure 4.8: Level of technology required to implement PAT is too advanced

A significant proportion of the respondents (76%) believe that the number of equipment required for implementing PAT are numerous as shown in Table 4.10 and Figure 4.9 below.

Table 4.10: The number of equipment required to implement PAT are numerous.

	Frequency	Percent
Disagree	5	8.1
Agree	47	75.8
Strongly Agree	10	16.1
Total	62	100.0
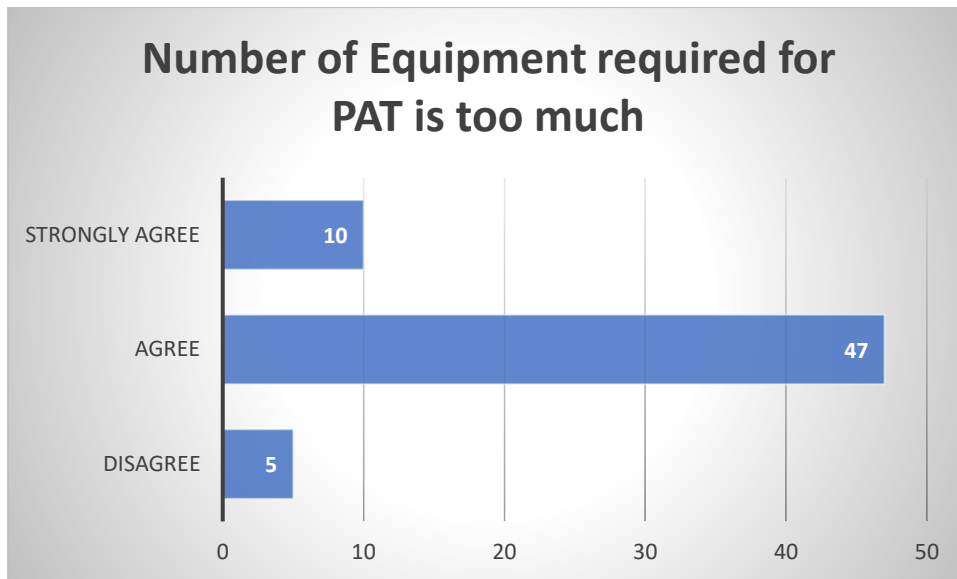
Figure 4.9: Number of equipment required for PAT is too much

The Table 4.11 and Figure 4.10 below shows that about 73% of the respondents strongly agree that the high maintenance costs associated with PAT represent an impediment to its implementation.

Table 4.11: The maintenance cost for PAT implementation is very high.

	Frequency	Percent
Neither Agree nor Disagree	1	1.6
Agree	16	25.8
Strongly Agree	45	72.6
Total	62	100.0
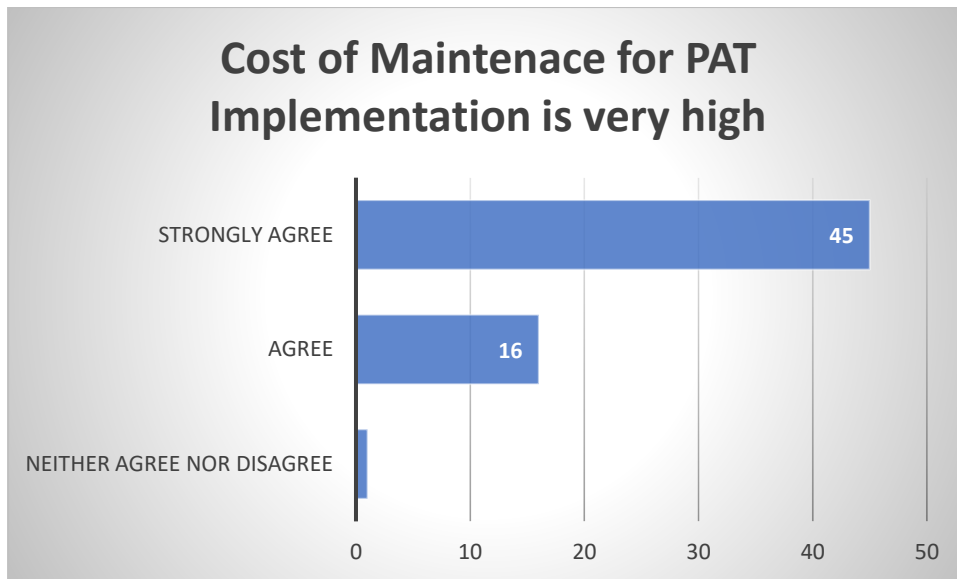
Figure 4.10: Cost of maintenance for PAT implementation is very high

The Table 4.12 and Figure 4.11 below show that the greater percentage of the respondents forming about 63% agree that there are no maintenance experts for PAT in Nigeria.

Table 4.12: There are no maintenance experts for PAT in Nigeria.

	Frequency	Percent
Strongly Disagree	1	1.6
Disagree	2	3.2
Neither Agree nor Disagree	16	25.8
Agree	39	62.9
Strongly Agree	4	6.5
Total	62	100.0
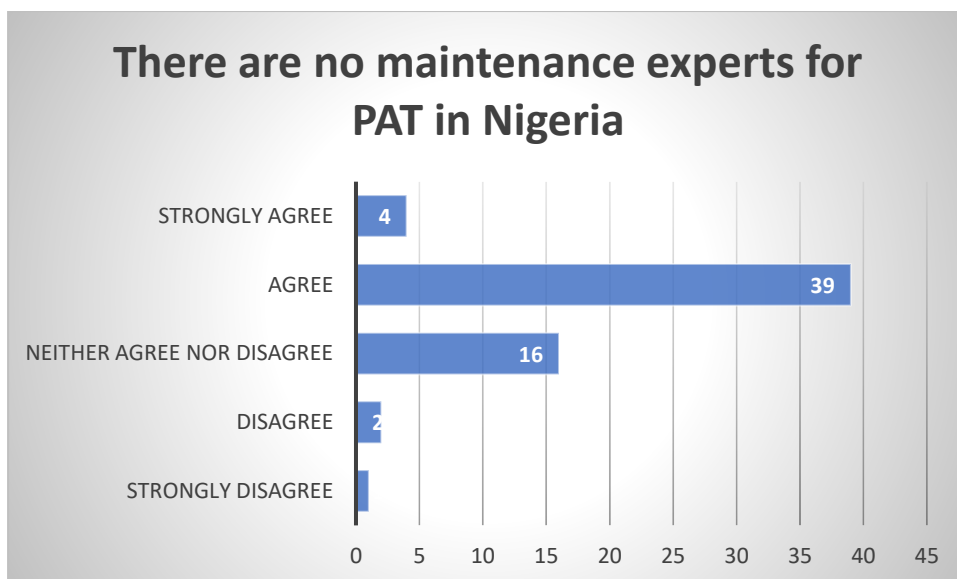
Figure 4.11: There are no maintenance experts for PAT in Nigeria

As seen from Table 4.13 and Figure 4.12 below show respondents' general agreement with the statement that says it is difficult to find local experts skilled in implementing PAT.

Table 4.13: It is difficult to find local experts skilled in implementing PAT.

	Frequency	Percent
Disagree	10	16.1
Neither Agree nor Disagree	11	17.7
Agree	35	56.5
Strongly Agree	6	9.7
Total	62	100.0
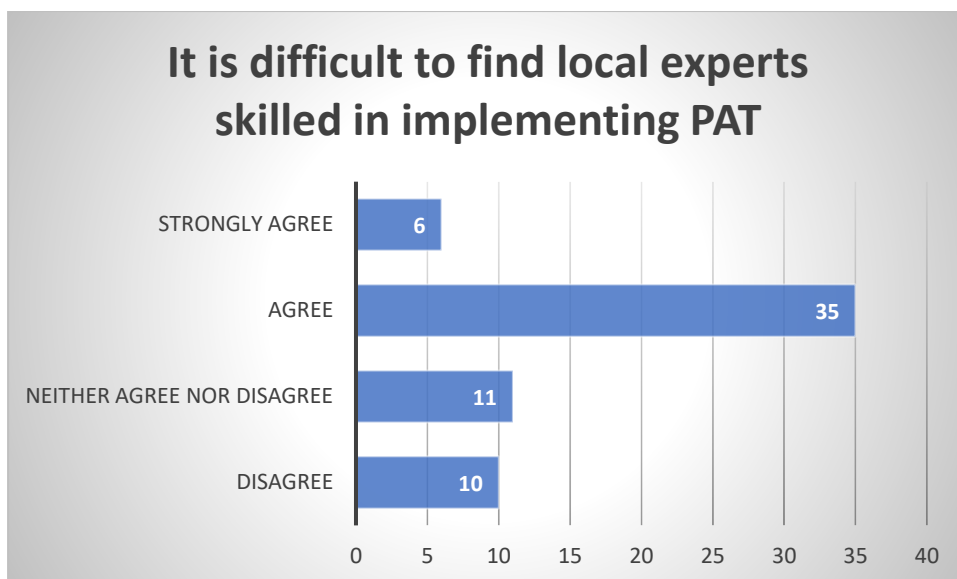
Figure 4.12: It is difficult to find local experts skilled in implementing PAT

The Table 4.14 and Figure 4.13 below shows that a majority of the respondents disagree that PAT is overrated for the pharmaceutical industry.

Table 4.14: PAT is overrated for the pharmaceutical Industry.

	Frequency	Percent
Strongly Disagree	3	4.8
Disagree	28	45.2
Neither Agree nor Disagree	25	40.3
Agree	5	8.1
Strongly Agree	1	1.6
Total	62	100.0
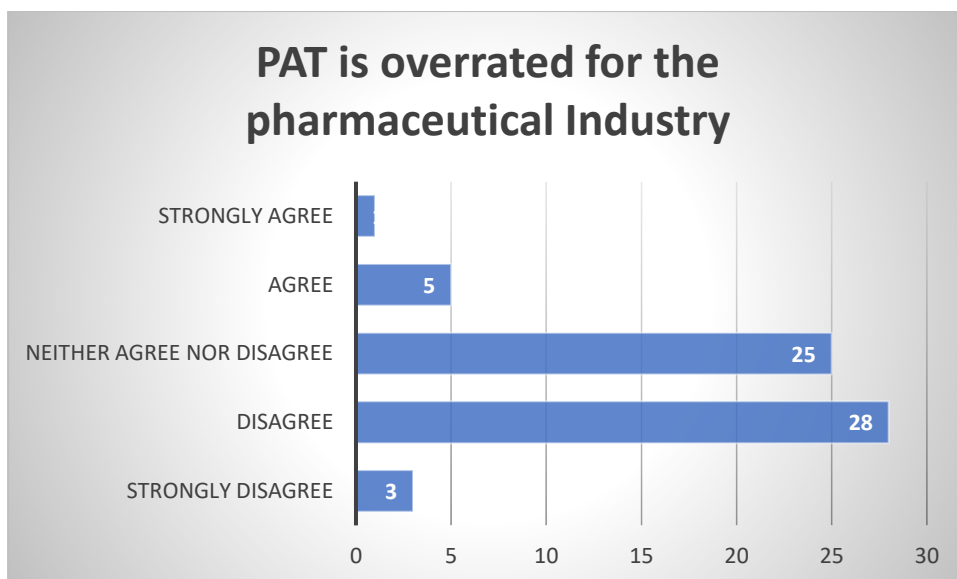
Figure 4.13: PAT is overrated for the pharmaceutical industry

From Table 4.15 and Figure 4.14 below, there is no clear majority on whether most stakeholders in the Nigerian pharmaceutical industry are not knowledgeable in PAT.

Table 4.15: Most stakeholders are not knowledgeable in PAT.

