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Assessment of the Awareness, Implementation, and Barriers to Continuous Manufacturing Processes (CMP) in Palestine. A Cross-sectional Study (2024)

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M.Sc. Thesis

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Assessment of the Awareness, Implementation, and Barriers to Continuous Manufacturing Processes (CMP) in Palestine. A Cross-sectional Study (2024).

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Dedication.

To my dear family,

To my mother, whose prayers and supportive guidance have guided me throughout my life.

To my husband Salah and my children, thank you for your endless patience, support, and belief in me, especially during the most challenging times.

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This achievement reflects your support, and I share it with all of you.

Abeer.

Declaration.

I confirm that this thesis, submitted for the Master's degree in Applied Industrial Technology, is my original work, except where specific references are made. I also declare that it has not been submitted, in whole or in part, for any academic degree at any other university or institution.

Name: Abeer Mohammad Hussin Imar

Signed: 

Date: 20/5/2025

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Abstract:

This study examines the awareness, implementation, and perceived barriers to adopting continuous manufacturing processes (CMP) in the Palestinian pharmaceutical industry. Despite the sector's growing significance for public health and economic development, most factories continue to use traditional batch manufacturing methods, resulting in inefficiencies, quality inconsistencies, and slow responsiveness. CMP has emerged as a promising alternative worldwide, providing benefits such as cost reduction, improved product quality, and increased production flexibility.

We conducted a cross-sectional survey involving six pharmaceutical companies, gathering data through questionnaires and interviews. The questionnaire, developed by Dr. Mohammad Abu Assab, served as our primary research tool. A total of 80 participants from these companies responded. The results indicated a high level of awareness with overall mean score of (3.68), equivalent to (73.6%), a moderate of implementation, with overall mean score (3.46), equivalent to (69.3%) and moderate perceived barriers with overall mean score (3.33) equivalent to (66.7%). The main challenges identified included limited financial resources, lack of regulatory understanding, and insufficient workforce training. Additionally, statistical analysis showed that certain demographic influenced awareness and implementation levels factors (such as company category, educational qualifications, specialization, job title, total work experience, and type of production line).

We recommend enhancing infrastructure, improving the regulatory framework, and providing specialized training programs to support the transition to continuous manufacturing. These steps will strengthen the competitiveness and sustainability of the pharmaceutical sector in Palestine.

Keywords: Continuous Manufacturing Processes (CMP), Pharmaceutical Industry, Palestine, Awareness, Implementation, Barriers, Process Optimization.

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List of Abbreviations.

Abbreviation	Meaning
CMP:	**Continuous Manufacturing Processes.**
FDA:	**Food and Drug Administration.**
QbD:	**Quality by Design.**
QbT:	**Quality by Testing.**
PAT:	**Process Analytical Technology.**
CM:	**Continuous Manufacturing.**
GMP:	**Good Manufacturing Practices.**
SPSS:	**Statistical Package for the Social Sciences.**
R&D:	**Research and Development.**
QC:	**Quality Control.**
QA:	**Quality Assurance.**
EMA:	**European Medicines Agency.**
ICH:	**International Council for Harmonization.**
APIs:	**Active pharmaceutical ingredients**
CQAs:	**Critical quality attributes**
CMAs:	**Critical material attributes.**
CPPs:	**Critical process parameters**
ACS:	**American Chemical Society**
GCI:	**Green Chemistry Institute**
AAPS:	**American Association of Pharmaceutical Scientists**
NDAs:	**New drug applications**
NPV:	**Net present value**
CPV:	**Continued Process Verification**

Chapter One:

Introduction.

1.1 Background.

1.1.1 Global Pharmaceutical Industry:

The pharmaceutical industry, one of the largest global business sectors, aims to create high-performance dosage forms that enhance physical and mental well-being or assist in treating, curing, preventing, or diagnosing diseases (Select USA, 2014). A dosage form is a pharmaceutical product composed of active and inactive chemical components, prepared in a specific shape and concentration to deliver the prescribed medical dose to the user (Allen et al., 2014; Kanetkar, 2020; Shah, 2011; Tovey, 2018). Among the various dosage forms, solid dosage forms, particularly pharmaceutical tablets are the most widely used and in high demand globally (Allen et al., 2014). Despite the high demand for such dosage forms, the manufacturing process within the pharmaceutical industry has several shortcomings (Ahmad,2020; Kanetkar, 2020; Phys.org, 2019).

1.1.2 The Pharmaceutical Industry in Palestine:

At the national level, the situation is equally significant. In Palestine, the pharmaceutical sector is one of the most vital industries, playing a crucial role in supplying essential medications to local markets. This sector enhances national health security by decreasing reliance on imported pharmaceutical products and contributes to the Palestinian economy through job creation, local investment, and support for export activities. Local industry reports indicate that the sector meets approximately 55% of the local market pharmaceutical needs and employs a highly skilled and educated workforce, achieving an estimated efficiency rate of around 50% (Abu Rjeila, 2019).

The pharmaceutical industry in Palestine encounters numerous challenges, such as distribution difficulties, restrictions on importing raw materials and production equipment, and obstacles in meeting international standards and ensuring product quality. According to the report (The Pharmaceutical Landscape in Occupied Palestine) by Candice Choo-Kang (2023), these issues

hinder the sector competitiveness on a global scale, especially amid fluctuating economic conditions (People's Dispatch, 2023).

1.1.3 Challenges in Manufacturing Due to COVID-19:

The pharmaceutical sector has faced ongoing structural challenges and has been tested by unexpected global crises. While the COVID-19 pandemic accelerated advancements in vaccine development and medical innovation, it also severely negatively impacted the pharmaceutical industry. It disrupted global supply chains, clinical trials, and manufacturing processes, exposing critical weaknesses in traditional batch manufacturing systems. These challenges underscored the pressing need for more agile, efficient, and reliable production methods to maintain a continuous supply of medicines during health crises, both locally and globally (Chaudhary, 2021).

In Palestine, the pharmaceutical industry faced significant challenges due to the COVID-19 pandemic. A joint report from the Ministry of National Economy and the Palestinian Central Bureau of Statistics (2020) indicated that approximately 63% of industrial businesses faced difficulties in sourcing raw materials, while around 89% experienced financial difficulties. This situation resulted in a decline in the financial resources needed to operate these establishments. These statistics highlight the weaknesses in the current manufacturing systems, particularly in pharmaceutical production, when faced with such unexpected crises (Ministry of National Economy (MONE) & Palestinian Central Bureau of Statistics (PCBS) ,2020).

This situation emphasized the urgent need for more flexible and resilient pharmaceutical manufacturing systems. As a result, the pandemic increased pressure on local pharmaceutical manufacturers, driving them to seek modern solutions that enhance the capacity of the industry to manage future disruptions. Consequently, understanding the components of pharmaceutical drugs and the manufacturing processes is essential for helping manufacturers control costs, gain a competitive advantage, and improve product availability for consumers (MONE & PCBS, 2020).

1.1.4 Limitations of Innovation in the Pharmaceutical Industry:

The success of the pharmaceutical industry can be attributed to its innovative formulations. However, this innovation is largely limited to formulation development, with little advancement in modernizing manufacturing processes (Ahmad, 2020). This limited focus poses a significant challenge for the industry, as it continues to prioritize the discovery of new drugs while depending on traditional production techniques, unlike other chemical industries that have adopted technological advancements (Chatterjee, 2012; Lee, 2017).

In the FDA AAPS Annual meeting, the Acting Commissioner of Food and Drugs, Dr. Janet Woodcock, claims, “Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing” (Chatterjee, 2012).

1.1.5 Transitioning to Continuous Manufacturing:

Despite the pharmaceutical industry primarily relying on outdated batch manufacturing techniques, the shift towards continuous manufacturing represents a significant improvement in production methods within the sector (Chatterjee,2012; Phys.org, 2019). Continuous production

not only offers substantial financial, operational, and customer benefits but also addresses many of the existing challenges faced by the industry (Lee, 2017; Phys.org, 2019). Furthermore, investors and incentives from the Food and Drug Administration are supporting the pharmaceutical sector in thoroughly evaluating the advantages of this shift (Chatterjee, 2012; Select USA, 2014).

1.1.6 Major Challenges in Implementing Continuous Manufacturing:

Shifting to continuous manufacturing presents challenges that require a deep understanding of the manufacturing process and the key characteristics of the materials involved (Lee, 2017; Massey, 2019). It is crucial to consider the various operational characteristics and variables that can influence the final output of this manufacturing approach. With the right information and resources, the industry can effectively transition to optimizing all forms of pharmaceutical drugs, (Lee, 2019; Massey, 2019).

1.1.7 Pharmaceutical Manufacturing Process and Unit Operations:

Once the overall framework for pharmaceutical manufacturing is established, the production process can be broken down into several unit operations, including weighing, mixing, granulation, compaction, coating, and packaging. The industrial-scale production of medications by pharmaceutical companies is referred to as drug manufacturing. This method typically involves integrating multiple unit operations in a controlled sequence to ensure product quality and consistency (Thomas Publishing Company, 2021).

1.1.8 The Importance of Accurate Measurement in Drug Production:

Depending on the intended formulation and type of dosage form to be produced, operation lines may be adjusted to include various unit operations in different sequences to optimize the manufacturing process (Kane, 2017). Weighing, milling, and mixing are essential unit operations that remain consistent across all drug production processes, regardless of the order and mode of operation. However, other unit operations may vary. (Wilson Tool, 2021).

Accurately measuring and dispensing each ingredient per dose is one of the most important procedures in any medication production process, regardless of the desired final result, this is the initial step (Thomas, 2021; Wilson Tool, 2021). To guarantee appropriate pharmacological characteristics, the weight of each chemical employed in this case needs to be carefully calculated based on the intended dosage (Kane, 2017; Niazi, 2010; Thomas, 2021).

1.1.9 The Integrated Role of Automation in Preventing Drug Defects and Minimizing Recall-Related Losses:

The manufacturers have switched from manual operation to automated operation with the necessary mechanical components in order to prevent problems with weight accuracy and quality control (Rogers et al., 2013).

Identifying potential drug defects and manufacturing issues that could result in financial losses or health risks for consumers is crucial once the final product of the drug manufacturing process is produced (Rana & Hari Kumar, 2013). Modern technology enables mechanized feeding,

electronic medication monitoring, and ongoing process improvements (Abdalla, 2021; Lee, 2019). However, the U.S. government has observed a rise in drug recalls in recent years due to these drug-related problems (Abdalla, 2021).

Significant revenue losses for the Food and Drug Administration (FDA) can reach billions of dollars. A study by Catlin Crisis Management Group estimated that Tylenol manufacturers faced a loss of $900 million due to medicine recalls, resulting in facility closures and job losses. (U.S. Food and Drug Administration, 2021).

Understanding the potential issues that can lead to a medication recall and how to prevent them is essential for avoiding significant losses. Major defects in medications can result from improper formulation, which may cause functional failures, incorrect machine settings, or ineffective granule moisture, all of which can lead to appearance issues. Various deficiencies, such as weight fluctuations, double impressions, inadequate tensile strength, and others, can also compromise the quality of a medication. It is clear that the manufacturing process presents challenges that pharmaceutical companies must address promptly, necessitating innovation in current drug production methods (Rana & Hari Kumar, 2013).

1.1.10 Challenges in 21st Century Pharmaceutical Manufacturing:

By the end of the 20th century, most major industrial sectors had adopted assembly-line and continuous production technologies (Adamo et al., 2016). This shift was particularly noticeable in the petrochemical, food, automotive, and electronics industries. In contrast, pharmaceutical manufacturing primarily relies on conventional batch processes. Facilities are designed for large-scale batch production of blockbuster medications using centralized manufacturing plants (Srai et al., 2015). This approach divides the production process into distinct procedures that are clearly separated in both time and space (Badman & Trout, 2015).

Synthesis, which involves the manufacturing of drug substances, and formulation, the manufacturing of drug products, are the two primary components of drug production found in various countries (Plumb, 2005). As a result, supply chains become significantly longer, with materials potentially taking weeks to move between sites (Shah, 2004; Srai et al., 2015; Srai et al., 2015).

Before transferring the material to the next unit, samples are taken from each batch created during the manufacturing process and sent to a different laboratory for in-process control measurements (Yu, 2008). The lengthy supply chains and complex production process of pharmaceutical products, which can involve 10 to 20 steps, often result in a production time of 12 to 24 month(Adamo et al., 2016; Shah, 2004; Srai et al., 2015).

Pharmaceuticals are manufactured in a campaign-like manner, where specific intermediates are created in batches, and a predetermined quantity is collected before moving on to the next step (Srai et al., 2015; Teżyk et al., 2016]. This manufacturing method necessitates that factories maintain substantial storage capacity, significantly increasing production costs and, consequently, the price of the final product (Shah, 2004; Srai et al., 2015). Furthermore, safety concerns are intensified by the storage of large quantities of hazardous and potentially active pharmaceutical intermediates (Mascia et al., 2013).

When developing batch technologies, scaling up presents a significant challenge. A process that has been created and optimized in the lab can change dramatically when implemented at the pilot or operational scale. However, ensuring an adequate supply for clinical trials takes precedence, leaving little time for extensive re-optimization during drug development (Suresh & Basu, 2008). Consequently, the initial operating procedure is often approved for industrial-scale use and submitted for regulatory approval. Once the product is on the market, any changes aimed at improving production efficiency must again navigate the costly and time-consuming approval process (U.S. FDA, 2004).

The prevalent practice of quality assurance is perhaps the biggest disadvantage of the batch-based structure in pharmaceutical manufacturing. Strict regulatory oversight aims to ensure consistent quality, which is essential for pharmaceutical products (Plumb, 2005).

Samples from raw materials, intermediates at each phase, and final products are analyzed using the Quality by Testing (QbT) technique, as outlined in references (Rantanen & Khinast, 2015; Su et al., 2019). If any measured parameters exceed regulatory specifications, reprocessing or destroying the entire batch can lead to significant delays and increased costs (Yu, 2008). Rather than promoting a deeper understanding of the process and identifying the root causes of these deviations, the tightly controlled process parameters are mainly intended to minimize fluctuations (Plumb, 2005).

The pharmaceutical sector is currently sluggish and highly rigid due to its existing medication production structure, which prevents it from responding quickly to changes in consumer demand (Lee et al., 2015). The problems with the industry manufacturing strategy are significant contributors to many reported medicine shortages, posing a potential public health risk (U.S.FDA, 2019; U.S.FDA,2018). Furthermore, the costs associated with new pharmaceutical research and development have outpaced market growth, while recent trends in drug development show a declining number of blockbuster products entering the market (Badman & Trout, 2015; DiMasi et al., 2016; Mascia et al., 2013; Shah, 2004). To adapt to evolving market demands, lower costs, and produce medications with greater consistency and quality, a more flexible, robust, and efficient manufacturing system is increasingly necessary (Lee et al., 2015).

1.1.11 Manufacturing Processes and Industry Trends: Batch versus Continuous:

The pharmaceutical manufacturing sector has remained unchanged for the past 50 years, continuing to rely on the traditional batch manufacturing process (Chatterjee, 2012; Kanetkar, 2020; Phys.org, 2019). However, the production of pharmaceutical drugs now demands a new approach that can eliminate the risk of defects and manufacturing issues. This shift is essential not only for enhancing product quality but also for increasing the capital gain of pharmaceutical companies, especially in light of recent technological advancements and the need for production optimization (Lee, 2017).

1.1.12 Batch Manufacturing Process:

A systematic manufacturing approach in which drug products are produced in specified quantities over predetermined time periods (Lee, 2017; McLaughlin, 2019). Each customized batch

undergoes a series of distinct production phases before achieving the final product (McLaughlin, 2019). Despite ongoing innovations aimed at optimizing drug manufacturing, most facilities continue to rely on batch processing due to its reliability, low setup costs, and established procedures (Chauhan & Gupta, 2019; Phys.org, 2019; Massey, 2019; McLaughlin, 2019;). Furthermore, batch processing allows for manufacturing adjustments in response to the evolving demands of the industry. However, the processing methods may vary depending on the medicinal ingredients used and the parameters of the production process (General Kinematics, 2021).

❖ **Disadvantages of Batch Manufacturing.**

- ✓ Products are produced in smaller quantities (Chauhan & Gupta, 2019; General Kinematics, 2021; McLaughlin, 2019).
- ✓ There is increased variability (Chauhan & Gupta, 2019; General Kinematics, 2021; McLaughlin, 2019).
- ✓ More room Increased potential for contamination and human errors (Chauhan & Gupta, 2019).
- ✓ Implementing efficient process control is more challenging (General Kinematics, 2021).
- ✓ There is a higher risk of contamination and human error due to long intervals between batches.
- ✓ This method is slow and inefficient for drug production, which can delay market distribution.
- ✓ According to U.S. FDA Enforcement Statistics, drug recalls increased by 1,200% from 2004 to 2015 due to manufacturing errors or contamination (Abdalla, 2021).
- ✓ The pharmaceutical industry faces annual losses of up to $50 billion as a result of inefficient manufacturing processes (Abdalla, 2021).

1.1.13 Continuous Manufacturing Process:

In contrast to batch production, continuous manufacturing enables pharmaceutical ingredients to move seamlessly through various unit operations, non-stop until the final product is completed (Plumb, 2005).