	Frequency	Percent
Strongly Disagree	2	3.2
Disagree	18	29.0
Neither Agree nor Disagree	17	27.4
Agree	24	38.7
Strongly Agree	1	1.6
Total	62	100.0
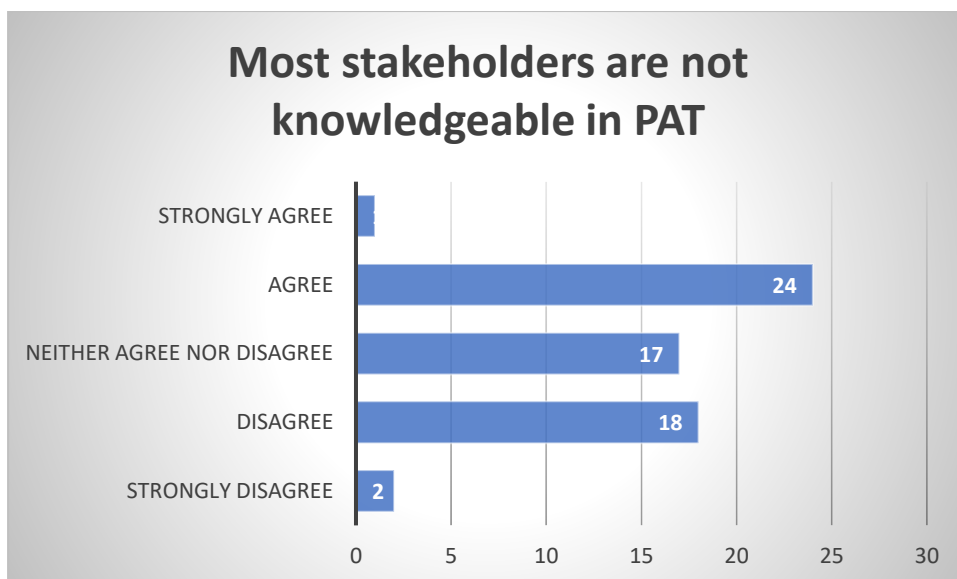
Figure 4.14: Most stakeholders are not knowledgeable in PAT

As seen from Table 4.16 and Figure 4.15 below, a majority of the respondents (60%) believe that PAT is not a necessity for the pharmaceutical industry. This may be true considering that batch processing has been successful in delivering quality drugs that have sustained humanity for ages. The question would be for how many more years can conventional batch processing sustain the industry looking into the future.

Table 4.16: PAT is not a necessity for pharmaceutical manufacturing.

	Frequency	Percent
Strongly Disagree	2	3.2
Disagree	12	19.4
Neither Agree nor Disagree	7	11.3
Agree	37	59.7
Strongly Agree	4	6.5
Total	62	100.0
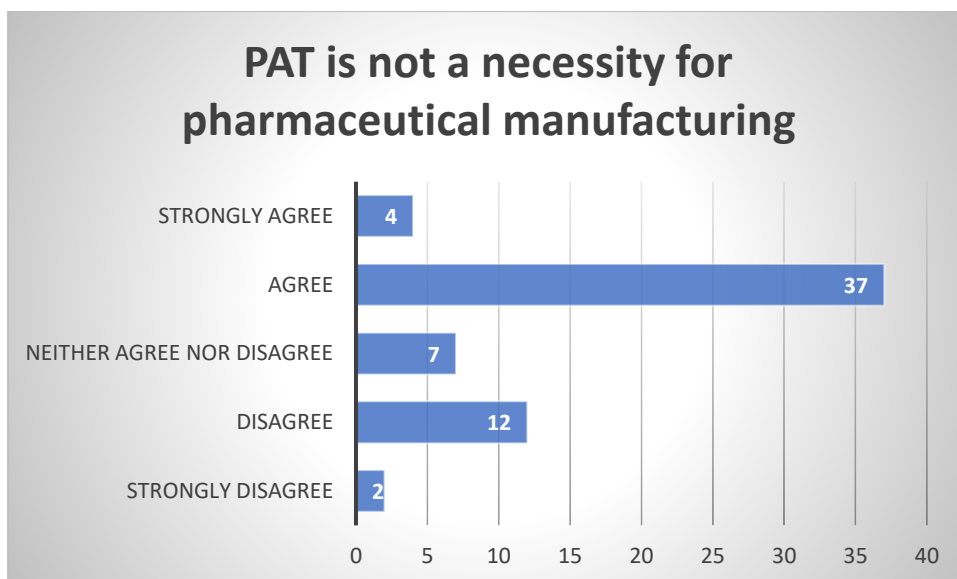
Figure 4.15: PAT is not a necessity for pharmaceutical manufacturing

The Table 4.17 and Figure 4.16 below show that 58% of the respondents agree that the Nigerian pharmaceutical industry is not yet mature for PAT implementation.

Table 4.17: The pharmaceutical industry in Nigeria is not mature for PAT.

	Frequency	Percent
Disagree	14	22.6
Neither Agree nor Disagree	6	9.7
Agree	36	58.1
Strongly Agree	6	9.7
Total	62	100.0
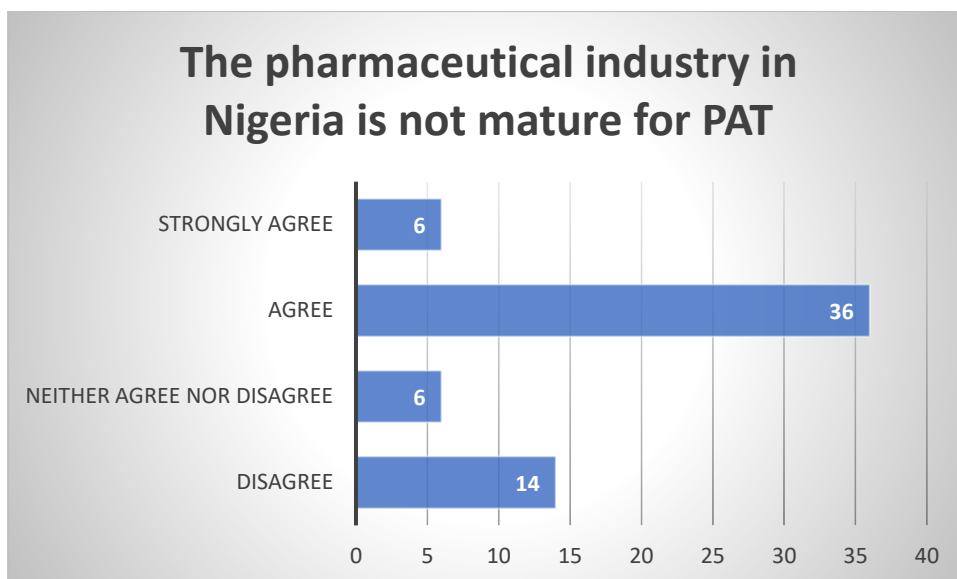
Figure 4.16: The pharmaceutical industry in Nigeria is not mature for PAT

The Table 4.18 and Figure 4.17 below show that majority of the respondents agree with the fact that PAT is different from conventional pharmaceutical manufacturing.

Table 4.18: There is no difference between PAT and conventional pharmaceutical manufacturing.

	Frequency	Percent
Strongly Disagree	4	6.5
Disagree	33	53.2
Neither Agree nor Disagree	21	33.9
Agree	4	6.5
Total	62	100.0
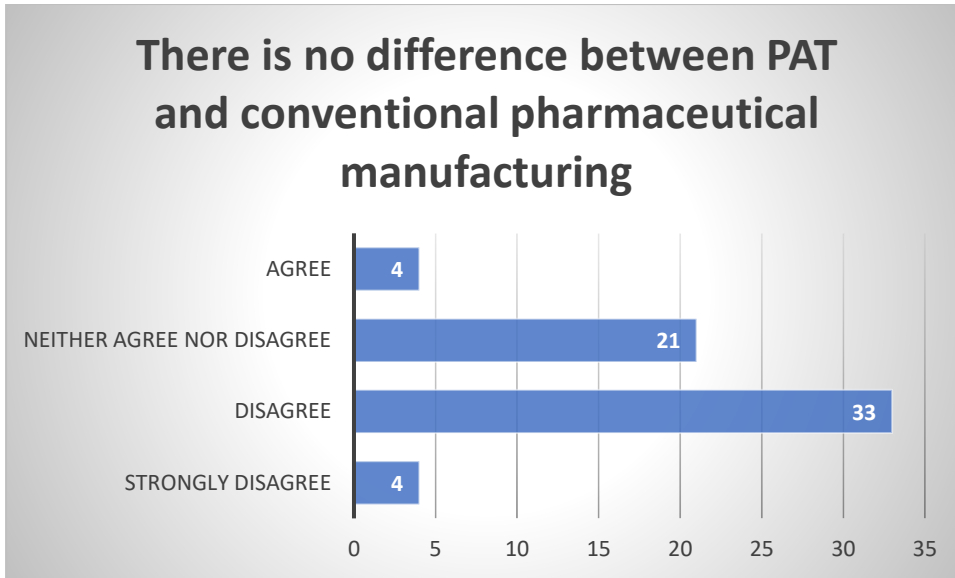
Figure 4.17: There is no difference between PAT and conventional pharmaceutical manufacturing

The Table 4.19 and Figure 4.18 below show that the respondents are split between whether conventional batch manufacturing is better than PAT.

Table 4.19: Some drugs are better manufactured using conventional batch processing.

	Frequency	Percent
Disagree	13	21.0
Neither Agree nor Disagree	29	46.8
Agree	20	32.3
Total	62	100.0
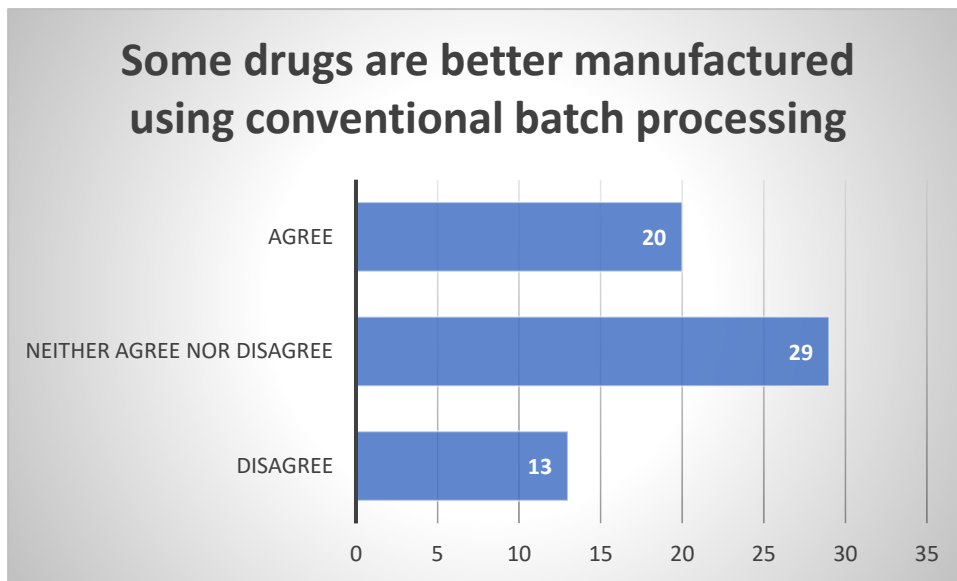
Figure 4.18: Some drugs are better manufactured using conventional batch processing

The Table 4.20 and Figure 4.19 below show that majority of the respondents disagree with the statement that conventional manufacturing will produce the same results as PAT.

Table 4.20: Conventional manufacturing will produce the same results as PAT.

	Frequency	Percent
Strongly Disagree	2	3.2
Disagree	31	50.0
Neither Agree nor Disagree	19	30.6
Agree	9	14.5
Strongly Agree	1	1.6
Total	62	100.0
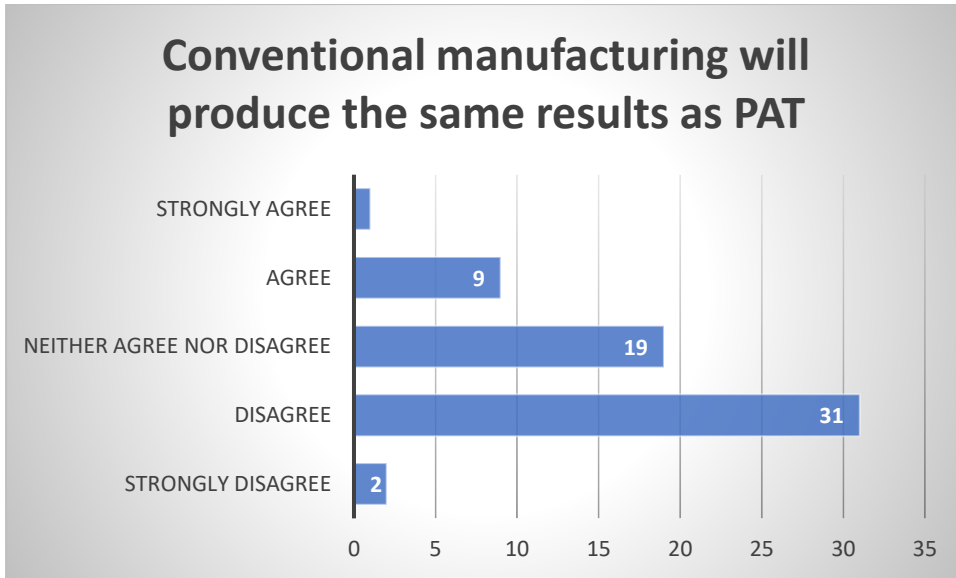
Figure 4.19: Conventional manufacturing will produce the same results as PAT

The Table 4.21 and Figure 4.20 below show that an overwhelming majority of the respondents agree that there are not spare parts for major components of PAT such as process analyzers, representing an impediment to its implementation.

Table 4.21: Process analyzers for PAT have no spare parts available.

	Frequency	Percent
Disagree	4	6.5
Neither Agree nor Disagree	6	9.7
Agree	48	77.4
Strongly Agree	4	6.5
Total	62	100.0
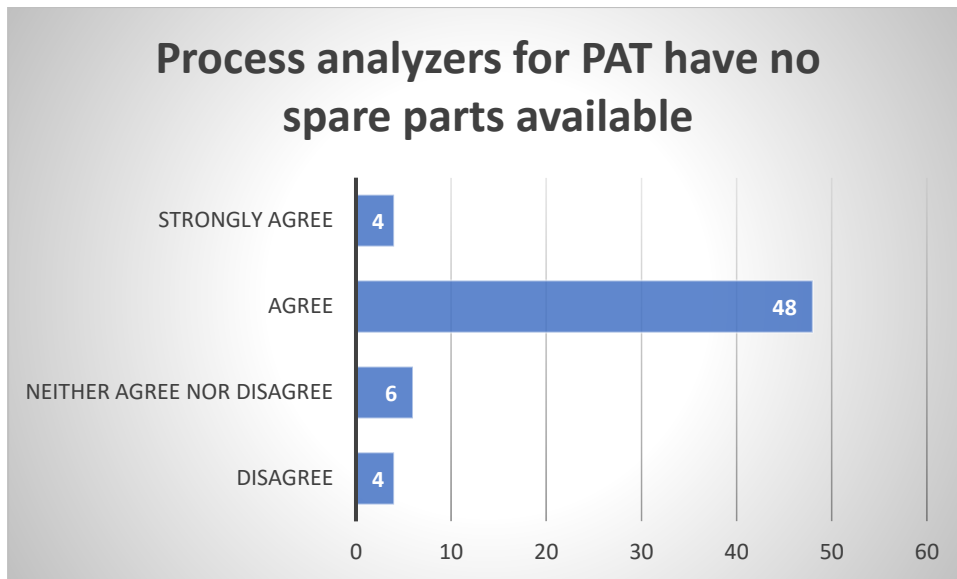
Figure 4.20: Process analyzers for PAT have no spare parts available

The Table 4.22 and Figure 4.21 below show that about 90% of the respondents agree that implementing PAT will lead to increase in the price of drugs, with 40% strongly agreeing to the statement.

Table 4.22: Implementing process analyzers for PAT will increase the price of drugs.

	Frequency	Percent
Disagree	2	3.2
Neither Agree nor Disagree	4	6.5
Agree	31	50.0
Strongly Agree	25	40.3
Total	62	100.0
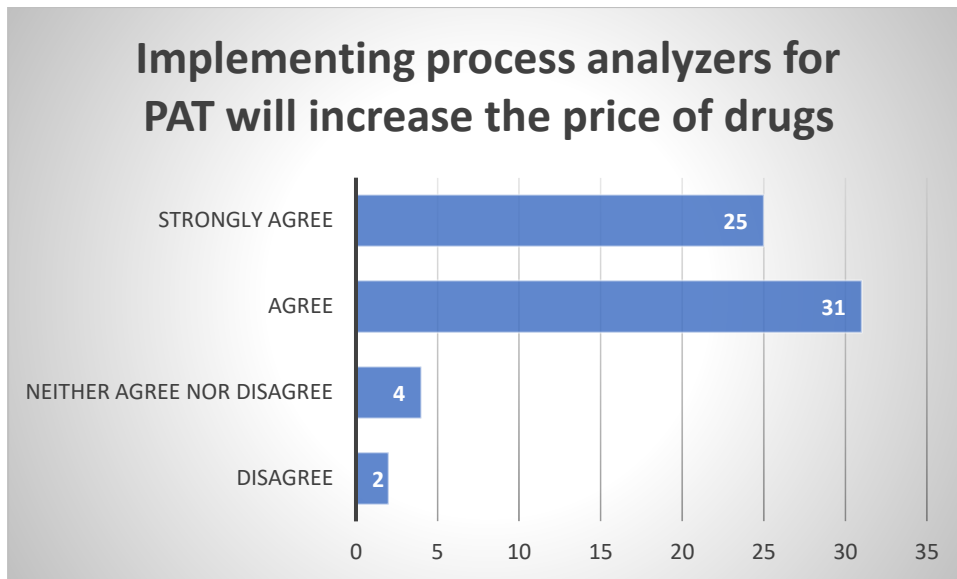
Figure 4.21: Implementing PAT will increase the price of drugs

The Table 4.23 and Figure 4.22 below show that majority of the respondents, making about 64% believe that PAT is prone to system failures.

Table 4.23: PAT is prone to system failures.

	Frequency	Percent
Disagree	6	9.7
Neither Agree nor Disagree	16	25.8
Agree	29	46.8
Strongly Agree	11	17.7
Total	62	100.0
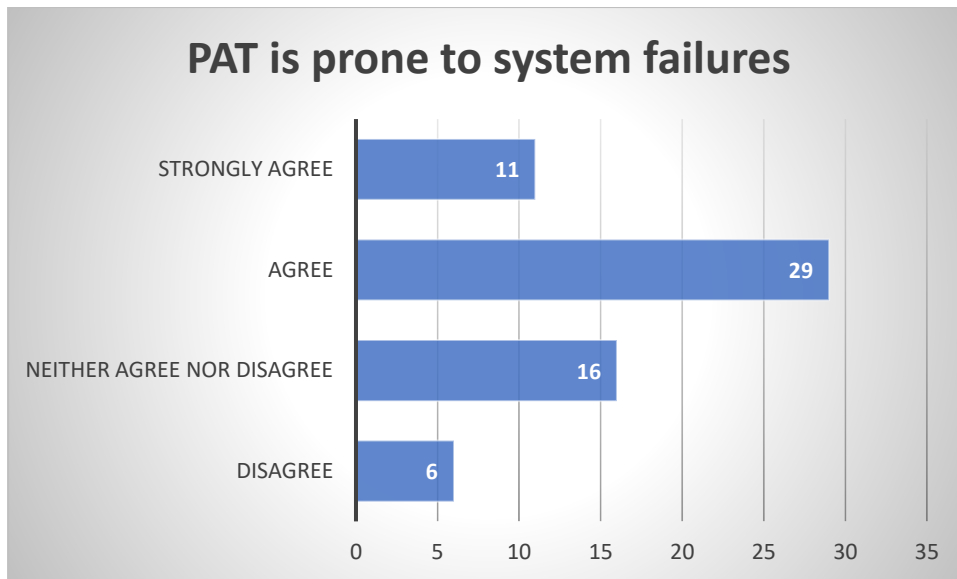
Figure 4.22: PAT is prone to system failures

Furthermore, the Table 4.24 and Figure 4.23 below show that majority of the respondents, forming about 83%, agree that cost of system failure with PAT is very expensive.

Table 4.24: System failure with PAT is expensive.

	Frequency	Percent
Disagree	4	6.5
Neither Agree nor Disagree	6	9.7
Agree	37	59.7
Strongly Agree	15	24.2
Total	62	100.0
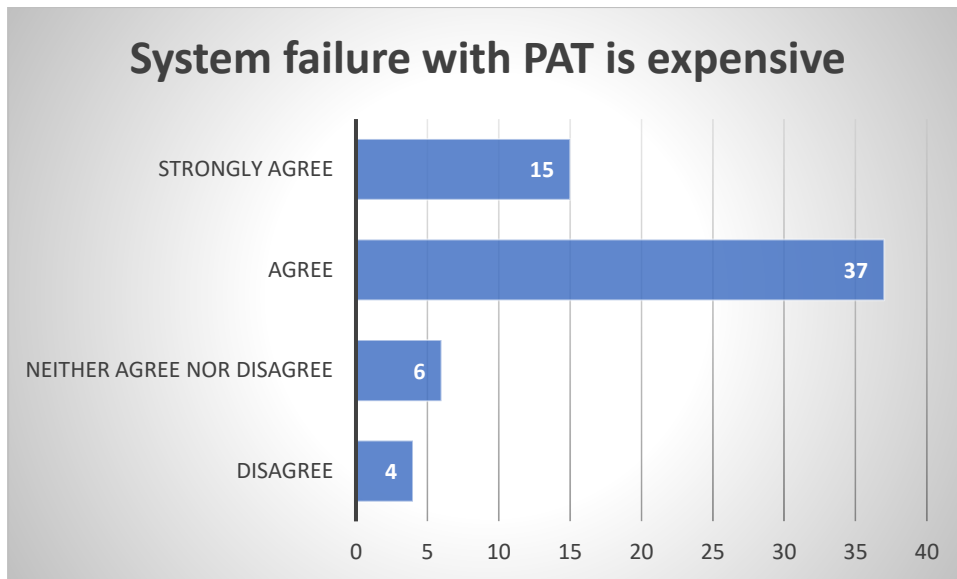
Figure 4.23: System failure with PAT is expensive

The Table 4.25 and Figure 4.24 below show that about 72% of the respondents agree that it is difficult to address system failure with PAT.

Table 4.25: It is difficult to address system failure with PAT.

	Frequency	Percent
Strongly Disagree	1	1.6
Disagree	8	12.9
Neither Agree nor Disagree	8	12.9
Agree	42	67.7
Strongly Agree	3	4.8
Total	62	100.0
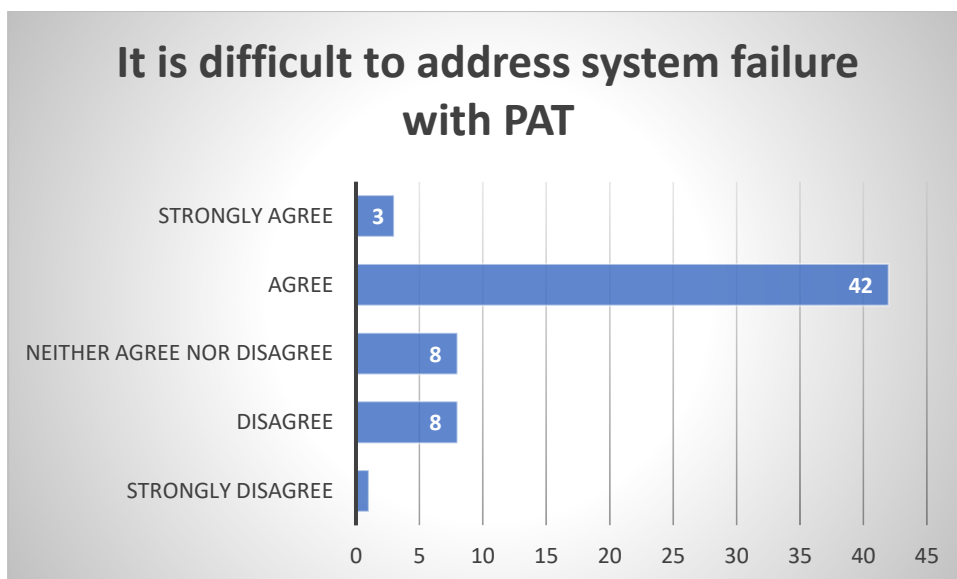
Figure 4.24: It is difficult to address system failure with PAT

4.2.2 Health Professionals Questionnaire

The second set of questionnaires was shared to health professionals to rate the quality, price and effectiveness of the drugs listed by the manufacturers. The Table 4.26 below shows that all the respondent-health professionals gave consent for their data to be used in this research. There were 107 participants in all that answered the questionnaire.

Table 4.26: Respondents consent

Consent	Participants	Percent
Yes	**107**	**100**
No	**0**	**0**
Total	**107**	**100**

The Table 4.27 below shows that the respondents include 32 pharmacists, 33 nurses and 42 medical doctors. The Figure 4.25 shows that the medical doctors were the largest group of respondents.

Table 4.27: What is the title of your health profession?