❖ **The Advantages of Continuous Manufacturing.**

1. Improved Product Quality.

- ✓ Continuous manufacturing processes reach a steady state following the initial start-up phase, maintaining consistent process parameters over time (Plumb, 2005).
- ✓ In contrast, managing the fluctuating conditions of batch processes is significantly more difficult than monitoring and controlling variables at a fixed set point. As a result, consistent product quality can be achieved through the implementation of appropriate analytical techniques (Plumb, 2005).

- ✓ Quality control tools can be integrated directly into the production line, enabling real-time error detection.
- ✓ In the event of an error, only the affected portion of the product needs to be discarded, rather than the entire batch (Nasr et al., 2017).
- ✓ This approach leads to better process control and a more stable product.

2. Enhanced Efficiency and Time Savings.

- ✓ Continuous operations, unlike batch manufacturing, involve the constant feeding and discharging of products and raw materials from the machinery.
- ✓ This method eliminates holding time between technical phases by allowing materials to flow continuously (Lee et al., 2015).
- ✓ As demonstrated in other industries, production can be significantly increased compared to batch operations (Adamo et al., 2016).
- ✓ Simply increasing operating hours can enhance productivity and enable a quicker response to sudden shifts in demand (Allison et al., 2015; Mascia et al., 2013).
- ✓ After the startup phase, the process reaches a steady state where operational parameters remain stable over time.
- ✓ Utilizing parallel production lines accelerates drug development, removing the need for traditional scale-up strategies (Mascia et al., 2013).
- ✓ Production can be further increased by extending runtime and increasing process size.

3. Economic Benefits and Cost Reduction.

- ✓ Continuous technologies have significantly lowered operational and investment costs, with potential savings of up to 40% (Schaber et al., 2011).
- ✓ Although initial setup costs may be higher, continuous manufacturing ultimately enhances profitability by minimizing errors and reducing the need for drug recalls (Schaber et al., 2011).
- ✓ The elimination of expensive and extensive inventory storage for intermediates allows for a smaller production footprint (Lee et al., 2015, Schaber et al., 2011).
- ✓ Pharmaceutical companies benefit from these cost reductions, which in turn increase revenue and make medications cheaper for consumers (Chatterjee, 2012; Massey, 2019; Phys.org, 2019; Schaber et al., 2011]. Additionally, faster operations can help prevent drug shortages by reducing operating hours and ensuring better sales revenue through increased production level (Schaber et al., 2011).
- ✓ This approach leads to improved yields, cost-effectiveness, and a higher return on invested capital (Schaber et al., 2011).

4. Enhanced Process Control and Flexibility.

- ✓ The entire batch does not need to be discarded in the event of an error, as the faulty portion of the product can be precisely identified (Nasr et al., 2017).
- ✓ Continuous manufacturing systems operate as integrated units, merging multiple production steps into one efficient process (Byrn et al., 2015).
- ✓ This transition provides pharmaceutical companies with greater control over the production process and allows for better adaptation to changing consumer demands.

5. Simplified Supply Chain and Integration.

- ✓ This approach improves manufacturing strategies by streamlining extended supply chains through the integration of previously separated segments, such as formulation and synthesis (Badman & Trout, 2015; Srai et al., 2015).

6. Safety with Reduced Human Intervention.

- ✓ High-level automation in continuous manufacturing minimizes human intervention, which in turn reduces the toxicity and safety concerns associated with traditional batch manufacturing. This approach eliminates interruptions between technological steps and protects sensitive active pharmaceutical ingredients (APIs), such as those used in the production of anticancer drugs and hormones, which require stringent protective equipment (Baxendale et al., 2015).

- ✓ By streamlining the process, continuous manufacturing not only minimizes errors but also enhances production efficiency. Ultimately, this method accelerates drug production, making it safer and more reliable.

7. Faster Market Access and Regulatory Facilitation.

- ✓ Process improvement is typically quicker and simpler with continuous technologies, leading to a better-understood and improved procedure for regulatory approval.

- ✓ Drugs made using continuous methods can be produced in as little as one day, according to the US Food and Drug Administration (FDA), while batch processes can take up to a month (Chauhan & Gupta, 2019).

8. Risk Reduction.

Elimination of failed batches.

1.1.14 Regulatory Frameworks and the Adoption of Continuous Manufacturing in the Industry

Inefficiencies and production delays are common challenges in traditional pharmaceutical manufacturing. (Figure 1.1). Illustrates the differences in procedures and operating times between batch and continuous manufacturing processes. By reducing operating hours and increasing

production rates, faster and more streamlined operations can help prevent drug shortages and enhance overall sales revenue (Chauhan & Gupta, 2019).

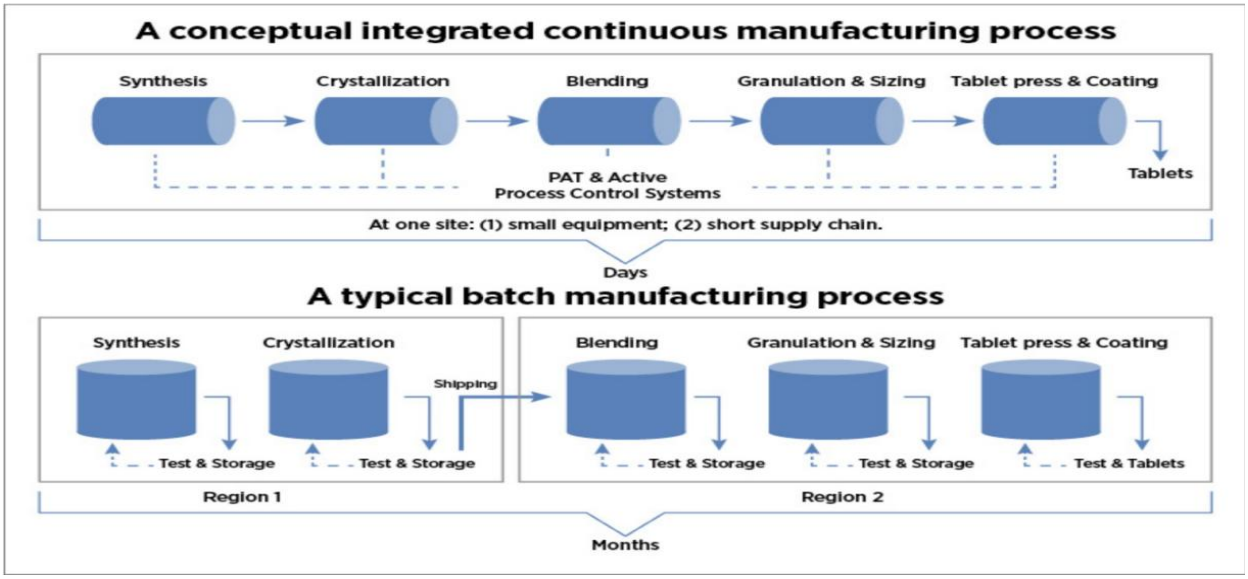

Figure 1.1: Flow diagram showing the procedures and operating times for continuous and batch manufacturing (Chauhan & Gupta, 2019).

As shown in the (Figure1.1). Continuous manufacturing provides significant benefits in efficiency and process integration. This method has already achieved notable success in industries like electronics, automotive, and food (Lee, 2017; Massey, 2019). If implemented effectively, the pharmaceutical industry could significantly benefit from continuous production. The National Science and Technology Council reports that facilities adopting this approach have experienced a 40–50% reduction in variable costs, directly enhancing operational success (Adamo et al., 2016).

Following the demonstrated efficiency of continuous manufacturing, regulatory efforts have been made to accelerate its adoption in the pharmaceutical sector. Dr. Peter Marks, Director of the FDA Center for Biologics Evaluation and Research, discussed the FDA ongoing initiatives to promote this technology. These efforts include publishing research articles and draft guidelines to assist companies in modernizing their production processes, as well as offering incentives for facilities transitioning to continuous manufacturing (Chatterjee, 2012; Lee, 2017; Massey, 2019; Srai et al., 2015).

These regulatory initiatives are already influencing the pharmaceutical industry, leading several companies to adopt new practices. The well-known American pharmaceutical corporation Eli Lilly has announced a €35 million investment to build and operate a continuous production plant in Ireland (Badman & Trout, 2015). This facility will enable the company to produce goods more quickly in smaller spaces. Additionally, pharmaceutical companies are currently obtaining FDA approval to manufacture drugs, such as HIV-1 Prezista tablets, using continuous manufacturing techniques. To enhance the quality of medications for American consumers, the FDA recently published a statement indicating its ongoing efforts in process assessment and quality assurance to facilitate the approval of more continuously produced medications (Teżyk et al., 2016).

Despite growing interest and initial investments, the widespread adoption of continuous manufacturing faces significant challenges. High start-up costs, the need for new operational

protocols, and underdeveloped regulatory frameworks have initially hindered the implementation of this technology (Adamo et al., 2016).

As previously mentioned, these challenges are being progressively addressed by regulatory bodies like the FDA through proactive measures. They have offered incentives, published guidelines, and provided technical support to manufacturers (Chatterjee, 2012; Lee, 2017; Massey, 2019; Srai et al., 2015). Additionally, initiatives such as Eli Lilly €35 million investment in a continuous production facility the industry commitment to overcoming these obstacles and advancing toward modern production solutions (Badman & Trout, 2015).

1.1.15 Scientific Motivation and Technological Advancements in Continuous Manufacturing:

The transition to continuous pharmaceutical manufacturing was motivated by the need to enhance efficiency, flexibility, and speed in production processes. Industry stakeholders, academia, and regulatory bodies initiated this shift toward continuous technologies to address the limitations of traditional batch-based manufacturing. This significant change in the pharmaceutical sector was inspired by the idea of a more robust, flexible, cost-effective, and rapid manufacturing method (Simon et al., 2019; Vanhoorne & Vervaet, 2020).

The ACS GCI Roundtable was established in 2005 by the American Chemical Society (ACS) Green Chemistry Institute (GCI) in collaboration with several multinational pharmaceutical companies, including Novartis, Pfizer, Roche, Sanofi, Eli Lilly, and Johnson & Johnson (American Chemical Society, 2005).

One of the round table key study priorities is continuous processing (Poechlauer et al., 2012; Poechlauer et al., 2013). In 2004, the U.S. Food and Drug Administration (FDA) introduced the first framework to promote the use of Process Analytical Technologies (PAT) (U.S. FDA, 2004). These innovative analytical methods enhance process understanding and improve product quality, making them suitable for real-time monitoring of processes (Simon et al., 2015).

In the years following the FDA initiatives (U.S. FDA, 2019), the International Council for Harmonization (ICH) and the European Medicines Agency (EMA) released several additional guidelines (International Council for Harmonization, 2018; Mihokovic, 2017) focused on enhancing quality through the Quality by Design (QbD) approach for quality assurance, rather than relying on Quality by Testing (QbT). Recently, the FDA identified Continuous Manufacturing (CM) as a key tool for modernizing the pharmaceutical industry (U.S. FDA, 2019). The guidelines emphasize that quality should be integrated into the product itself, rather than assessed exclusively via QbT (Yu, 2008; Yu et al., 2014).

Pharmaceutical Quality by Design (QbD) is a systematic approach to development that starts by defining the product critical quality attributes (CQAs), the critical material attributes (CMAs) of the starting materials, and the critical process parameters (CPPs). By linking (CMAs) and (CPPs) to (CQAs), it becomes possible to understand how changes in process parameters and material attributes influence product quality. This understanding allows for the establishment of a defined operating range of parameters that can consistently produce the desired level of product quality. Nearly all major pharmaceutical innovators are currently developing advanced technologies (Nasr et al., 2017).

Six pharmaceutical products that have been released to the market Vertex's Orkambi® and Symdeko®, Johnson & Johnson Prezista®, Eli Lilly Verzenio®, Pfizer Daurismo®, and Chinoin Severin® are all at least partially produced using continuous technologies that have received regulatory approval (Badman et al., 2019; Teżyk et al., 2016).

While significant effort was required to achieve this progress, there is obviously more space for improvement. It is clear that the transition to CM is a lengthy and costly process that demands extensive research (McKenzie et al., 2006).

New continuous processes that are not yet implemented must be developed, and the applicability of current technologies should be continuously evaluated. Additionally, transforming the training and mindset of CM professionals requires a significant amount of time (Nasr et al., 2017).

The literature on continuous pharmaceutical manufacturing, including the entire production line is expanding. Significant research has been conducted in areas such as continuous crystallization, flow chemistry (Baxendale et al., 2015), and continuous mixing and tableting (Byrn et al., 2015). However, linking these individual stages into a single streamlined production system is more complex than studying each process in isolation (Nepveux et al., 2015).

To fully leverage the benefits of continuous manufacturing (CM) as outlined in section 1.1.13 distinct technological processes must be integrated into a single continuous manufacturing line that includes both raw materials and final dosage forms.

Yet, the current literature reveals that only a limited number of studies address continuous systems involving two or more connected stages. Even fewer studies cover end-to-end continuous processes that span from raw material synthesis to final product formulation.

This gap may be due to the fact that many scientists and engineers tend to specialize in either synthesis or formulation, but rarely both, since these areas have traditionally been handled separately. Therefore, advancing integrated continuous technologies will require a major shift in mindset and cross-disciplinary collaboration (Teżyk et al., 2016; Plumb, 2005).

1.2 Problem Statement.

The pharmaceutical industry in Palestine encounters several challenges that hinder its capacity to satisfy the increasing demand for high-quality, affordable medicines. These challenges consist of high production costs, inconsistent product quality, and sometimes limited access to essential medicines.

The industry limited production flexibility, which slows down its ability to adapt to changing market demands. Furthermore, prolonged storage periods increase the risk of material deterioration, leading to inconsistencies in content and negatively impacting product quality.

Scaling up production in batch manufacturing systems presents a significant challenge. This process typically requires investment in larger equipment, which results in increased time demands, higher financial costs, and the need for additional space burdens that local manufacturers often find difficult to manage. Batch production increases reliance on material properties and is closely associated with lengthy supply chains. These long and fragmented supply chains show limited resilience to sudden changes in regulations or market conditions. This was clearly illustrated during the COVID-19 pandemic, when pharmaceutical manufacturers in

Palestine experienced significant disruptions in the availability of raw materials and the continuity of production.

Given these challenges, continuous manufacturing (CM) presents a promising and innovative solution. By integrating multiple processing steps into a single, continuous flow, CM significantly improves efficiency, enhances product quality, and reduces costs. Additionally, CM allows for quicker adaptation to changing market demands and increases the overall flexibility of pharmaceutical production systems.

The understanding and identification of these challenges were enhanced through personal interviews with experienced practitioners from local pharmaceutical manufacturing companies.

1.3 Aim of the Study.

This study aims to assess the level of awareness, implementation, and potential barriers associated with Continuous Manufacturing (CM) among pharmaceutical manufacturing companies in Palestine.

1.4 Objectives of the Study.

The specific objectives of this research are as follows:

- ✓ To evaluate the knowledge of Continuous Manufacturing Processes (CMP) among Palestinian pharmaceutical companies.
- ✓ To assess the adoption rate of Continuous Manufacturing Processes (CMP) within the Palestinian pharmaceutical industry.
- ✓ To identify the primary obstacles that prevent Palestinian pharmaceutical producers from adopting Continuous Manufacturing Processes (CMP).
- ✓ To determine whether there are statistically significant differences in respondents' awareness and application of CMP based on their professional and demographic characteristics, including years of experience, job title, field of expertise, educational background, and company category.

1.5 Research Questions and Hypotheses .

Q1: What is the level of awareness regarding Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q2: What is the level of implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q3: What is the extent of barriers to implementing Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q4: Are there statistically significant differences in the awareness levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional

variables (educational qualification, field of specialization, job- title, years of experience in the pharmaceutical sector**,** and company variable)?.
This question was examined by testing five null hypotheses.

❖ **The Null hypotheses are stated as follows:**

H_{01}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

H_{02}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

H_{03}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job - Title variable

H_{04}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

H_{05}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company variable.

Q5: Are there statistically significant differences in the implementation levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job- title, years of experience in the pharmaceutical sector, company variable)?.
This question was also examined by testing five null hypotheses.

❖ **The Null hypotheses are stated as follows:**

H_{01}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

H_{02}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

H_{03}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job -Title variable.

H_{04}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

H_{05}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company variable.

1.6 Significance of the Study.

The pharmaceutical industry in Palestine is a vital sector that faces significant challenges, which hinder its ability to meet the increasing demand for high-quality medicines. Key issues include high production costs, inconsistent product quality, and difficulties in adapting to changing market demands. Additionally, the industry limited production flexibility further complicates its response to the rising need for medicines.

This study is significant as it explores the innovative approach of Continuous Manufacturing (CM) within the Palestinian pharmaceutical industry. CM represents a technological advancement that enhances efficiency, reduces costs, and addresses the challenges faced by local pharmaceutical companies. By assessing the awareness and implementation of CM practices in Palestinian companies, as well as the barriers to adoption, this research provides valuable insights into the potential transformation of the industry.

Additionally, this study fills a notable gap in the literature concerning the pharmaceutical industry in Palestine, particularly related to continuous manufacturing, which has been largely neglected. The findings aim to improve local production practices and bolster the sustainability of the pharmaceutical sector in Palestine.

1.7 Scope and Limitations.

This study aims to evaluate the awareness, application, and barriers to the adoption of continuous manufacturing processes (CMP) in pharmaceutical manufacturing companies in Palestine. The sample consisted of managers, department heads, and supervisors from various departments within the selected companies, ensuring an unbiased distribution without favoring specific individuals.

The study examined seven pharmaceutical companies located throughout Palestine. Three of these companies are based in Ramallah: Al-Quds Pharmaceuticals, Birzeit Pharmaceuticals, and Dar Al-Shifa Pharmaceuticals. One company is situated in Bethlehem (Beit Jala Pharmaceuticals), two are in Jericho (Palolia and Allison Pharmaceuticals), and one is located in Nablus (Sama Pharmaceuticals).

Although the study originally intended to include all seven companies, only six participated, we were unable to contact Sama Pharmaceuticals in Nablus due to current circumstances and access limitations, despite making repeated attempts.

Data was collected through personal interviews and paper questionnaires. A significant challenge was the low response rate, especially from Jerusalem Pharmaceuticals, which hindered the collection of a larger number of completed questionnaires. Additionally, logistical and field constraints limited our ability to reach some companies within the planned timeframe.

Chapter Two:

Literature Review.

2.1 Limitations of Conventional Manufacturing Systems.

- **Article Title: A Comparative Investment Analysis of Batch Versus Continuous Pharmaceutical Manufacturing Technologies.**

Journal: Journal of Pharmaceutical Innovation.

Publisher: Springer Nature.

Year of Publication: 2022.

Author: Cristina V. Rossi.

Traditional batch manufacturing has been the standard in the pharmaceutical industry due to its historical development and regulatory familiarity. However, recent years have highlighted its economic limitations. A study by Rossi (2022) conducted a comparative investment analysis of batch versus continuous pharmaceutical manufacturing technologies. Published in the Journal of Pharmaceutical Innovation, this research employed investment models and financial simulations to assess the cost-effectiveness of each approach.

The findings indicated that batch manufacturing to have higher operational costs, energy consumption, and downtime related to equipment cleaning and product changeovers. In contrast, continuous manufacturing showed a more favorable net present value (NPV), particularly under U.S. tax policies that promote capital-intensive technologies. Rossi's study presents a compelling financial case for transitioning away from traditional batch production, especially when considering long-term economic sustainability and scalability within the pharmaceutical sector (Rossi, 2022).

❖ **Article Title: Process Modelling and Simulation for Continuous Pharmaceutical Manufacturing of Ibuprofen**

Journal: Chemical Engineering Research and Design.
Publisher: Elsevier.
Year of Publication: 2015.
Authors: Jolliffe, H. G., & Gerogiorgis, D. I.

Traditional batch manufacturing has long been a cornerstone of pharmaceutical production. However, as Jolliffe and Gerogiorgis (2015) demonstrate in their study, batch-based systems have several operational and economic limitations. Published in Chemical Engineering Research and Design, the article employs process modeling and simulation to compare batch and continuous production methods for manufacturing ibuprofen. The study identifies key drawbacks of batch production, including limited scalability, increased variability in product quality, inefficiencies from downtime between batches, and challenges in inventory management. The authors also note that batch systems incur significantly higher operational costs due to longer processing times, greater labor demands, and increased energy consumption. These findings underscore that traditional batch manufacturing is less suited to modern pharmaceutical requirements and note the benefits of transitioning to continuous manufacturing for enhanced efficiency, quality, and cost control (Jolliffe & Gerogiorgis, 2015).

❖ 2.2 Transitioning to Continuous Manufacturing.

Article Title: Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production.
Journal: Journal of Pharmaceutical Innovation.
Publisher: Springer Nature.
Year of Publication: 2015.
Authors: Sau L. Lee, Thomas F. O'Connor, Xiaochuan Yang, Celia N. Cruz, Sharmista Chatterjee, Rapti D. Madurawe, Christine M. V. Moore, Lawrence X. Yu, Janet Woodcock.

Lee et al. (2015) offer a crucial regulatory perspective on the transition from traditional batch manufacturing to continuous manufacturing (CM) in pharmaceutical production. Published in the Journal of Pharmaceutical Innovation, the article outlines a detailed road map that reflects the U.S. Food and Drug Administration's (FDA) strategic involvement in modernizing pharmaceutical processes.

The article aims to highlight the benefits of converting traditional batch manufacturing into continuous manufacturing systems. The authors report a 50% reduction in production time and a 15% improvement in product quality, demonstrating the clear advantages recognized by companies that are more aware of these changes.

The authors, all senior officials at the FDA, emphasize how regulatory frameworks have evolved to proactively support the adoption of continuous manufacturing (CM). This shift is not just a reaction to industry trends; it is a strategic initiative aimed at enhancing drug quality, manufacturing reliability, and product availability. The study demonstrates the FDA's transformation from a reactive regulator into a promoting agency that fosters innovation in manufacturing through flexible, science-based, and risk-informed oversight.

At the heart of the FDA support is the promotion of key enabling technologies. The agency promotes Quality by Design (QbD), a systematic and knowledge-based approach to pharmaceutical development, as well as Process Analytical Technology (PAT), which enables real-time quality assurance during production. These tools help minimize variability and ensure more consistent product outcomes.

The FDA has supported the implementation of CM by establishing clear regulatory pathways, creating guidance documents, providing early-stage consultations with manufacturers, and initiating pilot programs. Additionally, it boosts industry confidence by publishing case studies, organizing public workshops, and employing transparent communication strategies.

While the study focuses on the U.S., it underscores broader implications. The FDA leadership has played a significant role globally, indirectly supporting international harmonization efforts like the ICH Q13 guideline on continuous manufacturing. Lee et al. (2015) present foundational evidence that regulatory engagement, combined with technological innovation, can greatly expedite the pharmaceutical industry's shift to more modern and efficient production systems (Lee et al., 2015).

- **Article Title**: Regulatory and Quality Considerations for Continuous Manufacturing.
  Journal: International Journal of Pharmaceutics.
  Publisher: Elsevier.
  Year of Publication: 2017.
  Authors: Tushar S. Borkar, Shamsher S. Jadhav, & Kiran D. Patil.

The study by Borkar, Jadhav, and Patil (2017), published in the International Journal of Pharmaceutics, provides a detailed analysis of the regulatory and quality challenges linked to the implementation of continuous pharmaceutical manufacturing (CM). The authors explore how regulatory frameworks are adapting to support the transition from traditional batch manufacturing to more modern, continuous production systems.

The article emphasizes the growing importance of regulatory bodies, not only in enforcing compliance but also as essential drivers of innovation. It focuses on key areas such as process integration, regulatory submission strategies, and adherence to Good Manufacturing Practices (GMP). Furthermore, the study emphasizes the critical role of Quality by Design (QbD) principles and the implementation of Process Analytical Technology (PAT**)** in ensuring real-time quality assurance.

Borkar et al. identify existing regulatory gaps and offer actionable recommendations to address them. Their suggestions include developing clearer guidance documents and harmonizing global regulatory standards. This analysis emphasizes the importance of a supportive regulatory environment that can accelerate the adoption of continuous manufacturing by reducing uncertainty and promoting scientific, risk-based approaches to pharmaceutical production (Borkar et al., 2017).

- **Document Title**: ICH guideline Q13 on continuous manufacturing of drug substances and drug products.

Issuing Organization: International Council for Harmonization (ICH).

Year of Publication: 2023.
Available at: EMA – ICH Q13 Guideline.

In 2023, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a comprehensive guideline titled ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products. This document marks a significant regulatory milestone by providing harmonized scientific and technical principles to support the implementation and lifecycle management of continuous manufacturing (CM) for both drug substances and finished products. ICH Q13 serves as a globally endorsed regulatory reference that greatly impacts industry practices and regulatory expectations.

The guideline defines a batch in continuous manufacturing as being based on time, the quantity of material processed, or other scientific justifications. This flexible definition enables production to be responsive to real-time market demands. Furthermore, ICH Q13 emphasizes important elements of continuous manufacturing, including dynamic process understanding, system integration, real-time monitoring through Process Analytical Technology (PAT), and robust control strategies.

Another key aspect of the guideline is its focus on Continued Process Verification (CPV), a contemporary validation strategy that facilitates real-time monitoring of production parameters. This approach ensures that the process consistently produces products that meet quality specifications. By moving away from traditional batch-based quality validation to continuous assurance of process control, CPV has become a fundamental component of modern pharmaceutical quality systems.

ICH Q13 outlines the scientific principles and regulatory considerations for continuous manufacturing (CM), including guidance on regulatory submissions and global harmonization. This guideline applies to new drug applications (NDAs), generics, and biosimilars, while also facilitating the transition of legacy products from batch to continuous manufacturing platforms. It offers operational guidance and strategic regulatory clarity for manufacturers globally, emphasizing that regulatory agencies are actively innovation in pharmaceutical production systems (International Council for Harmonisation,2023).

2.3: Challenges to implementing CM.

- **Title of study:** Continuous manufacturing versus batch manufacturing: benefits, opportunities and challenges for manufacturers and regulators

Journal: GaBI Journal (Generics and Biosimilars Initiative Journal).

Publisher: Pro Pharma Communications International.

Year of Publication: 2021

Authors: Hock, S. C., Siang, T. K., & Wah, C. L.

In their 2021 peer-reviewed article published in GaBI Journal, Hock, Siang, and Wah examine the practical and regulatory challenges that hinder the broader adoption of continuous manufacturing (CM) in the pharmaceutical industry. Their study reveals that, despite increasing global interest in CM, several significant obstacles persist. A key issue is the absence of harmonized regulatory guidelines, which complicates international product approvals and reinforces the preference for traditional batch manufacturing systems.

Moreover, the substantial initial investment required for CM technologies, particularly in automation and process analytical technologies (PAT) discourages many manufacturers, especially in the generics sector. The authors also identify critical technical challenges, such as ensuring material traceability, developing robust control strategies, and managing new safety risks associated with automated continuous systems.

Additionally, the industry's skills gap presents a notable obstacle, as implementing CM demands advanced technical expertise that is not yet widespread among regulatory or manufacturing personnel. Operational inertia and cultural resistance to change within pharmaceutical organizations further hinder progress, compounded by uncertainty about how new technologies will fit into existing clinical and regulatory timelines.

While the authors acknowledge that CM offers long-term economic and quality benefits, they emphasize the necessity of overcoming these barriers for its successful and widespread implementation (Hock et al., 2021).

2.4: From Theory to Practice: Implementing Continuous Manufacturing in the Real World.

- **Title of Study**: Integrated Continuous Pharmaceutical Technologies. A Review.

Journal: Organic Process Research & Development.

Year of Publication: 2021.

Authors: András Domokos, Brigitta Nagy, Botond Szilágyi, György Marosi, Zsombor Kristóf Nagy.

The 2021 study Integrated Continuous Pharmaceutical Technologies A Review, authored by Domokos et al. and published in Organic Process Research & Development, offers an in-depth analysis of the current state and future prospects of continuous manufacturing (CM) in the pharmaceutical industry. The study emphasizes that traditional batch manufacturing, which has long been the standard in this sector, has seen little change despite significant technological advancements in other fields. The authors contend that CM presents considerable advantages, including faster, more flexible, and cost-effective production, as well as improved quality assurance.

The paper categorizes and reviews various continuous manufacturing (CM) technologies utilized throughout the pharmaceutical value chain, from drug substance synthesis to final drug product

formulation. It covers processes such as continuous flow chemistry, crystallization, filtration, drying, blending, granulation, and tableting. A primary emphasis is placed on integrating these processes into seamless end-to-end systems. However, the study highlights significant technical challenges associated with this integration, which necessitates a deep understanding of each process, real-time monitoring, and a systems-based approach to development.

The authors highlight the increasing support from regulatory agencies that now encourage for the adoption of CM practices. Consequently, pharmaceutical companies are investing more in research to move from theory to practical implementation. The paper advocates for a holistic and interdisciplinary approach to developing fully integrated pharmaceutical manufacturing systems, emphasizing both current advancements and ongoing challenges (Domokos et al., 2021).

2.5: Case Studies of Successful Implementation.

- **Title of Study**: Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study.

  Journal: Industrial & Engineering Chemistry Research.

  Publisher: American Chemical Society (ACS).

  Year of Publication: 2011.

  Authors: Spencer D. Schaber, Dimitrios I. Gerogiorgis, Rohit Ramachandran, James M. B. Evans, Paul I. Barton, & Bernhardt L. Trout.

The study titled Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study was authored by Spencer D. Schaber, Dimitrios I. Gerogiorgis, Rohit Ramachandran, James M. B. Evans, Paul I. Barton, and Bernhardt L. Trout. Published in 2011 in the Industrial & Engineering Chemistry Research journal by the American Chemical Society, it provides a case study that compares the economic implications of traditional batch manufacturing with integrated continuous manufacturing in the pharmaceutical sector. The study explores the feasibility and benefits of transitioning from batch to continuous manufacturing (CM) by modeling a full-scale production line capable of producing 2,000 tons of tablets annually. The researchers assess various process configurations in both upstream synthesis and downstream drug product formulation, emphasizing capital expenditures (CapEx), operating expenditures (OpEx), and total project costs over a 15-year period.

The results indicate that integrated continuous manufacturing can significantly lower capital expenditures (CapEx) by 20% to 76%, depending on factors like the cost of the key intermediate (KI) and the active pharmaceutical ingredient (API) loading. For instance, when the KI price reaches $3,000 per kilogram, CapEx savings can peak at 76% by employing a continuous process that incorporates recycling and direct tablet formation. Additionally, continuous manufacturing (CM) yields annual operating expenditure savings ranging from 6% to 40%. These savings are primarily due to reduced labor requirements, decreased material handling and storage needs, and significantly lower quality assurance/control costs. Notably, QA/QC expenses in CM processes

were reduced by approximately 50% due to the adoption of real-time monitoring technologies such as Process Analytical Technology (PAT).

The study pointed not only cost reductions but also the efficiency of CM in managing working capital and resources. Traditional batch processes require 35% of annual material costs to be tied up as working capital, whereas CM only needs 3.5%, owing to its continuous flow and reduced in-process inventory. Additionally, CM optimizes resource usage, consuming 21% less solvent and 61% less water, which enhances its sustainability advantage. The study also examines the impact of yield variation, revealing that even with CM yields modeled to be 10% lower than those of batch processes, the overall project cost remained comparable or favorable. When CM yields exceeded batch yields by 10%, total present cost savings reached up to 44%, emphasizing the economic potential of improving process efficiency.

Although the initial investment in development and equipment adaptation for continuous manufacturing (CM) is higher, the authors emphasize that the long-term benefits of CM far outweigh the initial challenges. Continuous processes ensure greater consistency in product quality, align with evolving regulatory expectations that promote a deep understanding of processes, and enable ongoing verification and optimization. Ultimately, the study presents strong evidence supporting the adoption of continuous pharmaceutical manufacturing, demonstrating its potential for superior economic performance while meeting quality and compliance requirements. This work serves as a valuable economic benchmark and provides strategic guidance for future investments in large-scale pharmaceutical production (Schaber et al., 2011).

The following studies provide a detailed illustration of how continuous manufacturing has evolved from theoretical concepts to practical industrial implementation [74,75].

- **Title of Study:** Continuous Granulation in the Pharmaceutical Industry.
  Journal: Chemical Engineering Science.
  Publisher: Elsevier.
  Year of Publication: 2005
  Authors: Vervaet, C., & Remon, J. P.

- **Title of Study:**Recent Progress in Continuous Manufacturing of Oral Solid Dosage Forms.
  Journal: International Journal of Pharmaceutics.
  Publisher: Elsevier.
  Year of Publication: 2020.
  Authors: Vanhoorne, V., & Vervaet, C.

The development of continuous manufacturing (CM) in the pharmaceutical industry has made significant strides over the past two decades, with foundational research and practical advancements building on one another. One of the earliest and most influential studies in this area was conducted by Vervaet and Remon (2005), who provided a conceptual review of continuous granulation as an alternative to traditional batch processes. Their article examined the use of twin-screw extrusion (TSE) as an innovative method for producing oral solid dosage forms. While their work was primarily theoretical, it aimed to highlight the potential benefits of CM, including shorter processing times, reduced labor costs, improved control over granule properties, and a

lower risk of cross contamination. However, the study also identified significant challenges that hindered implementation at that time, such as difficulties in controlling critical parameters like moisture content, torque, and residence time during granulation; a lack of advanced sensors and real-time monitoring tools; and uncertainties regarding compliance with existing regulatory frameworks (Vanhoorne & Vervaet, 2020; Vervaet & Remon, 2005).

Fifteen years later, Vanhoorne and Vervaet (2020) revisited the topic, this time emphasizing real-world applications and technological advancements. Their review highlights how the pharmaceutical industry has evolved from theory to practical implementation, particularly in the manufacturing of oral solid dosage forms. Unlike the 2005 review, this study presents fully operational continuous production lines, including continuous twin-screw granulation and continuous direct compression processes. Notably, many challenges identified in 2005 have been effectively addressed. The integration of Process Analytical Technology (PAT) into modern continuous manufacturing systems such as near-infrared (NIR) spectroscopy and Raman spectroscopy now allows for real-time measurement and control of critical process parameters like granule size, moisture, and uniformity. These innovations have overcome previous limitations related to process stability and quality assurance. Furthermore, the introduction of feedback and feedforward control systems has ensured consistent product quality, even in dynamic processing conditions (Vanhoorne & Vervaet, 2020; Vervaet & Remon, 2005).