	Frequency	Percent
Pharmacist	32	29.9
Nurse	33	30.8
Medical Doctor	42	39.3
Total	107	100
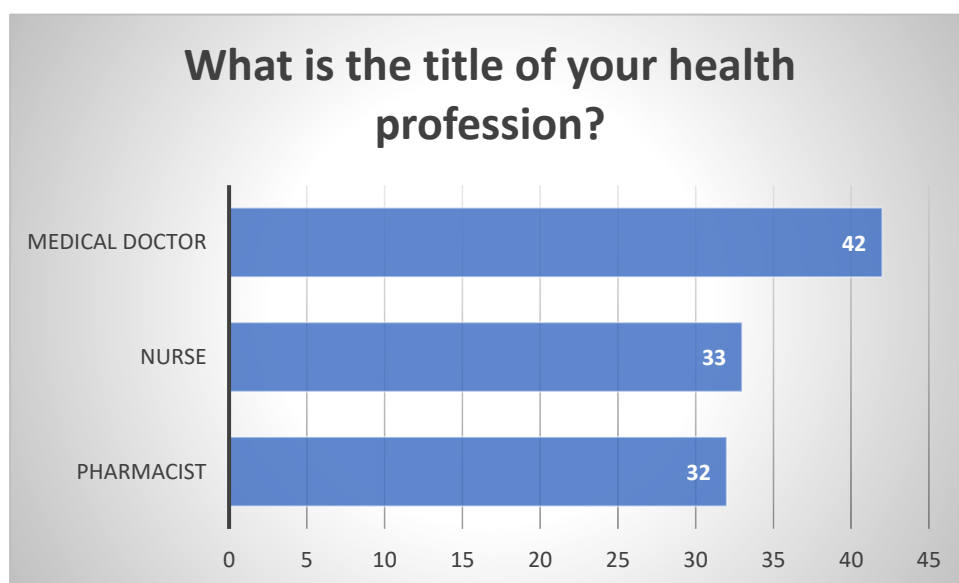
Figure 4.25: What is the title of your health profession?

The Table 4.28 and Figure 4.26 below shows the natural preference of the respondents when the various forms of solid dosages are concerned. There is a clear preference for capsules with 50 percent expressing preference. This is secondly followed by tablets and then powdery forms.

Table 4.28: What is your preferred form of solid dose medication?

	Frequency	Percent
Tablets	44	41.1
Capsules	53	49.5
Powder	8	7.5
Caplet	2	1.9
Total	107	100.0
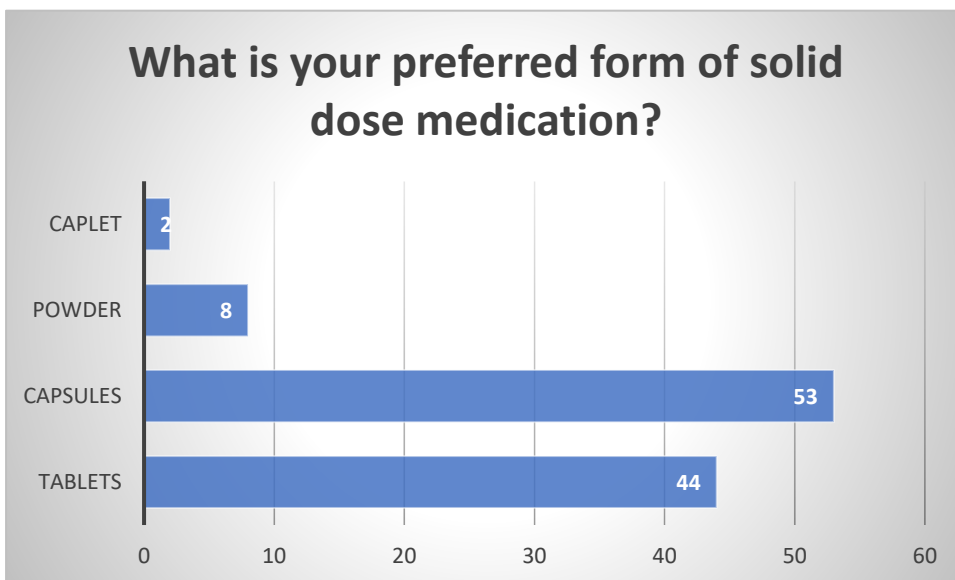
Figure 4.26: What is your preferred form of solid dose medication?

The Table 4.29 and Figure 4.27 show that an overwhelming majority of the health professionals surveyed feel that their experience with drugs in Nigeria has been good.

Table 4.29: What is your general experience with drugs in Nigeria as regards to doing what their manufacturers say?

	Frequency	Percent
Neither good nor bad	12	11.2
Good	95	88.8
Total	107	100.0
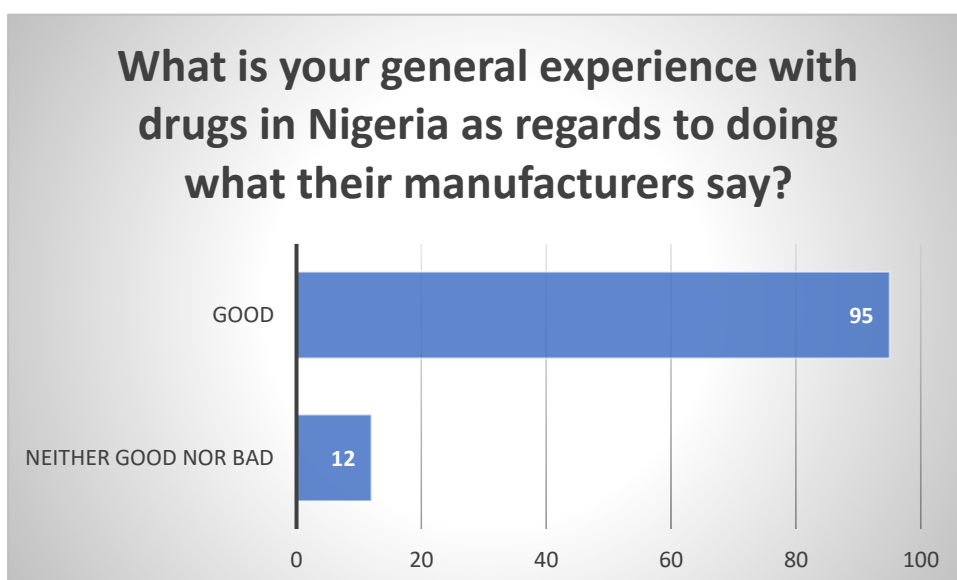
Figure 4.27: What is your general experience with drugs in Nigeria

In terms of the prices of drugs in Nigeria, the Table 4.30 and Figure 4.28 below show that the majority of health professionals surveyed, about 97%, believed that the prices of drugs are moderate.

Table 4.30: What is your general experience with the price of drugs in Nigeria?

	Frequency	Percent
Too Low	1	0.9
Moderate	104	97.2
Too High	2	1.9
Total	107	100.0
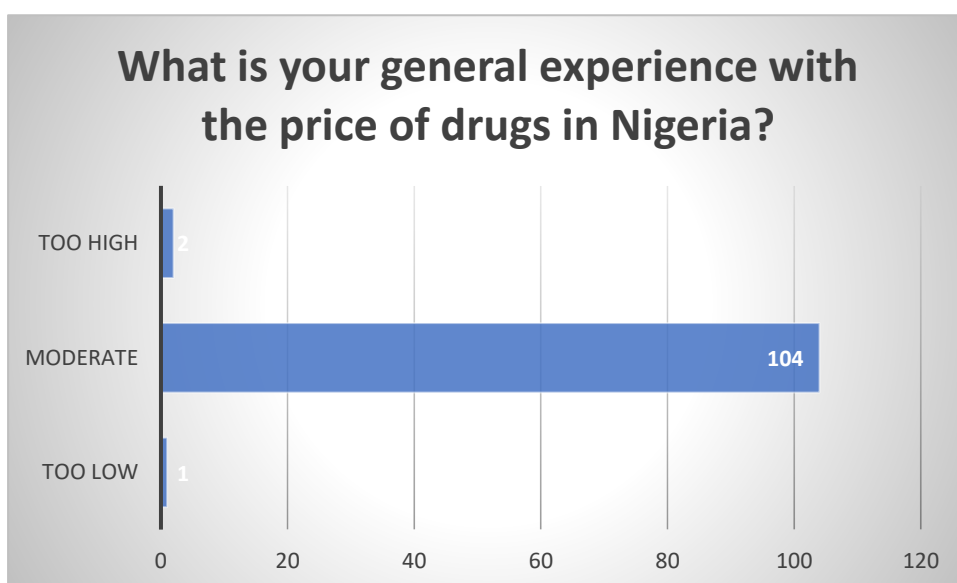
Figure 4.28: What is your general experience with the prices of drugs in Nigeria

In terms of the quality of drugs in Nigeria, the Table 4.31 and Figure 4.29 below show that the majority of health professionals surveyed, about 81%, believed that the quality of drugs is generally good.

Table 4.31: What is your general experience with the quality of drugs in Nigeria?

	Frequency	Percent
Neither good nor bad	20	18.7
Good	87	81.3
Total	107	100.0
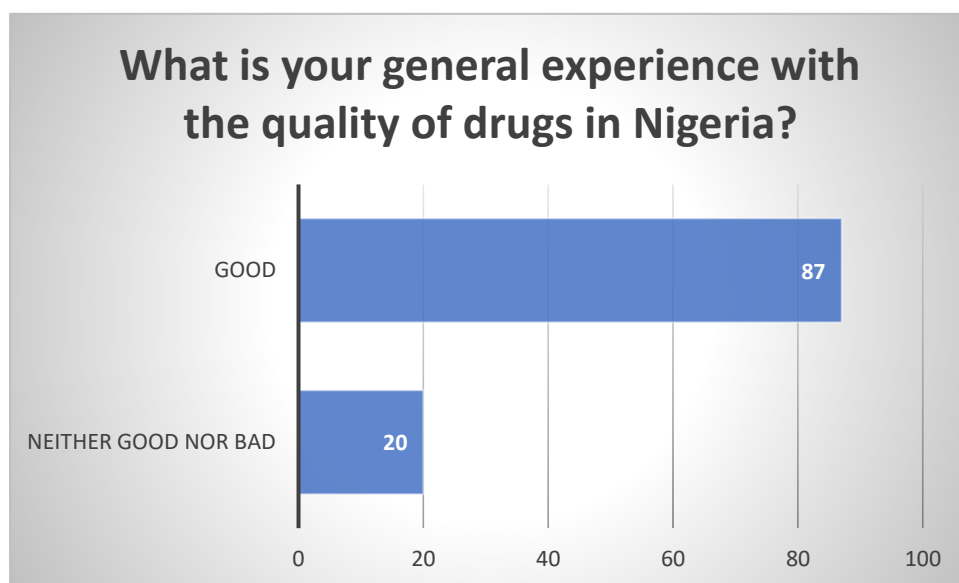
Figure 4.29: What is your general experience with the quality of drugs in Nigeria

4.3 Research Objectives

Objective 1:

What is the level of adoption of Process Analytical Technology (PAT) for solid dose manufacturing in the Nigerian pharmaceutical industry?

In order to achieve the above objective, the manufacturers were asked whether they do employ any form of PAT in their manufacturing process. The Table 4.32 and Figure 4.30 below show the summary of their responses to this question.