The regulatory uncertainty present in 2005 has been largely resolved. International guidelines, including ICH Q8 through Q13, now explicitly support continuous manufacturing approaches, offering clear pathways for regulatory approval. Pharmaceutical companies like Johnson & Johnson, Pfizer, and GSK have implemented continuous technologies not only in pilot plants but also in full-scale commercial operations. Vanhoorne and Vervaet highlight that continuous manufacturing has evolved from a theoretical concept into a mature industrial standard, merging the flexibility and efficiency envisioned by early researchers with the stringent process control and regulatory compliance required in modern drug production (Vanhoorne & Vervaet, 2020; Vervaet & Remon, 2005).

- **Study Title:** Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice.
  Journal: Journal of Pharmaceutical Sciences.
  Publisher: Elsevier.
  Year: 2018.
  Authors: Yu, L. X., & Lee, S. L.

Yu and Lee (2018) present a regulatory perspective on the shift from batch to continuous pharmaceutical manufacturing (CPM). They emphasize the role of agencies such as the FDA in facilitating this transition through flexible regulations and scientific collaboration. The paper asserts that continuous manufacturing is in line with Quality by Design (QbD) principles, providing advantages in real-time quality assurance. The authors stress that successful implementation relies on harmonizing regulatory frameworks with scientific progress to maintain consistent product quality and safety (Yu & Lee, 2018).

- **Study Title:** Meeting Supply and Training Challenges.
  Journal: Pharmaceutical Technology.
  Publisher: MJH Life Sciences.
  Year: 2021.
  Author: Markarian, J.
  Markarian (2021) explores the logistical and human capital challenges of implementing continuous manufacturing in the pharmaceutical industry. The study notes that success requires on both technological readiness and the availability of skilled personnel capable of managing data-intensive automated systems. Additionally, it underscores supply chain concerns, such as access to raw materials and supplier reliability. The article concludes that aligning workforce training with supply infrastructure is crucial for the adoption of continuous pharmaceutical manufacturing (CPM) (Markarian, 2021).

- **Study Title:** USP Workshop on Identifying and Addressing Barriers to Continuous Manufacturing Adoption.
  Publisher: United States Pharmacopeia.
  Year: 2023.
  Author: United States Pharmacopeia (USP).

The 2023 USP workshop gathered stakeholders from industry, academia, and regulatory bodies to address the main barriers to adopting continuous manufacturing. The findings emphasized several challenges, including the absence of standardized regulatory guidelines, a shortage of technical expertise, and high initial investment costs. The report recommends enhancing collaboration across sectors, building technical capacity, and harmonizing global regulations to accelerate implementation, particularly for smaller manufacturers (United States Pharmacopeia, 2023).

Chapter Three:

Method and Procedures.

This chapter offers an overview of our methodology for conducting the study. It includes study method, community under investigation, study sample, and verification of the questionnaire validity and reliability. Furthermore, it outlines the study procedures and the statistical methods used to analyze the results. Below is a description of these processes.

3.1 Study Approach.

To achieve the aims of the study, we employed a descriptive analytical method. This approach allows for the examination of a phenomenon, event, or current issue, facilitating the collection of information that addresses research questions without our interference. The goal is to describe the phenomenon under investigation, analyze the data, and clarify the relationships among different components and opinions, as well as the associated processes and effects. Method also entails a structured analysis and scientific interpretation, involving careful classification, examination, and analysis of the phenomenon or problem.

3.2 Study Population.

There are seven pharmaceutical manufacturing companies operating in Palestine, namely: **Jerusalem Company**/ Ramallah.

Biet Jala Company / Bethlehem.

Pharmacare Company/Ramallah.

Birzeit Company /Ramallah.

Palolia Company /Jericho**.**

Alison Company /Jericho.

Sama company /Nablus.

However, only six of them agreed to participate in the study. Therefore, the estimated study population included: managers, supervisors and heads of departments (Head of the production department, Technical Manager, Head of the (R& D) department, Head of quality control department (Q.C), Head of quality assurance, Inventory Manager, Maintenance Manager... etc.) and others responsible for manufacturing operations in Palestinian pharmaceutical companies. The total number of individuals included in the study population is approximately 120.

3.3 The study Sample.

A random sample of 80 completed forms was collected, representing an 80 % response rate out of the 100 distributed questionnaires. (Table 3.1) illustrates the distribution of the study sample across six Palestinian pharmaceutical companies:

Table 3.1: the distribution of the study sample across six Palestinian pharmaceutical companies.

Company	n (%)
1. Jerusalem company (JPC)	**5 (6.3%)**
2. Palolea company	**5 (3.6%)**
3. Alison company	**10 (12.5%)**
4. Birzeit Company (BPC)	**14 (17.5%)**
5. Pharmacare company	**19 (23.8%)**
6. Beit Jala company (BJP)	**27 (33.8%)**

n: frequency **(%) valid percent**

3.4 Study design.

A quantitative cross-sectional survey was conducted at six Palestinian pharmaceutical companies: **Jerusalem Company, Biet Jala Company, Pharmacare Company, Birzeit Company, Palolia Company, and Alison Company.** Data collection took place from September 2024 to November 2024, with data analysis starting in January 2025 after the completion of data collection.

3.5 Study Tool.

We used a detailed questionnaire developed by Dr. Muhammad Abu Assab, with his permission. This tool is designed to gather data from pharmaceutical manufacturers and serves as the primary instrument for analyzing awareness, implementation, and barriers to continuous manufacturing processes (CMP) within Palestinian pharmaceutical companies. The questionnaire includes closed-ended questions designed to meet the study objectives and research questions, covering a range of CMP related topics.

The questionnaire is divided into two sections**. The first section** gathers demographic and general information to characterize the sample, including details such as the company name, educational qualifications, specialization, job title, total work experience, and type of production line. **The second section** contains 71 questions: 23 focused on measuring awareness of continuous manufacturing, 29 on evaluating the extent of its implementation, and 19 on identifying barriers to continuous manufacturing.

A total of 100 questionnaires were symmetrically distributed among six companies, resulting in 80 completed responses and a response rate of (80 %) . The full questionnaire can be found in **(Appendix A) .**

3.6 Study Procedures and Data collection.

Primary data will be collected through questionnaires, personal interviews, and surveys with key stakeholders in the pharmaceutical industry in Palestine. We coordinated company visits using an official letter we issued to the targeted companies. A copy of this letter can be found in **(Appendix B)** .

I supervised the completion of the questionnaires immediately after the interviews, ensuring transparency and accuracy throughout the process. This hands-on approach helped maintain data integrity and ensured that all responses were carefully recorded.

We distributed **100 questionnaires** to the study sample. After collecting the completed questionnaires, it was determined **that 80 were** valid and suitable for statistical analysis, resulting in zero missing questionnaires and response rate 80%**.**

3.7 Ethical considerations.

This study and its accompanying questionnaire received approval from the Chemistry Department at Al-Quds University. The questionnaire, originally developed by Dr. Mohammad Abu Assab, was used with his formal consent. All data collected from the pharmaceutical companies were handled and analyzed confidentially to ensure their privacy and were used exclusively by us for the purposes of this study.

3.8 Data Analysis and Interpretation.

After collecting data through a paper-based questionnaire, SPSS version 22 was used for all data analysis. This analysis aimed to address the research questions and test the main hypotheses to address the objectives of the study. The collected data were analyzed in accordance with the following research questions:

Q1: What is the level of awareness regarding Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q2: What is the level of implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q3: What is the extent of barriers to implementing Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

Q4: Are there statistically significant differences in the awareness levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector, and company category)?
This question was examined by testing five null hypotheses.

Q5: Are there statistically significant differences in the implementation levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector, and company category.)?
This question was also examined by testing five null hypotheses.

Descriptive statistics were employed to analyze awareness, implementation, and barriers related to CMP. **Inferential statistics**, including hypothesis testing, were used to examine group differences based on the identified variables.

3.9 Validity.

To ensure the questionnaire validity, it was initially presented to a group of expert arbitrators. They evaluated its clarity, linguistic integrity, and relevance to the study objectives, ensuring **face validity** and **content validity,** feedback was then used to refine the questionnaire**. Construct validity** was assessed using Pearson item-total correlation.

The Pearson correlation coefficient was calculated for each question in relation to the overall score, which further confirmed the construct validity of the questionnaire**.** The Pearson correlation coefficient (r) ranges from -1 to +1, where values closer to +1 indicate a strong positive relationship, values near 0 suggest no correlation, and values approaching -1 reflect a strong negative relationship. Pearson correlation is a widely accepted method to assess the relationship between individual items and their respective total domain scores, thereby supporting construct validity.

The results presented in **Tables (3.2, 3.3, 3.4)** demonstrate statistically significant Pearson correlation values (R) for awareness, implementation, and barriers. Specifically, the values range from **(0.615 to 0.835)** for awareness, **(0.502 to 0.849)** for implementation, and **(0.252 to 0.792)** for barriers. The p-values (all = 0.000) are below the significance level of 0.05, confirming the statistical significance of these correlations.

These correlation values indicate strong internal consistency across the questionnaire, validating that the tool effectively measures the intended constructs of awareness, implementation, and barriers related to (CMP) in the pharmaceutical industry in Palestine.

Table 3.2: Pearson Correlation results for the level of Awareness to (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Value (R)	Sig	N	Value (R)	Sig	N	Value (R)	Sig
1	0.615**	0.000	9	0.697**	0.000	17	0.768**	0.000
2	0.625**	0.000	10	0.728**	0.000	18	0.835**	0.000
3	0.263*	0.019	11	0.654**	0.000	19	0.783**	0.000
4	0.538**	0.000	12	0.720**	0.000	20	0.733**	0.000
5	0.630**	0.000	13	0.750**	0.000	21	0.421**	0.000
6	0.614**	0.000	14	0.710**	0.000	22	0.450**	0.000
7	0.745**	0.000	15	0.832**	0.000	23	0.461**	0.000
8	0.787**	0.000	16	0.670**	0.000			

N: number of question Sig: significant P value R: value of Pearson Correlation

***. Correlation is significant at the 0.05 level (2-tailed).**

Table 3.3: Pearson Correlation results for the level of Implementation to (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Value (R)	Sig	N	Value (R)	Sig	N	Value (R)	Sig
1	0.793**	0.000	11	0.818**	0.000	21	0.661**	0.000
2	0.840**	0.000	12	0.818**	0.000	22	0.659**	0.000
3	0.722**	0.000	13	0.734**	0.000	23	0.692**	0.000
4	0.754**	0.000	14	0.752**	0.000	24	0.738**	0.000
5	0.824**	0.000	15	0.774**	0.000	25	0.743**	0.000
6	0.832**	0.000	16	0.849**	0.000	26	0.502**	0.000
7	0.848**	0.000	17	0.813**	0.000	27	0.690**	0.000
8	0.800**	0.000	18	0.808**	0.000	28	0.651**	0.000
9	0.851**	0.000	19	0.785**	0.000	29	0.626**	0.000
10	0.804**	0.000	20	0.724**	0.000			

N: number of question Sig: significant P value R: value of Pearson Correlation

*. Correlation is significant at the 0.05 level (2-tailed).

Table 3.4: Pearson Correlation results for the level of Barriers to (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Value (R)	Sig	N	Value (R)	Sig	N	Value (R)	Sig
1	0.566**	0.000	8	0.719**	0.000	15	0.387**	0.000
2	0.651**	0.000	9	0.709**	0.000	16	0.457**	0.000
3	0.560**	0.000	10	0.700**	0.000	17	0.589**	0.000
4	0.715**	0.000	11	0.694**	0.000	18	0.385**	0.000
5	0.702**	0.000	12	0.792**	0.000	19	0.252*	0.024
6	0.662**	0.000	13	0.466**	0.000			
7	0.655**	0.000	14	0.468**	0.000			

N: number of question Sig: significant P value R: value of Pearson Correlation

*. Correlation is significant at the 0.05 level (2-tailed).

3.1 Reliability.

We evaluated the tool stability by calculating the total score for the stability factor using Cronbach's Alpha. The results revealed a stability score of (0.935) for awareness of Continuous Manufacturing Processes (CMP), (0.973) for CMP implementation, and (0.891) for barriers to CMP. These findings indicate that the tool possesses sufficient stability to meet the study objectives, as the Cronbach Alpha values reflect a high level of internal consistency across all sections of the questionnaire. These results are displayed in (Table 3.5).

Note: Both Cronbach's Alpha and Pearson item-total correlation were utilized to evaluate the internal consistency of the questionnaire. Specifically, Cronbach's Alpha assessed the overall reliability of each domain, while the Pearson item-total correlation was used to examine construct validity by verifying the correlation of each item with its corresponding domain total.

Table 3.5: Cronbach' Alpha Values Indicating the Reliability of the Study Tool.

Scale	N of Item	Cronbach's Alpha
1. Awareness	**23**	**0.935**
2. Implementation	**29**	**0.973**
3. Barrier	**19**	**0.891**

3.11 Description of Sample Member Variables.

(Table 3.6) displays the distribution of respondents across various study variables. In terms of qualifications, (67.5%) hold a Bachelor's degree or lower, while (32.5%) possess a Master's degree or higher. For specialization, the distribution is as follows: (38.8%) in Pharmacy, (32.5%) in Chemistry, and (28.7%) in other fields. In the job category, (25%) of respondents are in management or higher, (22.5%) are department heads, (33.8%) are supervisors, and (18.8%) fall into other categories.

Regarding years of experience in the pharmaceutical industry, (17.5%) have 5 years or less, (23.8%) have 6-10 years, (16.3%) have 11-15 years, and (42.5%) have 16 years or more.

For In terms of company name, (6.3%) for Company 1, (6.3%) for Company 2, (12.5%) for Company 3, (17.5%) for Company 4, (23.8%) for Company 5, and (33.8%) for Company 6.

Finally, the type of production line shows that (27%) of respondents work with solid dosage forms, (33.6%) with liquid dosage forms, (23.2%) with semi-solid dosage forms, and (16.2%) with injectable dosage forms. **(Appendix C)** provides frequency tables displaying the numbers and percentages of participants responses to demographic variables, including qualification, specialization, job title, years of experience, company, and production line.

Table 3.6: Distribution of study sample according to the study variables.

Variables	Levels	N	%
Qualification	Bachelor degree	54	67.5
	Master degree	26	32.5
Specialization	Pharmacy	31	38.8
	Chemistry	26	32.5
	Others	23	28.7
Jop category	Management and above	20	25.0
	Department heads	18	22.5
	Supervisor	27	33.8
	Others	15	18.8
Years of experience in the pharmaceutical industry sector	5 years and less	14	17.5
	From 6-10 years	19	23.8
	From 11-15 years	13	16.3
	16 years and more	34	42.5
Company	Company 1	5	6.3
	Company 2	5	6.3
	Company 3	10	12.5
	Company 4	14	17.5
	Company 5	19	23.8
	Company 6	27	33.8
Type of production line	Solid dosage form	65	27.0
	Liquid dosage form	71	33.6
	Semi-solid dosage form	56	23.2
	Injectable dosage form	39	16.2

N: Numbers(frequencies). %: Percentage.

3.12 Figures Illustrating the Distribution of the Sample Variables.

The following figures visually represent the distribution of respondents across key demographic and job-related variables, offering a clearer interpretation of each variable alongside the tabular data presented in Table 3.6.

Figure 3.1: Respondent Distribution by Qualification

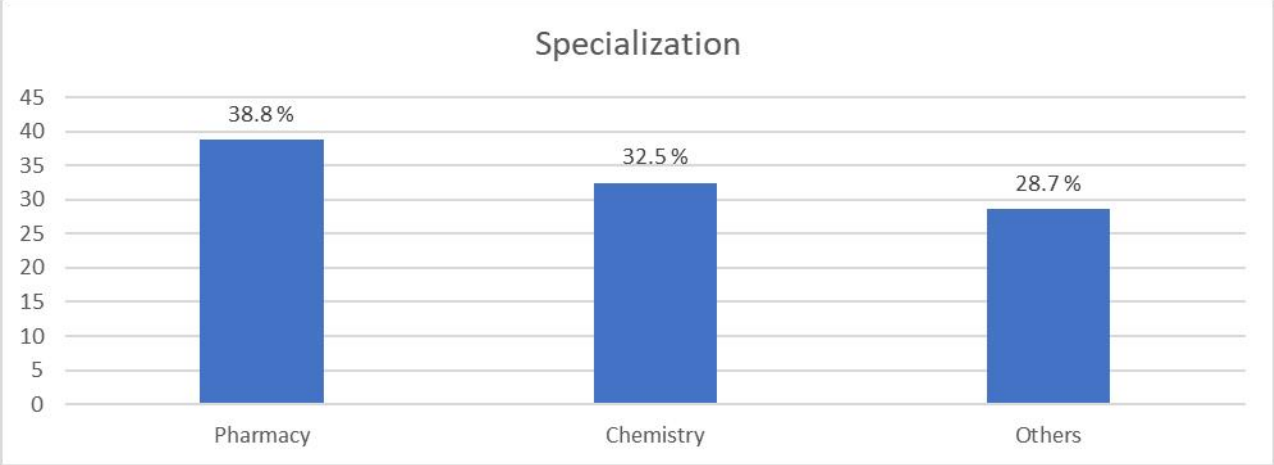

Figure 3.2: Respondent Distribution by Specialization.