Table 4.32: Do you employ PAT in the manufacturing of any solid dose drug?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	51	82.3	82.3	82.3
	Yes	11	17.7	17.7	100.0
	Total	62	100.0	100.0	
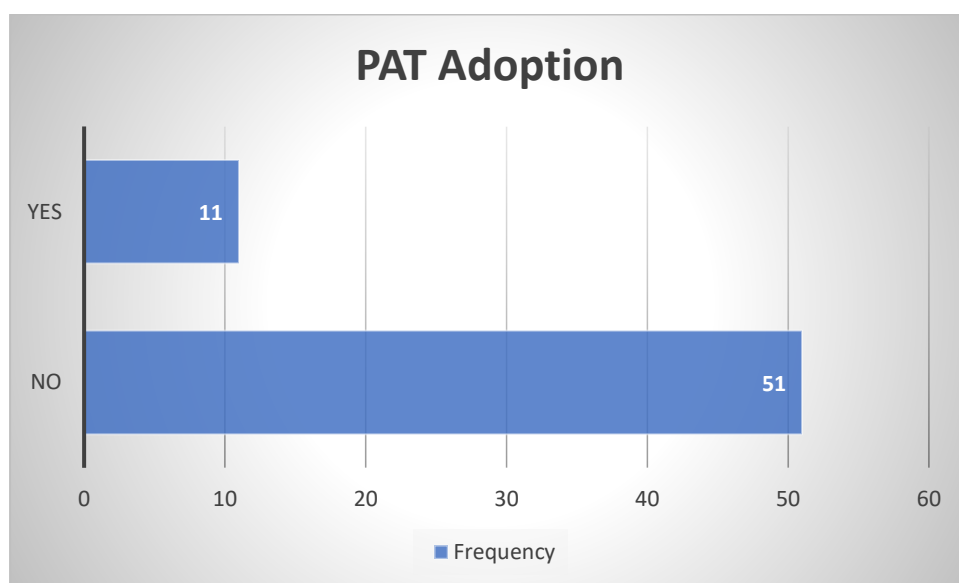
Figure 4.30: PAT adoption

From the above Table 4.32 and Figure 4.30, it was observed that PAT adoption is very low in the Nigerian Pharmaceutical Industry. 17.7% (11) of the manufacturers adopt (embrace) PAT, while 82.3% (51) do not adopt it.

Objective 2:

What are the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry?

To answer research question 2, a correlation analysis will be performed to present only the significant factors. The variable correlated against other variables is "Do you employ PAT in the manufacturing of any solid dose?".

The results are presented below in Table 4.33 – Table 4.43 based on hypotheses specifically postulated for addressing this objective:

Hypothesis:

H_0: There is no significant difference in the mean effect of the challenges on PAT adoption in the Nigerian pharmaceutical industry.

H_1: There is a significant difference in the mean effect of the challenges on PAT adoption in the Nigerian pharmaceutical industry.

Level of Significance: $\alpha = 0.05$

Decision Rule: Reject H_0 if P-Value (Asymptotic Significance) is greater than level of significance ($P > 0.05$), do not reject if otherwise (if $P < 0.05$).

Table 4.33: The technology level required to implement PAT is too advanced

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.509[a]	3	.023
Likelihood Ratio	9.371	3	.025
Linear-by-Linear Association	4.688	1	.030
N of Valid Cases	62		

a.

b. 4 cells (50.0%) have expected count less than 5. The minimum expected count is 1.06.

Table 4.34: PAT is overrated for the pharmaceutical industry

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	19.449[a]	4	.001
Likelihood Ratio	18.077	4	.001
Linear-by-Linear Association	12.201	1	.000
N of Valid Cases	62		

a. 8 cells (80.0%) have expected count less than 5. The minimum expected count is .18.

Table 4.35: Most Stakeholders are not knowledgeable in PAT

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.761[a]	4	.008
Likelihood Ratio	12.537	4	.014
Linear-by-Linear Association	9.516	1	.002
N of Valid Cases	62		

a. 7 cells (70.0%) have expected count less than 5. The minimum expected count is .18.

Table 4.36: PAT is not a necessity for pharmaceutical manufacturing

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	22.554[a]	4	.000
Likelihood Ratio	20.505	4	.000
Linear-by-Linear Association	16.731	1	.000
N of Valid Cases	62		

a. 6 cells (60.0%) have expected count less than 5. The minimum expected count is .35.

Table 4.37: My company is not given to PAT

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	24.999[a]	4	.000
Likelihood Ratio	26.510	4	.000
Linear-by-Linear Association	20.967	1	.000
N of Valid Cases	62		

a. 7 cells (70.0%) have expected count less than 5. The minimum expected count is .18.

Table 4.38: The pharmaceutical industry in Nigeria is not mature for PAT

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.465[a]	3	.004
Likelihood Ratio	12.498	3	.006
Linear-by-Linear Association	12.257	1	.000
N of Valid Cases	62		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is 1.06.

Table 4.39: There is no difference between PAT and conventional

pharmaceutical manufacturing

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15.333[a]	3	.002
Likelihood Ratio	16.911	3	.001
Linear-by-Linear Association	12.054	1	.001
N of Valid Cases	62		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .71.

Table 4.40: Process analyzers for PAT have no spare parts available

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	8.897[a]	3	.031
Likelihood Ratio	7.932	3	.047
Linear-by-Linear Association	7.549	1	.006
N of Valid Cases	62		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .71.

Table 4.41: Implementing process analyzers for PAT will increase the price of

drugs

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	8.897[a]	3	.031
Likelihood Ratio	7.932	3	.047
Linear-by-Linear Association	7.549	1	.006
N of Valid Cases	62		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .71.

Table 4.42: PAT is prone to system failures

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	12.534[a]	3	.006
Likelihood Ratio	11.615	3	.009
Linear-by-Linear Association	9.273	1	.002
N of Valid Cases	62		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is 1.06.

Table 4.43: It is difficult to address system failures with PAT

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	12.119[a]	4	.016
Likelihood Ratio	10.184	4	.037
Linear-by-Linear Association	9.461	1	.002
N of Valid Cases	62		

a. 6 cells (60.0%) have expected count less than 5. The minimum expected count is .18.

As seen from the previous results, each of the presented challenges had a P-Value less than the level of significance ($P < 0.05$). Hence, H_0 is rejected, and it is hereby concluded that there is a significant difference in the mean effect of the challenges on PAT adoption, with the significant ones presented above.

Conclusively, the most significant challenges of PAT adoption in the Nigerian pharmaceutical industry are:

1. The technology level required to implement PAT is too advanced.

2. PAT is overrated for the pharmaceutical industry.

3. Most Stakeholders are not knowledgeable in PAT.

4. PAT is not a necessity for pharmaceutical manufacturing.

5. My company is not given to PAT.

6. The pharmaceutical industry in Nigeria is not mature for PAT.

7. There is no difference between PAT and conventional pharmaceutical manufacturing.

8. Process analyzers for PAT have no spare parts available.

9. Implementing process analyzers for PAT will increase the price of drugs.

10. PAT is prone to system failures.

11. It is difficult to address system failures with PAT.

Objective 3:

To determine the impact of PAT adoption by pharmaceutical manufacturers on solid dose forms.

Here, a correlation analysis of PAT adoption will be performed against general experience with PAT adoption.

The result is presented below:

Hypothesis:

H_0: There is no significant impact of PAT adoption on solid dose forms.

H_1: There is a significant impact of PAT adoption on solid dose forms.

Level of Significance:

$\alpha = 0.05$

Decision Rule:

Reject H_0 if P-Value (Asymptotic Significance) is greater than level of significance (P > 0.05), do not reject if otherwise (if P < 0.05).

Table 4.44: Impact of PAT on solid dosage forms

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.005[a]	1	.942		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.005	1	.942		
Fisher's Exact Test				1.000	.713
Linear-by-Linear Association	.005	1	.943		
N of Valid Cases	62				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.06.
b. Computed only for a 2x2 table

As seen from the above results the P-Value is greater than the level of significance (P > 0.05). Hence, H_0 cannot be rejected, and it is therefore concluded that there is no significant impact of PAT adoption on solid dose forms, based on the general experiences of the manufacturers.

4.4 Hypothesis Testing

In this section, we shall be running a regression analysis (automatic linear model to be specific) Our choice is premised on its ability to optimize the result by discarding the variables with P > 0.05, while only retaining the influential variables with P < 0.05.

Level of Significance: $\alpha = 0.05$

Decision Rule:

Reject H_0 if P-Value (Asymptotic Significance) is greater than level of significance (P > 0.05), do not reject if otherwise (if P < 0.05).

Hypothesis 1

H_0: There is no significant difference in the mean effect of PAT adoption on price of solid drugs.

H_1: There is a significant difference in the mean effect of PAT adoption on price of solid drugs.

Model Summary

Target	Do you employ PAT in the manufacturing of any solid dose drug?
Automatic Data Preparation	On
Model Selection Method	Forward Stepwise
Information Criterion	-48.225

The information criterion is used to compare to models. Models with smaller information criterion values fit better.

Figure 4.31: Model summary for hypothesis 1

The predictor variables (price of the selected drugs) had 31.6% impact on the target variable (PAT adoption).

Effects

Target: Do you employ PAT in the manufacturing of any solid dose drug?

Source	Sum of Squares	df	Mean Square	F	Sig.
Corrected Model ▶	2.727	2	1.364	7.714	.002
Residual	4.773	27	0.177		
Corrected Total	7.500	29			

ThepriceofPiritonisexcellent   ThepriceofACAmoxicillinisexcellent_transformed

Least Important   Most Important

Display effects with sig. values less than...

.0001	.0005	.001	.005	.01	.05	.10	.20	1.00

Figure 4.32: Effects for hypothesis 1

As seen from the above results the P-Value is less than the level of significance ($P < 0.05$). Hence, H_0 is rejected, and there is a significant difference in the mean effect of PAT adoption on price of solid drugs.

Hypothesis 2:

H_0: There is no significant difference in the mean effect of PAT adoption on effectiveness of solid drugs.

H_1: There is no significant difference in the mean effect of PAT adoption on effectiveness of solid drugs.

Model Summary

Target	Do you employ PAT in the manufacturing of any solid dose drug?
Automatic Data Preparation	On
Model Selection Method	Forward Stepwise
Information Criterion	-48.777

The information criterion is used to compare to models. Models with smaller information criterion values fit better.

Worse   Better

36.3%

0%   25%   50%   75%   100%

Accuracy

Figure 4.33: Model Summary for hypothesis 2

The predictor variables (effectiveness of the selected drugs) had 36.6% impact on the target variable (PAT adoption) as seen in Figure 4.33 above.

Effects

Target: Do you employ PAT in the manufacturing of any solid dose drug?

Source	Sum of Squares	df	Mean Square	F	Sig.
Corrected Model ▶	3.214	3	1.071	6.500	.002
Residual	4.286	26	0.165		
Corrected Total	7.500	29			

TheeffectivenessofParacetamolisexcellent　　　　TheeffectivenessofEmtrimisexcellent

Least Important　　　　　　　　　　　　　　　　　　Most Important

Display effects with sig. values less than...

.0001　　.0005　　.001　　.005　　.01　　.05　　.10　　.20　　1.00

Figure 4.34: Effects for hypothesis 2

As seen from the Figure 4.34 above results the P-Value is less than the level of significance ($P < 0.05$). Hence, H_0 is rejected, and there is a significant difference in the mean effect of PAT adoption on effectiveness of solid drugs.

Hypothesis 3:

H_0: There is no significant difference in the mean effect of PAT adoption on quality of solid drugs.

H_1: There is a significant difference in the mean effect of PAT adoption on quality of solid drugs.

Model Summary

Target	Do you employ PAT in the manufacturing of any solid dose drug?
Automatic Data Preparation	On
Model Selection Method	Forward Stepwise
Information Criterion	-48.777

The information criterion is used to compare to models. Models with smaller information criterion values fit better.

Worse .... Better

36.3%

0%   25%   50%   75%   100%
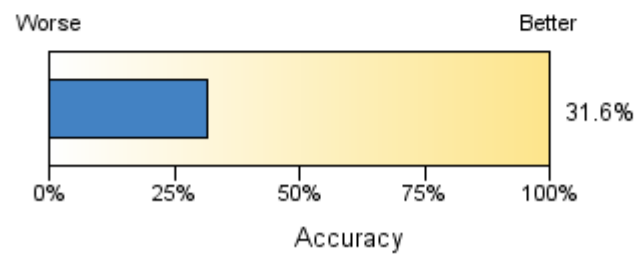
Accuracy

Figure 4.35: Model Summary for hypothesis 3

The predictor variables (quality of the selected drugs) had 36.6% impact on the target variable (PAT adoption) as shown in Figure 4.35 above.

Effects

Target: Do you employ PAT in the manufacturing of any solid dose drug?

Source	Sum of Squares	df	Mean Square	F	Sig.
Corrected Model ▶	3.214	3	1.071	6.500	.002
Residual	4.286	26	0.165		
Corrected Total	7.500	29			

ThequalityofArtelumisexcellent   ThequalityofVancloxisexcellent

Least Important   **Most Important**

Display effects with sig. values less than...

.0001	.0005	.001	.005	.01	.05	.10	.20	1.00

Figure 4.36: Effects for hypothesis 3

As seen from the Figure 4.36 above results, the P-Value is less than the level of significance ($P < 0.05$). Hence, H_0 is rejected, and there is a significant difference in the mean effect of PAT adoption on quality of solid drugs.

CHAPTER FIVE
DISCUSSION

5.1 Introduction

In the previous chapter, the findings from the analysis of data were presented. The purpose of this chapter is to discuss these findings in relation to the objectives, hypothesis and the wider literature. According to Leech, Barret and Morgan (2004), the discussion chapter is used for putting the findings in the context of the research literature, theory and the objectives of the research. It could also be a section which can include an explanation of why the results turned out in the direction they did. However, considering the scope of this research, the chapter format for discussion is adopted so that talking points can be comprehensive enough. The structure of this chapter will based on the research questions, objectives and hypotheses presented in the first chapter of this research. Based on the quantitative methodology adopted for this research, the findings can be taken to be the general state of affairs as regards the manufacturing of solid dosage forms in Nigeria.

5.2 Summary of Findings

The general aim of this research is to investigate the role and impact of Process Analytical Technology (PAT) on the Nigerian pharmaceutical industry, with specific regard to the manufacturing process of solid dosages. In order to achieve this, the first research question was designed to investigate the general level of PAT adoption in the industry. Based on the responses from the self-administered Google questionnaire, it can be conclusively stated that the level of PAT adoption in the Nigerian pharmaceutical industry is low. This is based on an adoption rate of 18 percent. The second research question was designed to investigate the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry. This is essentially a follow-up question designed to explain the result obtained in the first research question. If the level of adoption is significantly high, the challenges will be trivial or unimportant based on the manufacturers rating of Likert-type statements derived from identified challenges in literature. Out of twenty-one (21) identified challenges, the eleven (11) most significant challenges to PAT adoption in Nigeria are given below:

1. The technology level required to implement PAT is too advanced.

2. PAT is overrated for the pharmaceutical industry.

3. Most Stakeholders are not knowledgeable in PAT.

4. PAT is not a necessity for pharmaceutical manufacturing.

5. My company is not given to PAT.

6. The pharmaceutical industry in Nigeria is not mature for PAT.

7. There is no difference between PAT and conventional pharmaceutical manufacturing.

8. Process analyzers for PAT have no spare parts available.

9. Implementing process analyzers for PAT will increase the price of drugs.

10. PAT is prone to system failures.

11. It is difficult to address system failures with PAT.

The third objective of this research stems the research question designed to determine the impact of PAT adoption by pharmaceutical manufacturers on solid dosage forms. This research question was designed based on the general experience of the respondent health professionals. A lot of the respondents indicated that their experience with drugs in Nigeria had been good, whether or not the manufacturers of such drug employed PAT or not. Consequently, the result of the Chi-square correlation analysis led to the conclusion that there is no significant impact as regards PAT adoption for solid dose manufacturing, based on the general experience of health practitioners working with patients and drugs. Moreover, with regards to the hypotheses of this research, the three were design to test if PAT adoption had any significant effect on the price, effectiveness and quality of drugs based on Likert-type rating by health professionals. In all three cases, PAT had a significant impact. Therefore, this result, which is a more detailed investigation of the impact of PAT with a significant outcome, goes against the general experience of the health professionals, based on broad investigation.

5.3 Discussion with Respect to Research Questions

Perhaps, the research finding in regard to the first research objective was to be expected, given the wider context of Nigeria which seems to be besotted by a lot of challenges that would naturally make the implementation of PAT impracticable for pharmaceutical manufacturing. Some of these challenges identified by the World Health Organisation (WHO, 2014) include weak financial base, already high cost of production due to associated high cost of pharmaceutical machinery and ingredients imported from abroad, infrastructural problems such as lack of constant power supply, outdated technology, distribution systems that are weak and dearth of manufacturing expertise who are usually imported from Europe and Asia. More challenges exist in the form of incapacity of regulatory framework to align with international best practice such as the speed required for registration of drugs, lack of relevant training schools for pharmaceutical related courses, weak legal systems. According to Bolo and Vugigi (2016), the aforementioned challenges have made local pharmaceutical production uncompetitive in Nigeria and other developing countries. In addition, they will naturally discourage most manufacturers from considering PAT in their production process and thereby result in low level of adoption.

In relation to the second objective of this research which seeks the identification of the most significant challenges to PAT adoption in the Nigerian pharmaceutical industry, it is important to note that the challenges were constructed in a way that does not necessarily rest upon statements of facts. These challenges were identified based on perceivable constructs that may exists in the minds of decision makers as impediments to PAT adoption for pharmaceutical manufacturing in the Nigerian context. Essentially, the statements are constructed in the form of opinions that can fit the narratives of Nigerian manufacturers. Considering the eleven (11) significant challenges at a more detailed level, about 63% of the respondents felt that the technology to implement PAT is too advanced. PAT is indeed an advanced technology. The technology has been associated with many advanced pharmaceutical and biopharmaceutical processes and techniques such as metabolomics and near-infrared spectroscopy (Challa and Potumarthi, 2012).

In terms of PAT being overrated for the pharmaceutical industry, majority of respondents disagreed. This position agrees with what is dominantly asserted in literature. Although the implementation of PAT as a real-time control tool in commercial drug manufacturing continues to be very limited in practice, the value proposition of PAT in various phases of pharmaceutical manufacturing has been well-established in literature. Consider for instance the case of inline mid-IR probe technology where advances have eliminated the need for cumbersome probe alignment which was an integral requirement some few years back (Simon et al., 2015). Moreover, the integration of chemometric analysis techniques and spectral collection software now make it possible for scientists to gather quantitative information with ease. A slight majority of the respondents were of the opinion that PAT is not a necessity for pharmaceutical manufacturing. This may appear to be true given that conventional batch processes have been successful in delivering quality medications over the years. However, considering present and future challenges for the pharmaceutical industry, such as the risk of pandemics, PAT is now seen as a necessity, at least by regulators (Ombrosi, Casprini and Piccaluga, 2019) (Rodrigues et al., 2018) (Karmann et al., 2017) (Sayin et al., 2015).

Furthermore, a slight majority of the respondents were also of the opinion that most stakeholders in Nigeria are not knowledgeable in PAT with even more agreeing that the pharmaceutical industry in Nigeria is not mature for PAT and hence their companies are not given to it. As already established in this research, Nigeria is suffering from a dearth of pharmaceutical professionals. Ekeigwe (2019), discussed this under the heading of limited availability of human resources, noting that the situation is not that of paucity of schooled personnel but the lack of trained and competent personnel in both regulatory and manufacturing fields. Therefore, these issues could mean that the Nigerian pharmaceutical industry is living in the past or not yet mature for widespread PAT adoption. Other challenges that the respondents agreed to with significant majority bothers on their opinion that there are currently no spare parts in Nigeria for PAT implementation and implementing it will lead to an increase in the prices of drugs. Moreover, they also agree that PAT is prone to system failures which, in their opinion, is very difficult to address. The fact that the entire West African region imports most equipment and raw materials needed for pharmaceutical production (Ekeigwe, 2019), goes further to exacerbated these challenges.

With respect to the third objective of this research, the general experiences of the health professionals could not generate significant justification for PAT adoption by pharmaceutical manufacturers. These health professionals expressed positive remarks about drugs doing what their manufacturers say they do, whether those manufacturers employ PAT or not. Therefore, given that positive experiences of health practitioners with drugs could coexist with the low level of PAT adoption and in Nigeria, one could argue against the huge cost of implementing PAT based on the argument that it is not yet necessary until conventional batch processing starts failing to meet the requirements for medication. However, a better and counter argument would be that things must not be left out of hand before solutions are provided. In this way, problems can be anticipated and solutions provided beforehand. PAT itself has a learning curve for the industry. This learning curve cannot be allowed to start when new solutions are needed. Therefore, conventional batch processing must be eliminated before it becomes problematic.

The three hypotheses tested in this research led to the conclusion that PAT has a significant effect on the price, effectiveness and quality of drugs. This is in line with the prospects of PAT expressed in literature whereby it is adjudged to be beneficial to both manufacturers and consumers of pharmaceutical products. Generally, a well-understood manufacturing process is a necessity for consistently producing high quality products at the lowest price possible (Undey, 2012). Very vital to process understanding is the ability to measure process parameters in real time and is thus where PAT comes into play (Richard and Tweedie, 2015). Quite often than not, the expectation of manufacturers is that the high cost of PAT is justifiable by a number of results including high performance and high returns on investment (ROI). However, in practice, the result is too often the case of low performance and negative ROI (Richard and Tweedie, 2015). Therefore, even though PAT is established to be highly beneficial in theory, the practical reality of ROI makes it very hard for manufacturers to justify the huger initial investment.

CHAPTER SIX

CONCLUSION AND RECOMMENDATION

6.1 Synthesis of Research Findings

This research investigated the role and impact of PAT on solid dose manufacturing in the Nigerian pharmaceutical industry. The results show that indeed PAT plays a role in the Nigerian pharmaceutical industry even though the number of manufacturers that employ PAT is very low. Therefore, although PAT plays a role in the Nigerian pharmaceutical industry, the impact is not widespread. Based on inferential statistics, this impact is not significant. This satisfies the first objective of this research. The second objectives of this research investigated the challenges that impede manufacturers from implementing PAT in their manufacturing process for solid dosage forms. Out of about twenty-one (21) identified challenges, eleven (11) were statistically significant. Most of these challenges stem from the generally challenges besetting the pharmaceutical industry in Nigeria. The most significant challenges that the respondents agreed the strongest to relate to the cost of implementing PAT. Although the hypotheses tested revealed that PAT has a significant effect on the price, quality and effectiveness of solid dosage forms, the general experience of health practitioners could not justify PAT adoption. In other words, there was no statistical significant impact of PAT on the industry, based on the experiences of health practitioners who are the closest in contact with patients.

6.2 Conclusion

Pharmaceutical business is globally a tough business with very small profit margin, especially in developing countries like Nigeria. As a result, one problem that is very evident is the fact the manufacturers in the industry are risk averse and tend to not be driven by innovation. The profit margin available to these manufacturers has not had enough incentive to drive innovation. This problem was indeed identified by the FDA in their PAT white paper. Generally, the situation for the industry now is that regulators like the FDA are the ones driving innovation. In the Nigerian context, a lot of innovations related to drug quality, effectiveness and affordability is traceable to NAFDAC, the regulator of the pharmaceutical industry. Such innovation includes SMS original drug validation. In essence, regulators driving innovation for the

pharmaceutical industry may be a viable option because manufacturers will be sure that such innovations will not be hampered by future policies that could jeopardize their investments.

PAT is not a one-size-fits-all technology. It is a technology that leaves a lot of room for creativity on the part of manufacturers to exploit. It also has a learning curve and initial capital expense that may, at first, discourage its adoption. Currently, it seems that most manufacturers are not seeing past these initial hurdles, hence the low level of implementation across the globe. But when one considers the speed and scale with which the COVID-19 vaccine needed to be produced, all the initial investment in PAT will suddenly make more sense. The business model of the pharmaceutical industry also plays an important role. Given that the pharmaceutical industry is a heavily regulated industry, the onus is on the regulators to make the industry attractive for innovation. If this is not done, PAT will still continue to evolve albeit at a very slow pace; the pharmaceutical industry will continue to play catch-up to other industries in this area.

6.3 Recommendation

From the perspective of caregiving, where issues of health, life and death are concern, profit must not be the only underlying motivation. Manufacturers need to think long term in terms of associated cost with PAT implementation. They must also employ strategies for lowering the burden of the initial costs, such as by implementing vertical integration, reducing ownership share and increasing end customer value. Manufacturers who are able to bear the current pains of owning the process, stand the greatest chance of dominating affairs in the nearest future when more trying challenges begin to manifest. Moreover, as regards the issue of implementation, manufacturers first need to adopt PAT in their subconscious, especially those in more challenging environments such as that of developing countries. This is because, the barrier to fresh ideas first exist in the minds of decision makers. Human nature is generally known to be resistant to change, especially an uncomfortable one.

Furthermore, PAT is not just about sensors. There are other components such as inferential or predictive modelling that must be integrated to harness the full potentials therein. Therefore, the pharmaceutical industry must look into the training of its

professionals to reflect the dynamics of new challenges for the industry. Moreover, regulators too, have a very important role to play. The onus is on the regulators to drive innovation since the industry has no driving force for it. They should also rejig the business model of the industry to drive more profitability and encourage innovation. In the Nigerian context, the government has more work to do in addressing the wider challenges that are besetting the industry such as the lack of competent and trained professionals from various institutions.