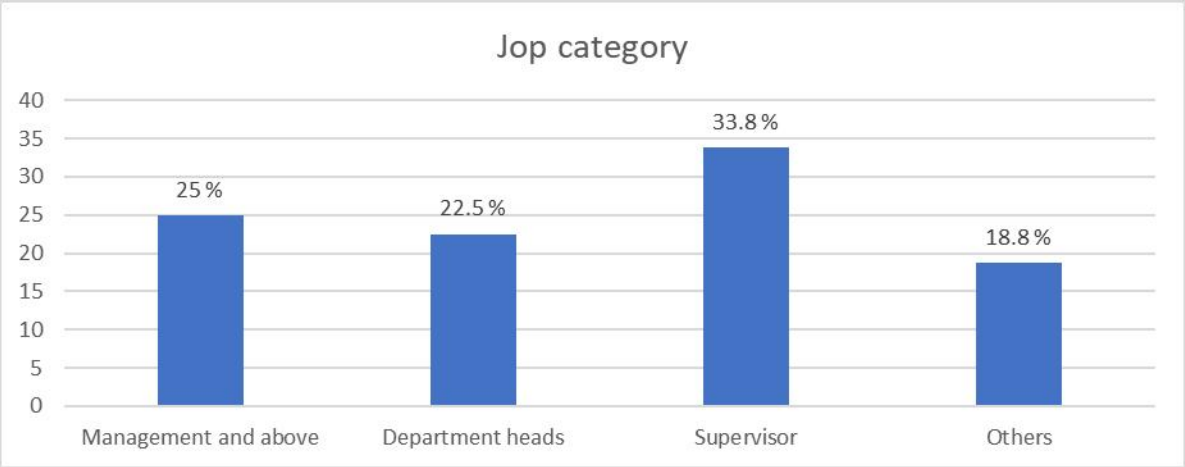

Figure 3.3: Respondent Distribution by Job Category.

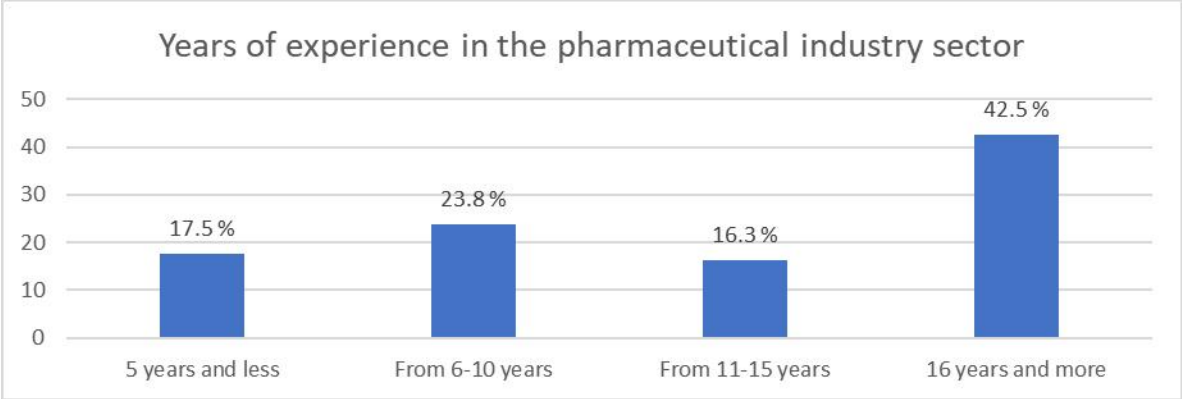

Figure 3.4: Respondent Distribution by Years of Experience in the Pharmaceutical Industry sector.

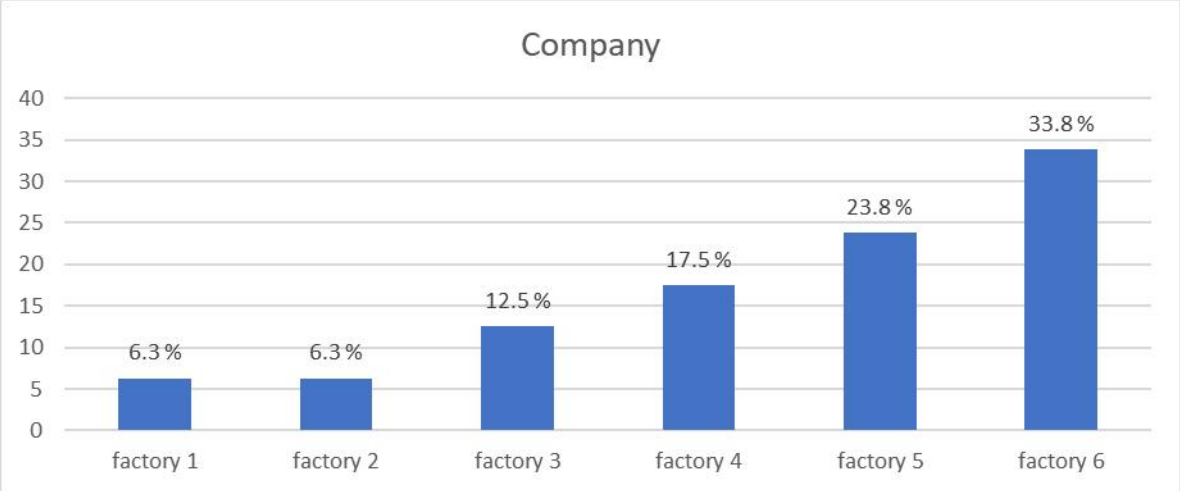

Figure 3.5: Respondent Distribution by Company.

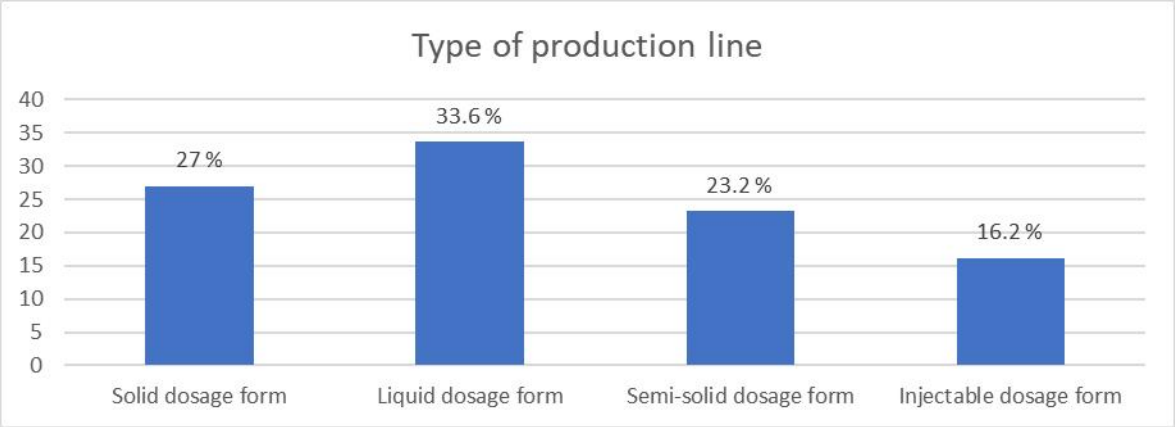

Figure 3.6: Respondent Distribution by Type of Production Line.

3.13 Statistical analyses.

This section outlines the statistical methods and tests used to analyze the collected data and address the study research questions. After collecting and verifying the validity of the questionnaires, the data were encoded and entered into Microsoft Excel and SPSS version 22 (Statistical Package for Social Sciences) for analysis. For all variables, a 5-point Likert scale was used to measure responses, where 5 = Strongly Agree and 1 = Strongly Disagree. The midpoint of this scale is 3 = Neutral, representing the boundary between agreement and disagreement. This standardized measurement allowed consistent evaluation across all questionnaire items. **(Appendix C, Appendix D)**, provides frequency tables that display the distribution of responses for all questionnaire items.

To interpret the arithmetic mean values derived from Likert-scale responses, a three-point classification was adopted based on equal distribution around the midpoint (3.00), as follows:

- An arithmetic mean from **1.00 to 2.33 = Low.**
- An arithmetic mean from **2.34 to 3.66 = Moderate.**
- An arithmetic mean from **3.67 to 5.00 = High.**

This interpretation method ensures clarity in understanding respondent tendencies and enables consistent categorization of perception levels.

To determine the appropriate inferential tests, **the Kolmogorov-Smirnov** test was conducted to assess data normality. Due to the non-normal distribution of the data, non-parametric tests, including **the Mann-Whitney test** and **the Kruskal-Walli's test**, were utilized to explore differences across groups based on demographic variables. The reliability of the instrument was evaluated using **Cronbach's Alpha** to assess internal consistency, and the Pearson correlation coefficient was employed to measure the correlation between individual items and the total scale score. Detailed results can be found in Chapter 4.

During the data preparation process for statistical analysis, categorical variables were numerically coded to enhance clarity and ensure consistent interpretation. The following variables were considered:

- ✓ **Specialization**: Participants specializations were categorized into three groups: Pharmacy Code 1, Chemistry Code 2, and a combined group of other specialization: (Chemical Engineering, Industrial Engineering, Biology, Food Processing, Marketing), designated as Code 3. This combined group was created due to the small number of participants in each of these individual specializations.
- ✓ **Job Category**: Job categories were similarly grouped. Management and above received Code 1, Department heads were assigned Code 2, Supervisors received Code 3, and a combined category of Others (including roles such as Director, President, and Consultant) was designated as Code 4. This grouping was necessary to account for the limited number of participants in these specific job roles.
- ✓ **Years of Experience in the Pharmaceutical Industry**: Respondents were categorized based on their years of experience: **5 years or less** Code 1**, 6-10 years** Code, **11-15years** Code 3, and **16 years or more** Code 4.
- ✓ **Company**: Companies were assigned codes from Code 1 to Code 6, corresponding to the following entities: Jerusalem Company (JPC) was assigned Code 1, Palolea Company was assigned Code 2, Alison Company was assigned Code 3, Birzeit Company (BPC) was assigned Code 4, Pharmacare Company (PLC) was assigned Code 5, and Beit Jala Company (BJP) was assigned Code 6.
- ✓ **Type of Production Line**: Production lines were categorized as follows: Solid dosage form Code 1, Liquid dosage form Code 2, Semi-solid dosage form Code 3, and Injectable dosage form Code 4.

The grouping of certain categories, especially under the (Others) designation, was implemented to ensure that all job roles and specializations had a sufficient sample size for meaningful analysis. This approach also mitigated the risk of unreliable results that could arise from having too few participants in specific groups.

Chapter Four:

Results:

4.1 Introduction.

This chapter presents the results of the study, focusing on the research subject **Assessment of Awareness, Implementation, and Barriers to Continuous Manufacturing Processes (CMP) Among Pharmaceutical Manufacturing Companies in Palestine: A Cross-Sectional Study**. It discusses the effects of each variable based on the responses of the sample members to the study tool and analyzes the statistical data obtained.

4.2 Descriptive Analysis of the Study Responses.

This section provides a descriptive analysis of the distribution of participants responses to the questionnaire items. Frequencies and percentages were calculated for the demographic information, as shown in **(Appendix C)** and illustrated in the figures referenced in Section 3.12. **(Appendix D)** presents the participants responses to the questionnaire items across the three dimensions. The frequency and percentage of each response were calculated according to the Likert scale (from Strongly Agree to Strongly Disagree).

4.3 Study Question Results.

This section presents the answers to the research questions. Descriptive statistics were used to summarize and describe the distribution of participant responses across the various dimensions of the study using the rating scale defined in **Section 3.13** to classify as low, moderate, or high, while inferential statistics were applied to draw conclusions and test the study hypotheses.

4.3.1 Results for the First Question:

Q1: What is the level of awareness regarding Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

To address this question, we calculated the arithmetic means and standard deviation of the participants responses to the questionnaire items regarding their knowledge of Continuous

Manufacturing Processes (CMP), as shown in (Table 4.1). The resulting values were then interpreted using the rating scale defined in **Section 3.13** to classify the level of awareness as low, moderate, or high.

Table 4.1-a: Means and Standard Deviations of Awareness Levels of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Sentences	Mean	SD	%
13	CMP improves product quality more than traditional batch manufacturing processes.	4.10	0.722	82.0
1	I recognize the difference between the continuous manufacturing process (CMP) and traditional batch manufacturing.	4.09	0.814	81.8
12	CMP improves production efficiency compared to traditional batch manufacturing processes.	4.05	0.810	81.0
15	Our management is aware of the benefits of CMP.	4.04	0.892	80.8
18	CMP reduces the waste of raw materials more than traditional batch manufacturing processes.	3.99	0.934	79.8
10	CMP provides greater control over manufacturing processes than traditional batch manufacturing processes.	3.98	0.856	79.6
14	The company management is aware of CMP's requirements.	3.96	0.834	79.2

Table 4.1-b: Means and Standard Deviations of Awareness Levels of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

9	CMP reduces the cost of production compared to traditional batch manufacturing processes.	3.89	0.811	77.8
11	CMP reduces the amount of space required compared to traditional batch manufacturing processes.	3.88	0.905	77.6
8	I realize the benefits of adopting CMP compared to traditional batch manufacturing processes.	3.86	0.978	77.2
17	Our management is aware of the continuous manufacturing principles.	3.86	0.807	77.2
2	I knew about the CMP through my work.	3.84	0.999	76.8
19	We are aware of the new technology used in CMP.	3.79	0.990	75.8
23	The CMP is more flexible than the traditional batch process.	3.75	0.893	75.0
21	CMP is used to develop new formulations more than traditional batch manufacturing processes.	3.71	0.917	74.2
20	We are aware of process analytical techniques (PAT) used in CMP.	3.62	0.998	72.4
7	I am knowledgeable about CMP.	3.61	1.073	72.2
16	I know about CMP through the international guidelines.	3.53	0.900	70.6
22	Capital expenditures in CMP are less than those in the batch process.	3.47	1.043	69.4
4	I learned about the CMP through self-learning.	3.30	1.072	66.0
5	I received training in the field of CMP.	2.94	1.205	58.8
6	I received qualifications in the CMP field.	2.88	1.140	57.6
3	I learned about the CMP through my undergraduate study.	2.60	1.086	52.0
Average		**3.6804**	**0.61523**	**73.6**

N: Number of Question. SD: Standard Deviations. %: Valid percent.

The previous (table 4.1), displays the arithmetic means and standard deviations of the study sample responses regarding the level of awareness of (CMP) among pharmaceutical companies in Palestine. The overall arithmetic mean was (**3.68)**, with a standard deviation of (**0.615)**. Based on the predefined rating scale, corresponding to **(73.6%)**, this reflects **a high level of awareness.**

The statements related to the first Dimension were organized in descending order based on their arithmetic means, from highest to lowest, to emphasize the items that had the most significant impact on the measured concept.

The results in (Table 4.1) indicate that the statement **(CMP improves product quality more than traditional batch manufacturing)** the highest arithmetic mean of (4.10). This was closely followed by the statement **(I recognize the difference between the continuous manufacturing process (CMP) and traditional batch manufacturing)** which had a mean of (4.09). In contrast, the statement **(I received qualifications in the CMP)** field had the lowest arithmetic mean of (2.60), and the statement **(I learned about the CMP through my undergraduate study)** had a mean of (2.88).

4.3.2 Results for the Second Question:

Q2: What is the level of implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

To answer this question, the arithmetic means and standard deviations were calculated for the responses of the study sample regarding the questionnaire items measuring the level of Implementation of (CMP) among pharmaceutical manufacturing companies in Palestine. The items within this dimension were distributed across three distinct sub-levels, as shown in (Table 4.2), and the arithmetic means and standard deviations were also calculated separately for each level to allow for a more detailed and accurate interpretation of the results.

Table 4.2: Means and standard deviations for the level of Implementation (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Fields	Mean	SD	%
1	**Management and Employees**	3.3552	0.82482	67.1
2	**Facility, Equipment, Devices, and Materials**	3.5339	0.70747	70.7
3	**The Supply Chains**	3.5750	0.66872	71.5
Average		**3.4642**	**0.68830**	**69.3**

N: Number of questions. SD: Standard Deviations. %: Valid percent.

(Table 4.2) presents the arithmetic means and standard deviations of responses from the study sample regarding the implementation of (CMP) in pharmaceutical companies in Palestine. The overall arithmetic mean for the total score was **(3.46)**, with a standard deviation of **(0.688)**. According to the predefined rating scale in **Section 3.13**. This score corresponds to **(69.3%)**, which reflects a **moderate level of implementation**.

The Supply Chains field had the highest mean score of (3.57), followed by the Facility, Equipment, Devices, and Materials field with a mean of (3.53), and lastly, the Management and Employees field with a mean of (3.35).

To enhance understanding, the questionnaire items related to the level of implementation were categorized into three sub-levels. The arithmetic mean for each sub-level was calculated to assess the degree of implementation in specific areas. Additionally, the items within each sub-level were

ranked in descending order based on their arithmetic mean values, highlighting the statements that had the most and least significant influence on each dimension.

Beginning with the **Management and Employee** level, we calculated the arithmetic means and standard deviations to assess the level of implementation based on the predefined rating scale. As shown in (Table 4.3).

Table 4.3: Means and standard deviations for the Management and Employees filed.

N	Sentence	Mean	SD	%
1	Our management is interested in converting from batch manufacturing to CMP.	3.54	0.885	70.8
11	Our workers can handle CMP operations effectively.	3.45	0.870	69.0
2	Our management is committed to implementing CMP.	3.44	0.869	68.8
6	Our management seeks to invest in the CMP.	3.44	0.939	68.8
9	Our management constantly seeks to apply the CMP.	3.44	1.004	68.8
10	The company exploits process analytical techniques (PAT) used in CMP.	3.40	0.936	68.0
7	Our management is dedicated to a specialized skills development training program in CMP.	3.38	0.919	67.6
12	Our workers can solve CMP problems effectively.	3.31	0.866	66.2
3	Our management attracted qualified employees in CMP.	3.30	1.048	66.0
5	Our workers were trained in CMP.	3.22	1.079	64.4
8	We have a specialized team in the company to study the requirements for CMP implementation.	3.21	0.990	64.2
4	Our management recruited experienced employees in CMP.	3.14	1.003	62.8
Average		**3.3552**	**0.82482**	**67.1**

N: Number of questions. SD: Standard Deviations. %: Valid percent.

(Table 4.3) shows the arithmetic means and standard deviations of the study sample responses concerning the Management and Employees dimension. The overall arithmetic mean is **(3.35),** with a standard deviation of **(0.824).** According to the predefined rating scale in **Section 3.13.** This suggests that the level of implementation in this dimension is **moderate,** with a percentage of **(67.1%).**

The results presented in (Table 4.3) reveal that the paragraph **(Our management is interested in converting from batch manufacturing to CMP)** received the highest arithmetic mean score of (3.54). This was followed closely by the paragraph **(Our workers can handle CMP operations effectively)** which had an arithmetic mean of (3.45). Conversely, the paragraph **(Our management recruited experienced employees in CMP)** recorded the lowest mean score at (3.14), while the paragraph **(We have a specialized team in the company to study the requirements for CMP)** had a mean of (3.21).

Continuing with the second level, **Facility, Equipment, Devices, and Materials**, we calculated the arithmetic means and standard deviations for the study sample responses to the relevant questionnaire items. As shown in (Table 4.4). Similar to the first level (Management and Employees), these results will be evaluated and compared using the predefined rating scale outlined in **Section 3.13**, allowing for the classification of the implementation level as low, moderate, or high.

Table 4.4: Means and standard deviations for Facility, Equipment, Devices, and Materials filed.

N	Sentence	Mean	SD	%
11	We ensure the specifications of materials used in CMP.	3.88	0.718	77.6
10	We use the necessary manufacturing materials for CMP.	3.83	0.708	76.6
14	All of our products can be produced through the CMP.	3.78	0.826	75.6
12	We have qualified warehouses to store materials needed for the CMP.	3.73	0.954	74.6
13	We verify the packaging materials used in CMP according to the required guidelines.	3.71	0.874	74.2
8	Our machines and equipment can be adjusted to suit the CMP.	3.65	0.813	73.0
9	Our machines and equipment can be rearranged sequentially according to CMP.	3.64	0.815	72.8
2	Our facility layout can be adjusted to operate the CMP.	3.56	0.824	71.2
6	Our machines and equipment cleaning times are suitable for CMP.	3.52	0.941	70.4
7	We have the required infrastructure for the CMP.	3.38	0.877	67.6
4	Our machines and equipment are suitable for CMP.	3.30	1.060	66.0
5	Our machines and equipment are arranged to be used sequentially according to CMP.	3.28	1.031	65.6
3	We have all the necessary machines and equipment for CMP.	3.15	1.092	63.0
1	Our facility layout is designed for the CMP.	3.09	1.034	61.8
Average		**3.5339**	**0.70747**	**70.7**

N: Number of questions. SD: Standard Deviations. %: Valid percent.

(Table 4.4) shows the arithmetic means and standard deviations of the study sample responses for the Facility, Equipment, Devices, and Materials dimension. The overall arithmetic mean is **(3.53)**, with a standard deviation of **(0.707).** Based on the predefined rating scale in **Section (3.13)**, these results corresponding to **(70.7%.)**, which reflects a **moderate level in Facility, Equipment, Devices, and Materials filed.**

(Table 4.4) shows that the statement **(We ensure the specifications of materials used in CMP)** received the highest average score of (3.88). It was closely followed by **(We use the necessary manufacturing materials for CMP)**, which scored (3.83). In contrast, **(Our facility layout is designed for the CMP)** had the lowest average score at (3.09), with **(We have all the necessary machines and equipment for CMP)** slightly higher at (3.15).

In the third and final level, concerning the implementation specifically, the Supply Chains. We calculated the arithmetic means and standard deviations for the study responses to the relevant questionnaire items. Following the approach used for the previous levels, these results were evaluated and interpreted based on the predefined rating scale outlined in **Section 3.13.** This classification determined the level of implementation as low, moderate, or high, as illustrated in (Table 4.5).

Table 4.5: Means and standard deviations for the Supply Chains filed.

N	Sentence	Mean	SD	%
1	Our contracts with suppliers are suitable for the CMP.	3.65	0.748	73.0
2	Our suppliers have quality certificates in CMP.	3.54	0.826	70.8
3	Our suppliers' delivery dates are suitable for CMP.	3.54	0.674	70.8
Average		**3.5750**	**0.66872**	**71.5**

N: Number of questions**.** **SD:** Standard Deviations. **%**: Valid percent.

(Table 4.5) presents the arithmetic means and standard deviations of the study responses regarding the Supply Chains level. The overall arithmetic mean is (3.57), with a standard deviation of (0.668). According to the rating scale defined in **Section 3.13**, this result corresponds to (71.5%), indicating a **moderate** level of implementation in the Supply Chains dimension.

The results presented in Table (4.5) show that the statement **(Our contracts with suppliers are suitable for the CMP)** achieved the highest average score of (3.65). This was followed by the statements **(Our suppliers have quality certificates in CMP)** and **(Our suppliers delivery dates are suitable for CMP)** both of which received an average score of (3.54).

4.3.3 Results for the Third Question:

Q3: What is the extent of barriers to implementing Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

To address this question, we calculated the arithmetic averages and standard deviations of the responses from the study sample regarding the questionnaire items related to the Barriers to (CMP) in Pharmaceutical Manufacturing Companies in Palestine, as displayed in (Table 4.6). Using the rating scale detailed in **Section 3.13**, the results were categorized to identify the degree of the barriers as low, moderate, or high.

Table 4.6: Means and standard deviations for the level of Barriers to (CMP) Among Pharmaceutical Manufacturing Companies in Palestine.

N	Sentences	Mean	SD	%
16	The CMP involves extensive research and development.	4.04	0.665	80.8
19	The CMP requires extensive process optimization.	4.02	0.746	80.4
18	The CMP requires continuous validation and monitoring.	3.97	0.779	79.4
15	The CMP requires more control and evaluation processes.	3.76	0.889	75.2
1	Adopting the CMP with its underlying technologies is expensive.	3.75	0.935	75.0
17	The CMP encounters complex regulatory approvals.	3.66	0.779	73.2
13	The CMP requires more physical space than the batch process.	3.52	0.795	70.4
14	Limited availability of the CMP-compatible resources, technologies, and materials.	3.44	0.777	68.8
7	The CMP poses quality management challenges.	3.31	1.063	66.2
10	Lack of awareness of the CMP and its benefits.	3.26	0.978	65.2
2	Lack of top management commitment to CMP.	3.15	0.929	63.0
9	Our workers are not sufficiently experienced in the CMP.	3.15	1.045	63.0
12	The CMP requires complex logistic issues.	3.14	1.016	62.8
4	Adopting the CMP with its underlying technologies is difficult.	3.09	1.070	61.8
8	Our workers are not sufficiently qualified to operate the CMP.	3.05	1.124	61.0
6	The CMP is not flexible.	2.86	1.088	57.2
11	The CMP system is complex to operate.	2.85	0.995	57.0
5	Adopting the CMP is not worth it.	2.80	1.095	56.0
3	Adopting the CMP is time-consuming.	2.54	0.954	50.8
Average		**3.3355**	**0.54756**	**66.7**

N: Number of questions. SD: Standard Deviations. %: Valid percent.

(Table 4.6) shows the arithmetic means and standard deviations of responses from the study sample regarding barriers to (CMP) among Pharmaceutical Manufacturing Companies in Palestine. The overall arithmetic mean is **(3.33)**, with a standard deviation of **(0.547)**. Based on

the rating scale defined in **Section 3.13**, this result corresponds to **(66.7%)**, indicating **a moderate level of perceived barriers.**

(Table 4.6) shows that the sentence **(The CMP involves extensive research and development)** has the highest arithmetic average at (4.04), followed closely by **(The CMP requires extensive process optimization)**, which has an average of (4.02). In contrast, the sentence **(Adopting the CMP is time-consuming)** received the lowest average at (2.54), while (Adopting the CMP is not worth it) follows with an average of (2.80).

4.3.4 Results for the Fourth Research Question:

This section addresses the fourth research question:

Q4: Are there statistically significant differences in the awareness levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector and company category)?
To investigate this question, we reformulated it into the following hypotheses, which aim to determine whether awareness levels significantly differ among respondents according to their demographic and General Information.

The statistical analysis employed non-parametric tests, as detailed in **Section 3.13**, to ensure compatibility with the data distribution.

The hypotheses are stated as follows:

H_{01}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

H_{02}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

H_{03}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

H_{04}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

H_{05}A: There are no statistically significant differences (at $p > 0.05$) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company category.

❖ **Results of the First Hypothesis:**

H_{01}A: There are no statistically significant differences (p-value > 0.05) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

The first hypothesis was evaluated using the **Mann-Whitney U test** for two independent samples to assess whether there are statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine, based on qualifications. The test results, including the mean ranks for each group, are presented in (Table 4.7).

Table 4.7: Results of the Mann-Whitney Test for Two Independent Samples on Awareness of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine, Based on Qualification.

Qualification	N	Mean Rank	Value of Z	Sig
Bachelors' degree	54	41.19	0.380	**0.704**
Master degree	26	39.08		

N = Number of respondents**. Mean Rank =** Average rank of responses**. Z=** value for Mann- test

Sig= significant P value.

As shown in (Table 4.7), the Z value for the total score was (0.380), with a significance level of ($p = 0.704$) which is greater than the threshold of 0.05 ($p > 0.05$). This result indicates that there are no statistically significant differences in the level of awareness of (CMP) among pharmaceutical manufacturing companies in Palestine based on the qualification variable as shown in (Figure4.1). Consequently, **the first hypothesis is accepted.**

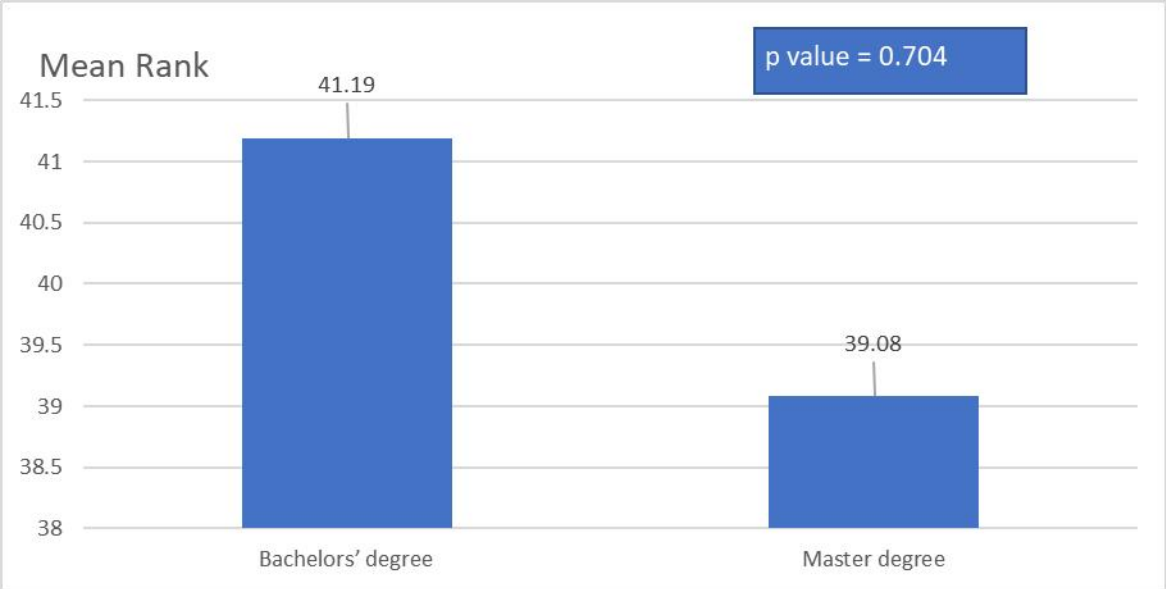

Figure 4.1: Mean Rank of Awareness Levels by Qualification (Bachelor vs. Master).

❖ **Results of the Second Hypothesis:**

H_{02A}: There are no statistically significant differences (at p > 0.05) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

The second hypothesis was tested using **the Kruskal-Walli's test**, which is suitable for comparing more than two independent samples. This test aimed to determine if there are statistically significant differences in awareness of (CMP) among respondents from pharmaceutical manufacturing companies in Palestine, categorized by their field of specialization. The results are presented in (Table 4.8).

Table 4.8: Results of the Kruskal-Walli's Test for More Than Two Independent Samples on the Level of Awareness of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine Based on the Specialization Variable.

Field (Specialization)	d.f	Kruskal-Walli's H	Sig
Average	2	7.847	0.020

d.f=degree of free. Sig= significant P value.

The results of the Kruskal- Walli's test presented in (Table 4.8) show a total score of (7.847) and a significance level of (p = 0.020), which is below the threshold for statistical significance at 0.05 (p

< 0.05), indicating that there are statistically significant differences in the level of awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical manufacturing companies in Palestine, based on the Specialization variable. Therefore**, the second hypothesis is rejected**.

Since statistically significant differences were detected, a rank order was calculated to pinpoint where these differences lie. The ranking of awareness levels across the different specializations is presented in (Table 4.9).

Table 4.9: Mean Ranks of Study Sample Responses by Specialization Variable.

Fields	Levels	N	Mean Rank
Average	**Pharmacy**	**31**	**31.37**
	Chemistry	**26**	**46.79**
	Others	**23**	**45.70**

N = Number of respondents.

(Table 4.9) presents the results of the mean rank analysis regarding awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical manufacturing companies in Palestine, categorized by specialization.

The data shows that respondents specializing in **Chemistry** have the highest mean rank of (46.79), followed closely by those in the **others** category with a mean rank of (45.70). In contrast, respondents with a specialization in **Pharmacy** have the lowest mean rank at (31.37).

These results suggest that the statistically significant differences in awareness levels, identified through the Kruskal-Walli's test, are primarily driven by the higher awareness among respondents from the **Chemistry** specialization. As illustrated in (Figure 4.2).

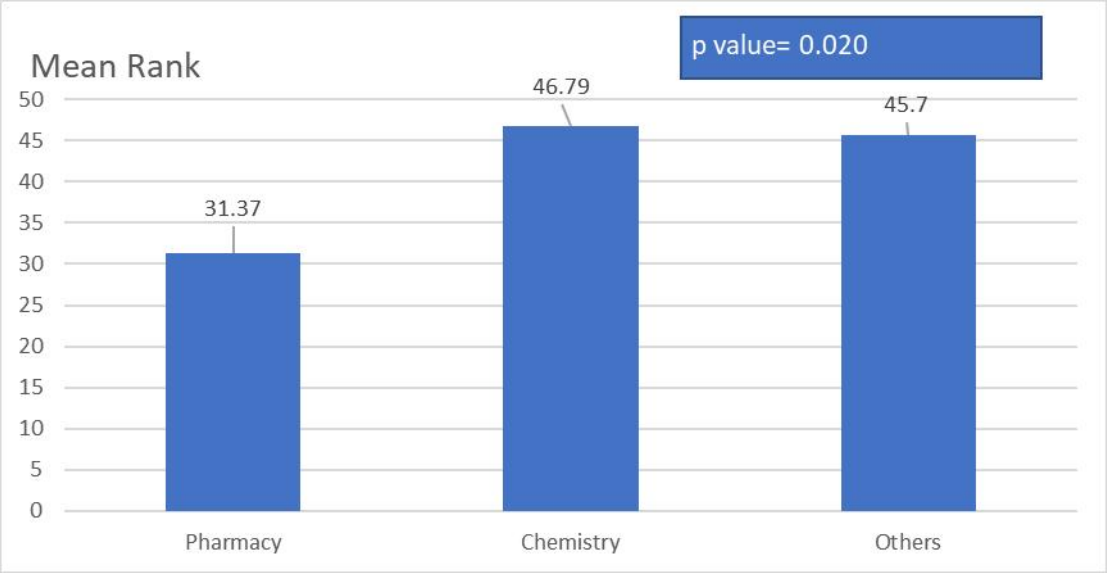

Figure 4.2: Mean Rank Comparison of Awareness Levels by Specialization Groups.

❖ **Results for the Third Hypothesis:**

H_{03A}: There are no statistically significant differences (at p > 0.05) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

The third hypothesis was tested using the same method as the second hypothesis, employing the **Kruskal-Walli's test** to assess whether there are statistically significant differences in the level of awareness of (CMP) among pharmaceutical manufacturing companies in Palestine, based on the Job Category variable, as shown in (Table 4.10).