6.4 Limitation/Future Research

The limitation of this research pertains to the fact that responses could not be gathered from all manufacturers in the Nigerian pharmaceutical industry. Given that the number of these manufacturers is not great, this research could have been better if all the manufacturers' responses were obtained. Although the questionnaires were sent to all of them on the registered list of manufacturers, only about half of them responded. Moreover, the identity of the particular persons that filled the questionnaire was not known. Therefore, it cannot be said, for sure, that the views of the respondent represented the view of the decision makers in the respective organisations. Future work could possibly employ a qualitative approach by interviewing key decision makers.

REFERENCES

Achouri, I.E., Rhoden, A., Hudon, S., Gosselin, R., Simard, J.-S. and Abatzoglou, N. (2021). Non-invasive detection technologies of solid foreign matter and their applications to lyophilized pharmaceutical products: A review. *Talanta*, 224, p.121885.

Baradez, M.-O., Biziato, D., Hassan, E. and Marshall, D. (2018). Application of Raman Spectroscopy and Univariate Modelling As a Process Analytical Technology for Cell Therapy Bioprocessing. *Frontiers in Medicine*, 5.

Berridge, J.C. (2009). PQLI ®: Current Status and Future Plans. *Journal of Pharmaceutical Innovation*, 4(1), pp.1–3.

Bolo, M. and Vugigi, S. (2016). Incentvising African Pharmaceutical Manufacturing: Policies for sustaining the take-of. The Scinnovent Centre Technical briefing note no. 1. Nairobi, Kenya: The Scinnovent Centre.

Brearley, A.M. and Foulk, S.J. (2010). Near-Infrared Spectroscopy (NIR) as a PAT Tool in the Chemical Industry: Added Value and Implementation Challenges. *Process Analytical Technology*, pp.493–520.

Bryman, A. & Bell, E. (2007). Business Research Methods. 2nd edition, New York. Oxford: University Press Inc.

Burgess, T.F. (2001). *Information System Services: Guide to the Design of Questionnaires*. University of Leeds.

Burggraeve, A., Van Den Kerkhof, T., Hellings, M., Remon, J.P., Vervaet, C. and De Beer, T. (2010). Evaluation of in-line spatial filter velocimetry as PAT monitoring tool for particle growth during fluid bed granulation. *European Journal of Pharmaceutics and Biopharmaceutics*, 76(1), pp.138–146.

Carifio J. and Perla R. J. (2007). Ten common misunderstandings, misconceptions, persistent myths and urban legends about Likert scales and Likert response formats and their antidotes. Journal of Social Sciences. 3(3):106-116.

Challa, S. and Potumarthi, R. (2012). Chemometrics-Based Process Analytical Technology (PAT) Tools: Applications and Adaptation in Pharmaceutical and

Biopharmaceutical Industries. *Applied Biochemistry and Biotechnology*, 169(1), pp.66–76.

Chiejina, A. (2014). *Nigeria's Pharma imports to hit $789m by 2018*. [online] Businessday NG. Available at: https://businessday.ng/science/article/nigerias-pharma-imports-to-hit-789m-by-2018/ [Accessed May 2021].

Cogdill, R.P., Anderson, C.A., Delgado-Lopez, M., Molseed, D., Chisholm, R., Bolton, R., Herkert, T., Afnán, A.M. and Drennen, J.K. (2005). Process analytical technology case study part I: Feasibility studies for quantitative near-infrared method development. *AAPS PharmSciTech*, 6(2), pp.E262–E272.

Cohen, L., Manion, L., & Morrison, K. (*2007*). Research Methods in Education (6th ed.). London and New York, NY: Routledge Falmer

Creswell, J. W. (2003). Research design: Qualitative, quantitative, and mixed method approaches (2nd ed.). London: Sage Publications.

Creswell, J. W. (2013). Research design: Qualitative, quantitative, and mixed method approaches.

Dave, R.H., Wu, S.H. and Contractor, L.D. (2011). To determine the end point of wet granulation by measuring powder energies and thermal properties. *Drug Development and Industrial Pharmacy*, 38(4), pp.439–446.

Doherty, S.J. and Kettler, C.N. (2005). On-Line Applications in the Pharmaceutical Industry. *Process Analytical Technology*, pp.329–361.

Ekeigwe, A.A. (2019). Drug manufacturing and access to medicines: the West African story. A literature review of challenges and proposed remediation. *AAPS Open*, 5(1).

FDA (2004). *Guidance for Industry PAT — a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. Silver Spring: Food and Drug Administration.

FDA (2009). *FDA Guidance for Industry: Q8(R2) Pharmaceutical Development Revision 2*. Silver Spring: Food and Drug Administration.

Federal Ministry of Health (2003). *National Drug Policy*. [online] . Available at: https://www.health.gov.ng/doc/DrugPolicy.pdf [Accessed Apr. 2021].

Fisher, A.C., Kamga, M.-H., Agarabi, C., Brorson, K., Lee, S.L. and Yoon, S. (2019). The Current Scientific and Regulatory Landscape in Advancing Integrated Continuous Biopharmaceutical Manufacturing. *Trends in Biotechnology*, [online] 37(3), pp.253–267. Available at: https://www.sciencedirect.com/science/article/pii/S0167779918302488.

Garson, G.D. (2012). *Structural equation modelling*. Raleigh, NC: statistical associates publishers.

Gibbs, G. (2007) Analysing Qualitative Data. SAGE Publications Ltd., New York, USA

Gupta, Y., O'Brien, T. and Ruiyao Gao (2013). Detection and Characterization of Acoustic Signals from a Granulation Process. *24th IET Irish Signals and Systems Conference (ISSC 2013)*.

Hickey, A.J. and Smyth, H.D.C. (2020). *Pharmaco-complexity. AAPS Introductions in the Pharmaceutical Sciences*. Cham: Springer International Publishing.

Ikoni Ogaji, J. and Alawode, A.O. (2014). Capacity Utilization in Pharmaceutical Industry in Nigeria. *Pharmaceutical Regulatory Affairs: Open Access*, 3(2).

Joshi A., Kale S., Chandel S. & Pal, D. (2015). Likert Scale: Explored and Explained. British Journal of Applied Science & Technology. 7. 396-403. 10.9734/BJAST/2015/14975.

Karmann, S., Follonier, S., Egger, D., Hebel, D., Panke, S. and Zinn, M. (2017). Tailor-madePATplatform for safe syngas fermentations in batch, fed-batch and chemostat mode withRhodospirillum rubrum. *Microbial Biotechnology*, 10(6), pp.1365–1375.

Kaynak, H. (2003). The relationship between total quality management practices and their effects on firm performance. *Journal of Operations Management*, [online] 21(4), pp.405–435. Available at: https://www.sciencedirect.com/science/article/pii/S0272696303000044.

Kessler, R.W. and Kessler, W. (2020). Best Practice and Performance of Hardware in Process Analytical Technology (PAT). *Comprehensive Chemometrics*, pp.237–274.

Lawal, I.O. (2009). *Library and Information Science Research in the 21st Century : a Guide for Practicing Librarians and Students*. Oxford: Chandos.

Leech, N., Barret, K. and Morgan, G.A. (2004). *SPSS for Intermediate Statistics Use and Interpretation, Second Edition*. Routledge Academic.

Lobsy J. and Wetmore A. (2014). CDC Coffee Break: Using Likert Scales in Evaluation Survey Work [Internet]; Cdc.gov. Retrieved:www.cdc.gov/dhdsp/pubs/docs/CB_February_14_2021.pdf

Low, D. and Chrisman, R. (2012). conclusions, Current status, and Future Vision of Process Analytical Technology in Biologics. In: C. Undey, D. Low, J.C. Menezes and M. Koch, eds., *PAT Applied in Biopharmaceutical Process Development and Manufacturing : an Enabling Tool for quality-by-design*. Boca Raton, Fl: Crc Press.

Lundsberg-Nielsen, L., Schlindwein, W.S. and Berghaus, A. (2018). Process Analytical Technology (PAT). *Pharmaceutical Quality by Design*, pp.227–255.

Magnello, M.E. (2006) Karl Pearson and the origin of modern statistics: An elastician becomes a statistician, Rutherford J, Vol. 1. Available online at: http://rutherfordjournal.org

Malhotra N. K. (2006). Questionnaire Design and Scale Development. In: Grover R, Vriens M, editors. The Handbook of Marketing Research. California: Sage Publications, Inc.

Mante, J., Gangadharan, N., Sewell, D.J., Turner, R., Field, R., Oliver, S.G., Slater, N. and Dikicioglu, D. (2019). A heuristic approach to handling missing data in biologics manufacturing databases. *Bioprocess and Biosystems Engineering*, 42(4), pp.657–663.

Marshall, C., & Rossman, G. B. (1999). *Designing qualitative research* (3rd ed.). Sage Publications, Inc.

Mgbakor M. N., Uzendu P. O. and Onicha A. P. (2014). Economic Analysis of Bread Production with High Quality Cassava Flour in Ndokwa West Local Government Area of Delta State, Nigeria. Journal of Agriculture and Veterinary Science. Volume 7, Issue 8 Ver. I.

Mittal, P., Vardhan, H., Ajmal, G., Bonde, G.V., Kapoor, R., Mittal, A. and Mishra, B. (2019). Genistein-Loaded Nanostructured Lipid Carriers for Intravenous Administration: A Quality by Design Based Approach. *International Research Journal Of Pharmacy*, 10(1), pp.119–134.

Momeni, A., Pincus, M. and Libien, J. (2018). *Introduction to Statistical Methods in Pathology*. Cham: Springer International Publishing.

Mugenda, A. and Mugenda, O. (2013). Research methods: Quantitative and qualitative approaches. Nairobi: ACTS Press

NAFDAC (2017). *NAFDAC Mandate – NAFDAC*. [online] Nafdac.gov.ng. Available at: https://www.nafdac.gov.ng/about-nafdac/nafdac-organisation/nafdac-functions/#:~:text=The%20act%20mandates%20the%20Agency,officially%20established%20in%20October%201992. [Accessed Apr. 2021].

Nagy, Z.K., Fujiwara, M. and Braatz, R.D. (2019). Monitoring and Advanced Control of Crystallization Processes. *Handbook of Industrial Crystallization*, pp.313–345.

Newing, H. (2011). *Conducting research in conservation: Social science methods and practice.* New York: Routledge

Ogada, T. (2019). *Building a Competitive and Socially Inclusive Local Pharmaceutical Manufacturing in West Africa through Enhancing Research, Innovation and Intellectual Property*. African Center for Technology Studies.

Okafor, U.G., Ibrahim Jatau Abubakar, Olukemi Alabi and Elijah Na Mohammed (2021). *Assessment of awareness and satisfaction of online renewal of practising license among pharmacists in Nigeria*. [online] ResearchGate. Available at: https://www.researchgate.net/publication/348949784_Assessment_of_awarenes

s_and_satisfaction_of_online_renewal_of_practising_license_among_pharmacis ts_in_Nigeria [Accessed 17 Apr. 2021].

Ombrosi, N., Casprini, E. and Piccaluga, A. (2019). Designing and managing co-innovation: the case of Loccioni and Pfizer. *European Journal of Innovation Management*, 22(4), pp.600–616.

Ostergaard, I., de Diego, H.L., Qu, H. and Nagy, Z.K. (2020). Risk-Based Operation of a Continuous Mixed-Suspension-Mixed-Product-Removal Antisolvent Crystallization Process for Polymorphic Control. *Organic Process Research & Development*, 24(12), pp.2840–2852.

Pazhayattil, A.B., Sayeed-Desta, N., Fredro-Kumbaradzi, E. and Collins, J. (2018). *Solid Oral Dose Process Validation the Basics, Volume 1*. Cham Springer International Publishing.

Peterson, K. (2014). On the monopoly: Speculation, pharmaceutical markets, and intellectual property law in Nigeria. *American Ethnologist*, 41(1), pp.128–142.

Rathbone, M.J., Hadgraft, J. and Roberts, M.S. (2003). *Modified-release drug delivery technology*. New York: Marcel Dekker.

Rathore, A.S. (2011). Follow-On Protein Products. *Comprehensive Biotechnology*, pp.521–529.

Richard, J. and Tweedie (2015). Process Analytical Instrumentation, the Challenges for In-situ Characterization of Complex Particulate Materials. *Procedia Engineering*, 102, pp.1714–1725.