Table 4.10: Results of the Kruskal-Walli's Test for More Than Two Independent Samples on the Level of Awareness of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine, Based on Job Category.

Fields	d.f	Kruskal-Walli's H	Sig
Average	**3**	**15.557**	**0.001**

d.f = degree of free. **Sig= significant P value**.

The results of the Kruskal-Walli's test, shown in (Table 4.10), indicate a test statistic of (15.557) and a significance level of (p = 0.001), which is below the accepted threshold for statistical significance at 0.05 (p < 0.05). This indicates the presence of statistically significant differences in

the level of awareness of (CMP) among pharmaceutical manufacturing companies in Palestine, based on the Job Category variable. **Therefore, the third hypothesis is rejected**.

To further explore these significant differences, a rank order analysis was performed to pinpoint the specific job categories contributing to the variation. The findings are presented in (Table 4.11).

Table 4.11: Mean Ranks of Study Sample Responses by Job Category.

Fields	Levels	N	Mean Rank
average	**Management and above**	**20**	**46.20**
	Department heads	**18**	**42.56**
	Supervisor	**27**	**46.61**
	Others	**15**	**19.43**

(Table 4.11), presents the mean rank values for the awareness of (CMP) among pharmaceutical manufacturing companies in Palestine, categorized by Job Category.

The results indicate that the highest awareness levels were reported among respondents in the Supervisor category (Mean Rank = 46.61) and Management and above category (Mean Rank = 46.20), followed by Department Heads (Mean Rank = 42.56). In contrast, respondents in the others category recorded the lowest awareness level with a Mean (Rank of 19.43).

These findings confirm that the statistically significant differences identified by the Kruskal-Walli's test are mainly attributed to the higher awareness among Supervisors and Management-level respondents. As shown in (Figure 4.3).

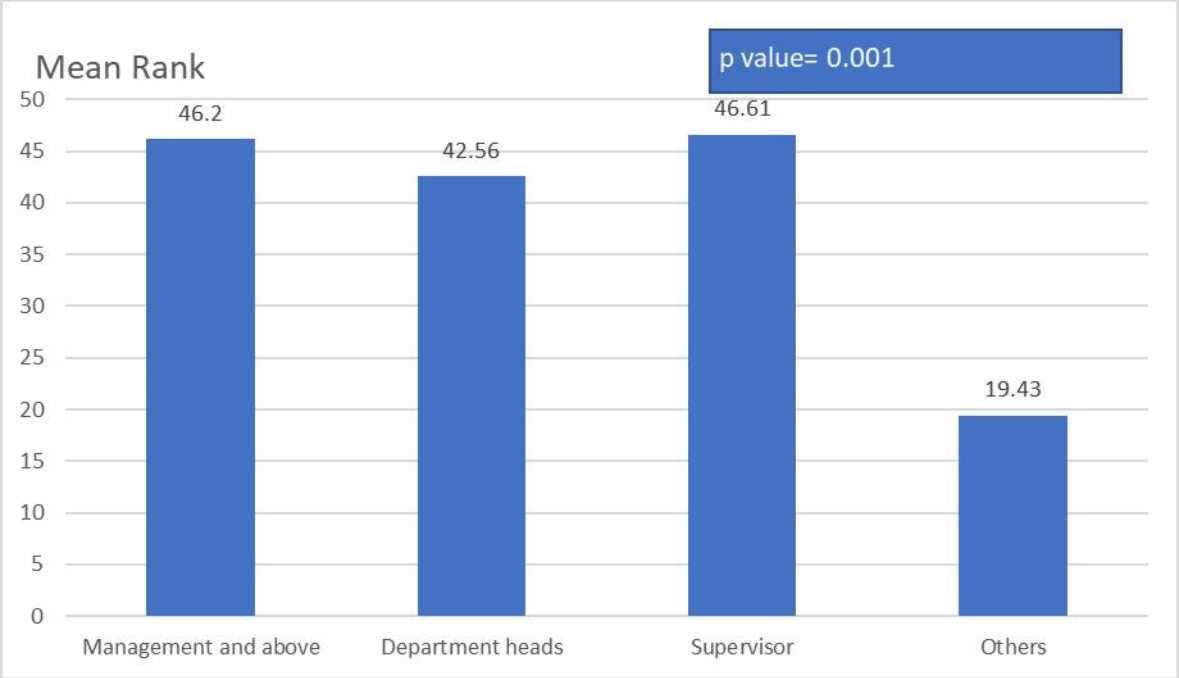

Figure 4.3: Mean Rank Comparison of Awareness Levels by Job Category.

❖ **<u>for the Fourth Hypothesis:</u>**

H_{04A}: There are no statistically significant differences (at p > 0.05) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

The fourth hypothesis was tested using **the Kruskal-Walli's test**, similar to the approach taken for the second and third hypotheses. This analysis aimed to determine if there are statistically significant differences in the level of awareness of (CMP) among pharmaceutical manufacturing companies in Palestine, based on their years of experience in the industry. The results can be found in (Table 4.12).

Table 4.12: Results of the Kruskal-Walli's test for multiple independent samples regarding the Level of Awareness of (CMP) among Pharmaceutical Manufacturing Companies in Palestine, based on years of experience in the pharmaceutical industry.

Fields	d.f	Kruskal-Walli's H	Sig
Average	**3**	**3.012**	**0.390**

d.f=degree of free. **Sig= significant P value**.

It is noted that the value of the Kruskal-Walli's test for the total score (3.012) and the level of significance (p = 0.390) is greater than the threshold for statistical significance at 0.05 (p > 0.05). This indicates that there are no statistically significant differences in the level of awareness of (CMP) among pharmaceutical manufacturing companies in Palestine based on years of experience in the pharmaceutical industry. **Therefore, the fourth hypothesis is accepted**.

Despite this lack of statistical significance, we calculated the ranks to highlight potential differences. (Table 4.13) presents the results of the ranking of mean differences based on years of experience in the pharmaceutical sector. Additionally, (Figure 4.4) visually depicts the distribution of awareness levels across different experience groups, illustrating the observed differences even though they are not statistically significant.

Table 4.13: Mean Ranks of Study Sample Responses by Years of Experience.

Fields	Levels	N	Mean Rank
Average	5 years and less	14	33.64
	From 6-10 years	19	36.82
	From 11-15 years	13	41.42
	16 years and more	34	45.03

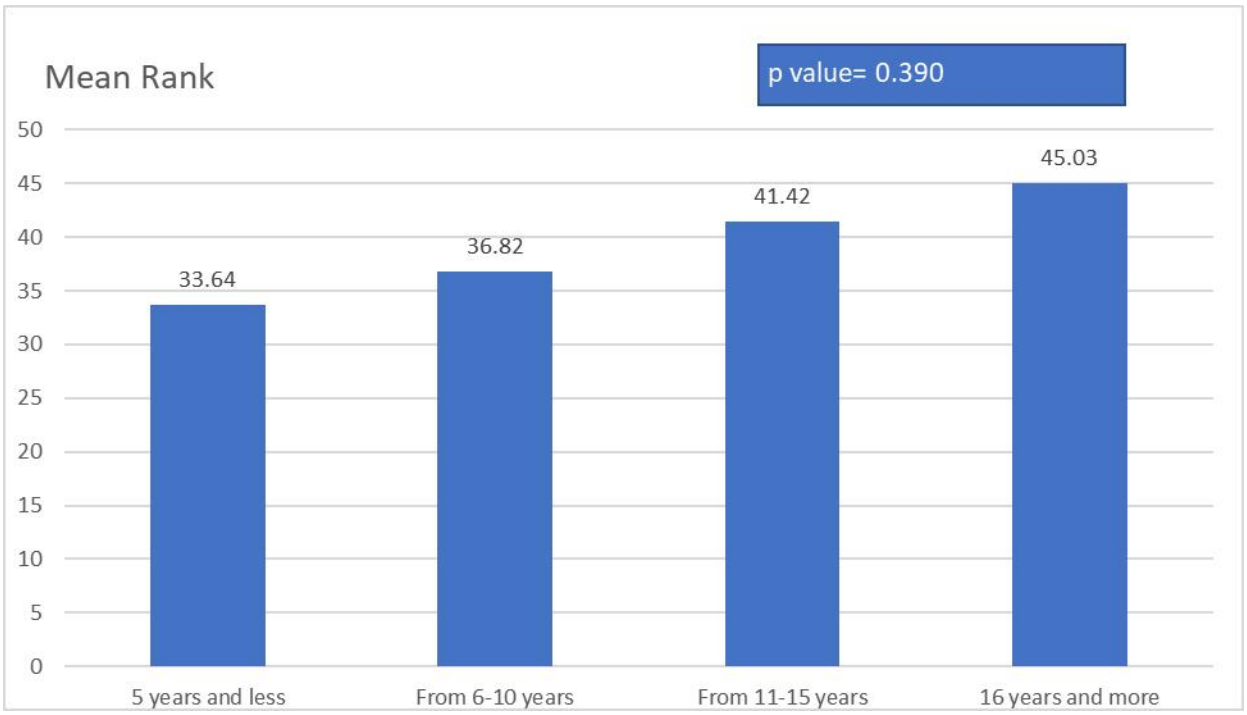

Figure 4.4: Distribution of Awareness Levels Across Different Experience Groups.
Illustrating the Observed Differences Despite the Lack of Statistical Significance.

❖ **Results of the fifth hypothesis:**

H_{05}A: There are no statistically significant differences (at p > 0.05) in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company category.

The fifth hypothesis was tested using **the Kruskal-Walli's test**, which is suitable for analyzing more than two independent samples, as was done for the second, third, and fourth hypotheses. This test aims to determine whether there are statistically significant differences in the awareness levels of (CMP) among pharmaceutical manufacturing companies in Palestine, based on the Company variable. The results of this analysis are presented in (Table 4.14**)**.

Table 4.14: Results of the Kruskal-Walli's test for more than two independent samples regarding the Level of Awareness of (CMP) among pharmaceutical manufacturing companies in Palestine, categorized by company.

Fields	d.f	Kruskal-Walli's H	Sig
Average	**5**	**7.828**	**0.166**

d.f=degree of free. **Sig= significant P value**.

(Table 4.14) shows that the Kruskal-Walli's test value for the total score was (7.828), with a significance level of ($p = 0.166$). This value exceeds the accepted significance threshold of 0.05, indicating that there are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical manufacturing companies in Palestine, based on the Company variable. **Consequently, the fifth hypothesis is accepted**.

Nonetheless, to investigate the direction of the observed differences, the rank order of the groups was calculated. Although these variations did not achieve statistical significance, they may still provide meaningful insights, as shown in (Figure 4.5). The results of the rank comparison are presented in (Table 4.15).

Table 4.15: Mean Ranks of Study Sample Responses Based on Company Variable.

Fields	Levels	N	Mean Rank
Average	Category 1	5	37.30
	Category 2	5	38.50
	Category 3	10	42.75
	Category 4	14	42.36
	Category 5	19	51.18
	Category 6	27	32.15

N = Number of respondents.

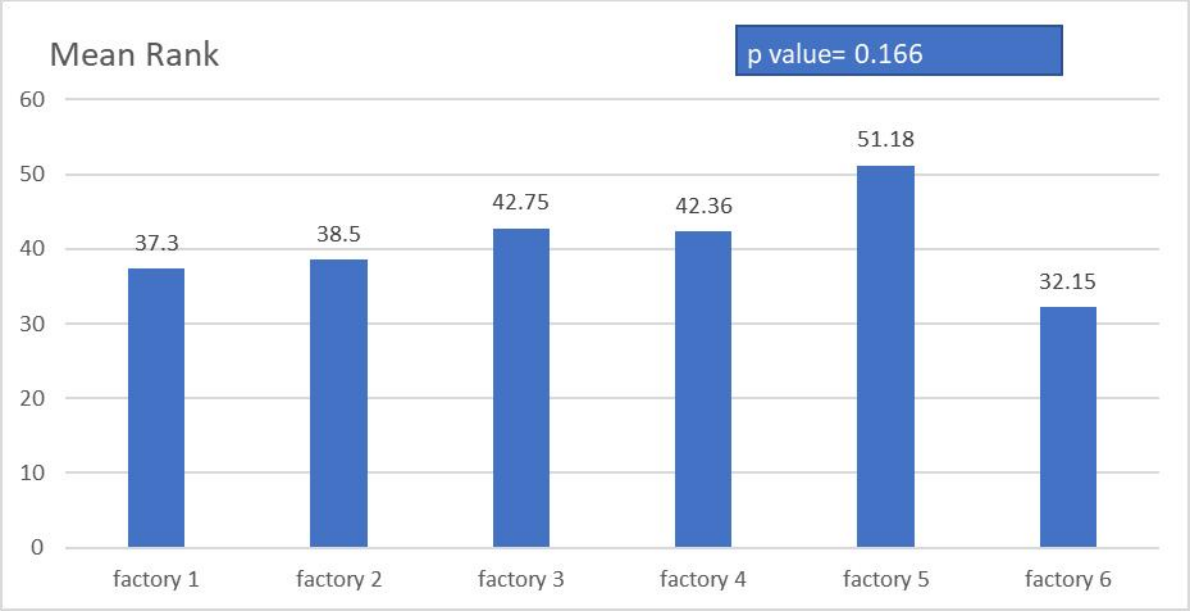

Figure 4.5: Mean Rank Comparison of Awareness Levels by Company Category.

4.3.5 Results for the Fifth Question:

Q5: Are there statistically significant differences in the implementation levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector, and years of experience in the current company)?

This section, like the fourth research question, aims to explore potential differences. To address this, we reformulated the question into specific hypotheses to assess whether implementation levels significantly vary among respondents based on their demographic and general information.

We employed non-parametric tests for the statistical analysis, as outlined in Section 3.13, to ensure compatibility with the data distribution.

The Null hypotheses are stated as follows:

H_{01}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

H_{02}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

H_{03}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

H_{04}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

H_{05}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company category.

❖ **Results of the First Hypothesis:**

H_{01}I: There are no statistically significant differences (at $p > 0.05$) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

The first hypothesis was examined using **the Mann-Whitney U test** for two independent samples. This test aimed to identify any statistically significant differences in the level of implementation of (CMP) among pharmaceutical companies in Palestine, categorized by qualifications. The results, including the mean ranks for each group, are presented in (Table 4.16).

Table 4.16: Results of the Mann-Whitney Test for Two Independent Samples on the Level of Implementation of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine Based on the Qualification Variable.

Fields	Qualification	N	Mean Rank	Value of Z	Sig
Management and Employees	Bachelor's degree	54	39.93	0.319	0.750
	Master degree	26	41.69		
Facility, Equipment, Devices, and Materials	Bachelor's degree	54	41.38	0.489	0.625
	Master degree	26	38.67		
The Supply Chains	Bachelor's degree	54	41.62	0.642	0.521
	Master degree	26	38.17		
Average	Bachelor's degree	54	40.43	**0.041**	**0.967**
	Master degree	26	40.65		

N = Number of respondents. **Mean Rank** = Average rank of responses**.** **Z**= value for test

Sig= significant P value.

The results in the previous table show that the Z value for the total score is (0.041), and the significance level is (0.967), which exceed the threshold for statistical significance at 0.05 ($p > 0.05$). This indicates that there are no statistically significant differences in the implementation of

(CMP) among pharmaceutical manufacturing companies in Palestine, based on the Qualification variable and across all fields. Therefore, **the first hypothesis is accepted**. Additional details are illustrated in (Figure 4.6).

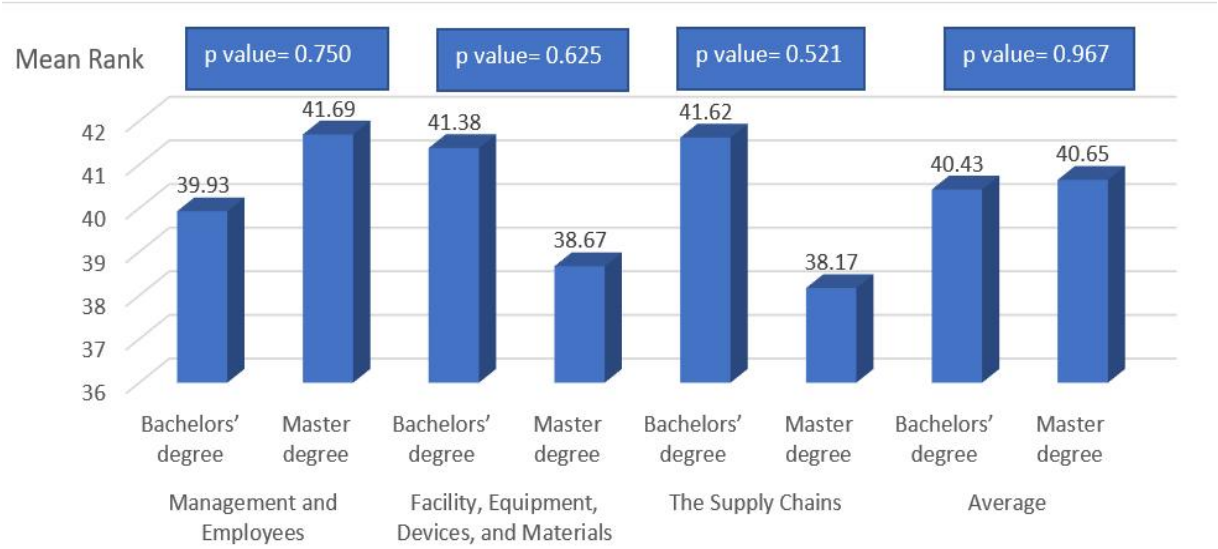

Figure 4.6: Comparison of CMP Implementation Levels Based on Qualification Variables.