Rodrigues, M., Baptista, B., Lopes, J.A. and Sarraguça, M.C. (2018). Pharmaceutical cocrystallization techniques. Advances and challenges. *International Journal of Pharmaceutics*, [online] 547(1), pp.404–420. Available at: https://www.sciencedirect.com/science/article/pii/S0378517318304216?casa_to ken=8I4eCcJ49pQAAAAA:bkuI1hELYoZ5Fh38roSjuvwC046KGDky6rYso0f QsUF9rZo36qzsOTyDNun7Tcman8xBRJNeQg [Accessed 30 Nov. 2020].

Salako, L.A. (1991). Drug supply in Nigeria. *Journal of Clinical Epidemiology*, 45, pp.15–19.

Salman Ben Zayed, Abdullah Bin Gani, Hesham Fathy Gadelrab and Mohd Khalit Bin Othman (2021). *Operational management in emergency healthcare*. Cham, Switzerland: Springer.

Sayin, R., Martinez-Marcos, L., Osorio, J.G., Cruise, P., Jones, I., Halbert, G.W., Lamprou, D.A. and Litster, J.D. (2015). Investigation of an 11 mm diameter twin screw granulator: Screw element performance and in-line monitoring via image analysis. *International Journal of Pharmaceutics*, 496(1), pp.24–32.

Simon, L.L., Pataki, H., Marosi, G., Meemken, F., Hungerbühler, K., Baiker, A., Tummala, S., Glennon, B., Kuentz, M., Steele, G., Kramer, H.J.M., Rydzak, J.W., Chen, Z., Morris, J., Kjell, F., Singh, R., Gani, R., Gernaey, K.V., Louhi-Kultanen, M. and O'Reilly, J. (2015). Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review. *Organic Process Research & Development*, 19(1), pp.3–62.

Siyanbola, W.O., Oladipo, O.G., Oyewale, A.A., Famurewa, A.J. and Ogundari, I.O. (2012). Academia-Industry Interactions in Nigeria Pharmaceutical Innovation System. *Procedia - Social and Behavioral Sciences*, [online] 52, pp.279–289. Available at: https://www.sciencedirect.com/science/article/pii/S1877042812039201.

Snee, R.D. (2016). Quality by Design: Building Quality into Products and Processes. *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries*, pp.461–499.

Streefland, M., Martens, D.E., Beuvery, E.C. and Wijffels, R.H. (2013). Process analytical technology (PAT) tools for the cultivation step in biopharmaceutical production. *Engineering in Life Sciences*, 13(3), pp.212–223.

Szilagyi, B., Eren, A., Quon, J.L., Papageorgiou, C.D. and Nagy, Z.K. (2020). Application of Model-Free and Model-Based Quality-by-Control (QbC) for the Efficient Design of Pharmaceutical Crystallization Processes. *Crystal Growth & Design*, 20(6), pp.3979–3996.

Tripathi, N.K. and Shrivastava, A. (2018). Scale up of biopharmaceuticals production. *Nanoscale Fabrication, Optimization, Scale-Up and Biological Aspects of Pharmaceutical Nanotechnology*, pp.133–172.

Tsang K. K. (2012). The use of midpoint on Likert scale: The implications for educational research. Hong Kong Teachers Centre Journal.

Ugbam, O.C. and Okoro, E.A. (2017). A Strategic Study of the Nigerian Pharmaceutical Sector: Organizational Leadership, Market-share, and Competitive Performance. *International Journal of Business, Humanities and Technology*, 7(1).

Undey, C. (2012). *PAT applied in biopharmaceutical process development and manufacturing : an enabling tool for quality-by-design*. Boca Raton, Fl: Crc Press.

Vanhoorne, V. and Vervaet, C. (2020). Recent Progress in Continuous Manufacturing of Oral Solid Dosage Forms. *International Journal of Pharmaceutics*, 579, p.119194.

WHO (2014). WHO prequalification: Building quality-assured Manufacturing Capacity in Nigeria. *WHO Drug Information*, [online] 28(4), pp.425–430. Available at: https://apps.who.int/iris/handle/10665/331090 [Accessed 17 Apr. 2021].

Wood, N. (2001). *The Health Project Book : a Handbook for New Researchers in the Field of Health*. London: Routledge.

World Bank (2017). *Nigeria | Data*. [online] Worldbank.org. Available at: https://data.worldbank.org/country/nigeria [Accessed 8 Apr. 2021].

Yamane, T., (1967). Statistics: An Introductory Analysis, 2nd edition, New York: Harper and Row.

Yu, L.X. (2008). Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. *Pharmaceutical Research*, 25(4), pp.781–791.

Yu, X., Yu, L.X., Teng, Y., Gaglani, D.K., Rege, B.D. and Rosencrance, S. (2019). Implementation of Pharmaceutical Quality by Design in Wet Granulation. *Handbook of Pharmaceutical Wet Granulation*, pp.703–733.

Zikmund, W. G. (2013). Business research methods. Mason, OH: South-Western.

Zomer, S., Zhang, J., Talwar, S., Chattoraj, S. and Hewitt, C. (2018). Multivariate monitoring for the industrialisation of a continuous wet granulation tableting process. *International Journal of Pharmaceutics*, 547(1-2), pp.506–519.

APPENDIX A

Manufacturers Questionnaire

GRIFFITH COLLEGE

THE ROLE AND IMPACT OF PROCESS ANALYTICAL TECHNOLOGY (PAT) IN SOLID DOSE MANUFACTURING IN NIGERIA

Dear Participant,

I am a master's student at Griffith College studying MSc Pharmaceutical Business and Technology.

This questionnaire, as part of my dissertation, is designed to measure the role and impact of process analytical technology (PAT) in solid dose manufacturing in Nigeria.

All information provided will be treated with confidentiality and used only for the purpose of this dissertation. Thanks for your precious time.

Yours faithfully,

Chinedu Nnadozie Chukwu

Chinedunnadozie.chukwu@student.griffith.ie

CONSENT *

By checking the agree box below, you agree to participate in this research voluntarily, having understood the nature of this project. The responses you supply will be anonymized, and it will not be possible to subsequently withdraw your response thereafter because there will be no personal identifying information attached to answers. By consenting to participate in this research, you are not waiving any of my legal rights.

[   ] Agree   [   ] Disagree

Please enter your email*:

………………………………………………………………….

RESEARCH QUESTIONNAIRE
SECTION A: DEMOGRAPHICS

Please fill in or tick (✓) where appropriate

1. **How would you describe your organizational rank?** Junior Level ( )   Mid-Level ( )   Senior Level ( )

2. **How old is your company?** 1-5 years ( )   6-30 years ( )   31+ years ( )

3. **How many employees does your company have?** 1-10 ( )   11- 50 ( )   51+ ( )

4. **Do you employ PAT in the manufacturing of any solid dose drug?** Yes ( )   No ( )

5. **What is the name of your prominent solid dose drug offering?**

   ………………………………………………………………………………………………
   …………………………………………

6. **What is the most used indication for the drug in 5 above?**

   ………………………………………………………………………………………………
   …………………………………………

7. **What is the form of the drug in 5 above?**
   Powder ( )   Tablets ( )   Capsules ( )

8. **What is your general view about employing PAT to manufacture drugs in Nigeria?**
   Good ( )   Neither good nor bad ( )   Bad ( )

SECTION B: CHALLENGES TO PROCESS ANALYTICAL TECHNOLOGY (PAT) ADOPTION IN NIGERIA

Please rate how you agree or disagree with the following statements based on your experience in the Nigerian pharmaceutical industry.

Tick (✓) the appropriate answer based on how closely each of the following statements represents your view: (1) Strongly disagree; (2) Disagree; (3) Neither agree nor disagree; (4) Agree; (5) Strongly agree

STATEMENTS	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Producing varieties of drugs is an impediment to Process Analytical Technology (PAT) Implementation					
The technology level required to implement PAT is too advanced					
The number of equipment required to implement PAT are numerous					
PAT requires frequent maintenance					
The maintenance cost for PAT implementation is very high					
There are no maintenance experts for PAT in Nigeria					
It is difficult to find local experts skilled in implementing PAT					
PAT is overrated for the pharmaceutical Industry					
Most stakeholders are not knowledgeable in PAT					
PAT is not a necessity for pharmaceutical manufacturing					
My company is not given to PAT					
The pharmaceutical industry in Nigeria is not mature for PAT					
There is no difference between PAT and conventional pharmaceutical manufacturing					
Some drugs are better manufactured using conventional batch processing					
Conventional manufacturing will produce the same results as PAT					

STATEMENTS	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Process analyzers for PAT are very expensive					
Process analyzers for PAT have no spare parts available					
Implementing process analyzers for PAT will increase the price of drugs					
PAT is prone to system failures					
System failure with PAT is expensive					
It is difficult to address system failure with PAT					

APPENDIX B

Health Professionals Questionnaire

GRIFFITH COLLEGE

THE ROLE AND IMPACT OF PROCESS ANALYTICAL TECHNOLOGY (PAT) IN SOLID DOSE MANUFACTURING IN NIGERIA

Dear Participant,

I am a master's student at Griffith College studying MSc Pharmaceutical Business and Technology.

This questionnaire, as part of my dissertation, is designed to measure the role and impact of process analytical technology (PAT) in solid dose manufacturing in Nigeria.

All information provided will be treated with confidentiality and used only for the purpose of this dissertation. Thanks for your precious time.

Yours faithfully,

Chinedu Nnadozie Chukwu
chinedunnadozie.chukwu@student.griffith.ie

CONSENT *

By checking the agree box below, you agree to participate in this research voluntarily, having understood the nature of this project. The responses you supply will be anonymized, and it will not be possible to subsequently withdraw your response thereafter because there will be no personal identifying information attached to answers. By consenting to participate in this research, you are not waiving any of my legal rights.

[   ] Agree   [   ] Disagree

Please enter your email*:
………………………………………………………………………….

RESEARCH QUESTIONNAIRE

SECTION A: DEMOGRAPHICS

Please fill in or tick (✓) where appropriate

9. **What is the title of your health profession?**

   ………………………………………………………………………………

10. **How many years of professional experience do you have?**

    Less than 1 year (   )   1 – 5 years (   )   6 – 10 years (   )   Over 10 (   )

11. **What is your preferred form of solid dose medication?**

    Powder (   )   Tablets (   )   Capsules (   )   Others (   )

12. **What is your general experience with drugs in Nigeria as regards to doing what their manufacturers say?**

    Good (   )   Neither good nor bad (   )   Bad (   )

13. **What is your general experience with the price of drugs in Nigeria?**

    Too high (   )   Moderate (   )   Too low (   )

14. **What is your general experience with the quality of drugs in Nigeria?**

    Good (   )   Neither good nor bad (   )   Bad (   )

SECTION B: SATISFACTION WITH VARIOUS MEDICATION

Please rate how you agree or disagree with the following statements based on your experience with the following drugs.

Tick (✓) the appropriate answer based on how closely each of the following statements represents your view: (1) Strongly disagree; (2) Disagree; (3) Neither agree nor disagree; (4) Agree; (5) Strongly agree

STATEMENTS	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
[The price of Paracetamol is excellent]					
[The effectiveness of Paracetamol is excellent]					

STATEMENTS	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
[The quality of Paracetamol is excellent]					
[The price of Ciprotab is excellent]					
[The effectiveness of Ciprotab is excellent]					
[The quality of Ciprotab is excellent]					
[The price of Emtrim is excellent]					
[The effectiveness of Emtrim is excellent]					
[The quality of Emtrim is excellent]					
[The price of Artelum is excellent]					
[The effectiveness of Artelum is excellent]					
[The quality of Artelum is excellent]					
[The price of Vanclox is excellent]					
[The effectiveness of Vanclox is excellent]					
[The quality of Vanclox is excellent]					
[The price of Piriton is excellent]					
[The effectiveness of Piriton is excellent]					
[The quality of Piriton is excellent]					
[The price of Evans Vit B Complex is excellent]					
[The effectiveness of Evans Vit B Complex is excellent]					
[The quality of Evans Vit B Complex is excellent]					
[The price of Beflam is excellent]					
[The effectiveness of Beflam is excellent]					
[The quality of Beflam is excellent]					

STATEMENTS	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
[The price of Glucobay is excellent]					
[The effectiveness of Glucobay is excellent]					
[The quality of Glucobay is excellent]					
[The price of AC Amoxicillin is excellent]					
[The effectiveness of AC Amoxicillin is excellent]					
[The quality of AC Amoxicillin is excellent]					