❖ **Results of the Second Hypothesis:**

H_{02}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

To examine the second hypothesis regarding the implementation of (CMP) among pharmaceutical companies in Palestine based on specialization, **the Kruskal-Walli's test** was used. This test determines if there are significant differences in CMP implementation across different specializations within the pharmaceutical sector. The results will indicate whether specialization impacts CMP implementation, as shown in (Table 4.17).

Table 4.17: Results of the Kruskal-Walli's test for multiple independent samples regarding the Level of Implementation of (CMP) among Pharmaceutical Manufacturing Companies in Palestine, based on the specialization variable.

Fields(specialization)	d.f	Kruskal-Walli's H	Sig
Management and Employees	2	3.214	0.200
Facility, Equipment, Devices, and Materials	2	6.613	**0.037**
The Supply Chains	2	1.013	0.603
Average	2	**4.868**	**0.088**

d.f=degree of free. **Sig=** significant P value.

The analysis was performed on each of the three-implementation level: **Management and Employees**, **Facility, Equipment, Devices, and Materials**, and **Supply Chains,** as well as the total score. The Kruskal-Walli's test yielded a result of (4.868), with a significance level for the total score of ($p = 0.088$). This value exceeded the threshold of 0.05, indicating no statistically significant differences in the overall implementation level across the specialization groups, therefore, the second hypothesis was accepted.

However, when examining the results for each level individually, it was found that the **Facility, Equipment, Devices, and Materials** level had a p-value lower than 0.05 ($p=0.037$), indicating statistically significant differences in this area. As a result, a further comparison of the mean ranks was conducted to determine which groups contributed to these differences. The detailed results of this comparison are provided in (Table 4.18), and the distribution of these differences is graphically represented in (Figure 4.7).

Table 4.18: Mean Ranks of Study Sample Responses by Specialization

Fields	Levels	N	Mean Rank
Management and Employees	Pharmacy	31	37.45
	Chemistry	26	47.19
	Others	23	37.04
Facility, Equipment, Devices, and Materials	**Pharmacy**	31	**33.60**
	Chemistry	26	**49.42**
	Others	23	**39.72**
The Supply Chains	Pharmacy	31	37.77
	Chemistry	26	40.65
	Others	23	44.00
Average	Pharmacy	31	35.21
	Chemistry	26	48.52
	Others	23	38.57

N = Number of respondents.

The results of the mean rank comparison in (Table 4.18) clearly indicate that the statistically significant differences in the **Facility, Equipment, Devices, and Materials** field are primarily due to the specialization variable.

The ranking shows that respondents with a **Chemistry** specialization recorded the highest mean rank, indicating a higher level of implementation of (CMP) in this field, followed by those from **other** specializations, and then **Pharmacy.**

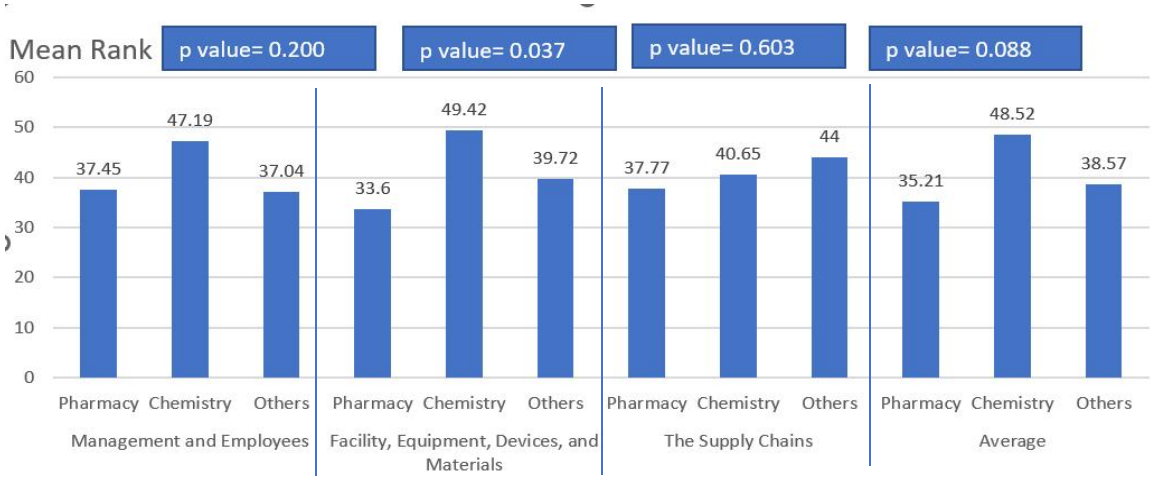

Figure 4.7: Comparison of Mean Ranks for Implementation Levels of Continuous Manufacturing Processes (CMP) by Specialization.

This pattern suggests that participants with a Chemistry background demonstrate a stronger focus on implementing CMP concerning facilities, equipment, devices, and materials, which may be linked to their technical familiarity with operational processes and material handling in pharmaceutical manufacturing environments.

❖ **Results for the Third Hypothesis:**

H_{03}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

To determine if there are statistically significant differences in the implementation levels of (CMP) among pharmaceutical manufacturing companies in Palestine based on the Job Category variable, **the Kruskal-Walli's test** was applied. This test was conducted for each category individually: Management and Employees, Facilities, Equipment, Devices, Materials, and Supply Chains, as well as for the overall average score. The results are summarized in(table 4.19)

Table 4.19: Results of the Kruskal-Walli's Test for Multiple Independent Samples on the Level of Implementation of (CMP) Among Pharmaceutical Manufacturing Companies in Palestine, Based on Job Category.

Fields (Jop-title)	d.f	Kruskal-Walli's H	Sig
Management and Employees	3	7.895	0.048
Facility, Equipment, Devices, and Materials	3	7.804	0.050
The Supply Chains	3	1.894	0.595
Average	3	**8.519**	**0.036**

d.f=degree of free. **Sig= significant P value**.

The findings reveal a **Kruskal-Walli's Test** is (8.519) for the total score, with a significance level of (0.036**)**, which is below the accepted threshold of 0.05 ($p < 0.05$)**.** This indicates statistically significant differences in the implementation of CMP among respondents based on the Job Category variable**.**

Notable differences were observed in the areas of **Management and Employees** and **Facilities, Equipment, Devices, and Materials**. However, the **Supply Chains** field did not exhibit any statistically significant differences ($p = 0.595$). Consequently, the average p-value across the fields led to **the rejection of the third hypothesis**, suggesting that job roles within pharmaceutical companies significantly influence the level of CMP implementation. To clarify these differences, we calculated the mean rank values for each job category, as presented in (Table 4.20).

Table 4.20: Results of the Mean Rank Comparison for Implementation Levels by Job Category.

Fields	Levels	N	Mean Rank
Management and Employees	Management and above	20	43.85
	Department heads	18	39.92
	Supervisor	**27**	**46.37**
	Others	15	26.17
Facility, Equipment, Devices, and Materials	Management and above	20	43.28
	Department heads	18	42.14
	Supervisor	**27**	**45.59**
	Others	15	25.67
The Supply Chains	Management and above	20	39.63
	Department heads	18	41.83
	Supervisor	**27**	**43.81**
	Others	15	34.10
Average	Management and above	20	43.60
	Department heads	18	40.31
	Supervisor	**27**	**46.67**
	Others	15	25.50

N = Number of respondents.

The analysis of mean ranks revealed that the Supervisor job category consistently received the highest scores in most areas. This suggests that supervisors are more actively involved in implementing CMP, likely due to their direct operational responsibilities. (Figure 4.8) visually represents these ranking differences, illustrating the distribution of implementation levels across various job categories.

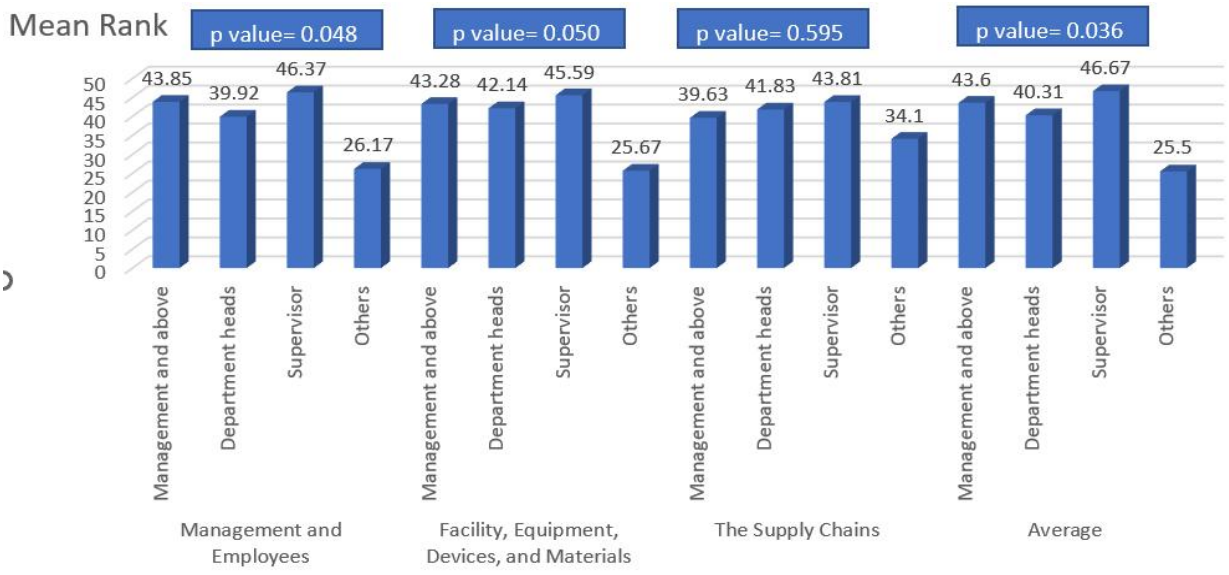

Figure 4.8: Mean Rank Comparison of Continuous Manufacturing Process (CMP) Implementation Levels by Job Category.

❖ **Results of the Fourth Hypothesis:**

H_{04}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

To test this hypothesis, **the Kruskal-Walli's test** was used to identify statistically significant differences among the different experience groups. The results are presented in (Table 4.21).

Table 4.21: Results of the Kruskal-Walli's Test for multiple independent samples regarding the Level of Implementation of (CMP) among pharmaceutical manufacturing companies in Palestine, based on years of experience in the pharmaceutical industry.

fields	d.f	Kruskal-Walli's H	Sig
Management and Employees	3	1.204	0.752
Facility, Equipment, Devices, and Materials	3	5.581	0.134
The Supply Chains	3	1.329	0.722
Average	3	1.842	**0.606**

d.f=degree of free. **Sig= significant P value.**

The test results indicate a total score of (1.842) and a significance level of (0.606), which exceeds the accepted threshold of 0.05 ($p > 0.05$). This suggests that there are no statistically significant differences in the implementation levels of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine, based on the variable of years of experience in the pharmaceutical industry.

This lack of significance was consistent across all fields. Consequently, **the fourth hypothesis is accepted**. To further analyze the results, we calculated the mean ranks for each category, as presented in (Table 4.22).

Table 4.22: Mean Rank Results of Respondents Answers Based on Years of Experience in the Pharmaceutical Industry Sector.

Fields	Levels	N	Mean Rank
Management and Employees	5 years and less	14	36.21
	From 6-10 years	19	37.95
	From 11-15 years	13	41.88
	16 years and more	34	43.16
Facility, Equipment, Devices, and Materials	5 years and less	14	34.00
	From 6-10 years	19	39.00
	From 11-15 years	13	53.77
	16 years and more	34	38.94
The Supply Chains	5 years and less	14	36.46
	From 6-10 years	19	37.76
	From 11-15 years	13	41.12
	16 years and more	34	43.46
Average	5 years and less	14	34.32
	From 6-10 years	19	39.34
	From 11-15 years	13	46.00
	16 years and more	34	41.59

N = Number of respondents.

The ranking results indicated no significant differences related to years of experience, as supported by the data. Furthermore, (Figure 4.9), visually illustrates the mean rank differences and the distribution of implementation levels across different years of experience in the pharmaceutical industry sector.

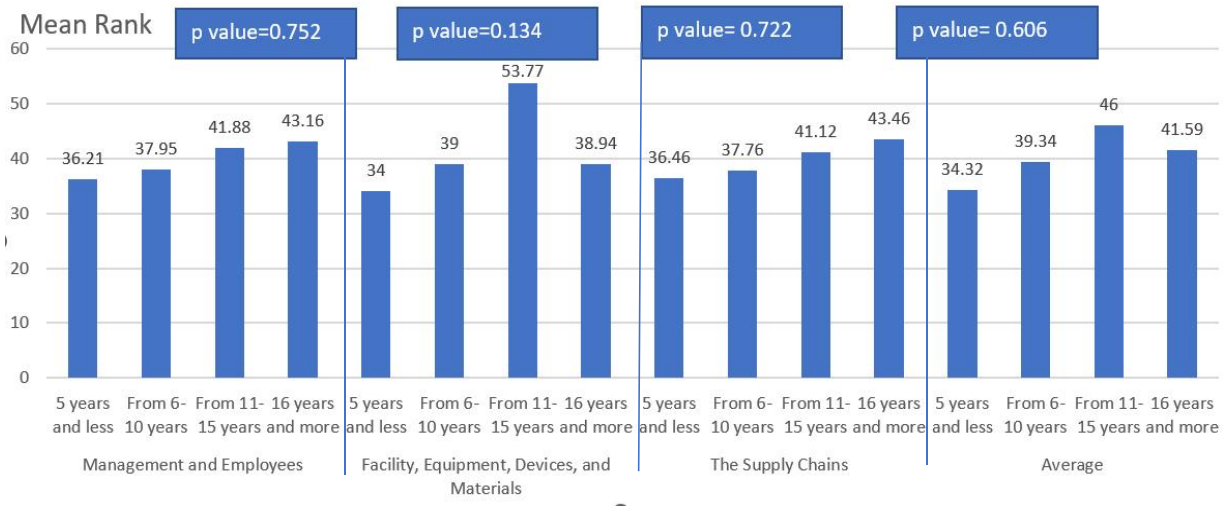

Figure 4.9: Distribution of Mean Ranks for Implementation Levels by Years of Experience in the Pharmaceutical Industry.

❖ **Results of the fifth hypothesis:**

H_{05}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company category.

Following the method used for the second, third, and fourth hypotheses, **the Kruskal-Walli's test** was applied to analyze the fifth hypothesis. It was used to assess whether there are statistically significant differences in the implementation levels of (CMP) among these companies, based on company category. The result is presented in (Table 4.23).

Table 4.23: Results of the Kruskal-Walli's Test for the Level of Implementation of (CMP) Among Pharmaceutical Companies in Palestine, Based on Company Type.

Fields	d.f	Kruskal-Walli's H	Sig
Management and Employees	5	21.091	**0.001**
Facility, Equipment, Devices, and Materials	5	32.160	**0.000**
The Supply Chains	5	21.264	**0.001**
Average	5	29.263	**0.000**

d.f=degree of free. **Sig= significant P value.**

(Table 4.22) presents the Kruskal-Walli's test for the total score at (29.263), with a significance level of (0.000), which is below the accepted threshold of 0.05 ($p < 0.05$). This indicates statistically significant differences in the level of CMP implementation among pharmaceutical manufacturing companies in Palestine, based on the company category variable and across all measured fields. **Consequently, the fifth hypothesis was rejected.**

To clarify the source of these differences, the mean rank values for each company category have been calculated and summarized in (Table 4.24). The distribution of these ranking results is visually represented in (Figure 4.10).

Table 4.24-a: Mean Rank Results of Study Sample Responses by Company Category.

Fields	Levels	N	Mean Rank
Management and Employees	Category 1	5	36.50
	Category 2	5	25.10
	Category 3	10	44.75
	Category 4	14	32.07
	Category 5	**19**	**60.21**

Table 4.24-b: Mean Rank Results of Study Sample Responses by Company Category.

	Category 6	27	33.02
Facility, Equipment, Devices, and Materials	Category 1	5	38.50
	Category 2	5	29.90
	Category 3	10	49.50
	Category 4	14	29.32
	Category 5	**19**	**63.97**
	Category 6	27	28.78
The Supply Chains	Category 1	5	39.60
	Category 2	5	19.10
	Category 3	10	42.55
	Category 4	14	26.86
	Category 5	**19**	**57.87**
	Category 6	27	38.72
Average	Category 1	5	37.90
	Category 2	5	26.80
	Category 3	10	48.00
	Category 4	14	29.43
	Category 5	**19**	**63.24**
	Category 6	27	30.48

N = Number of respondents.

The analysis of the mean rank values shows that respondents from **Company Category 5** reported the highest levels of (CMP) implementation across all measured fields. This finding suggests that the statistically significant differences identified by the Kruskal-Walli's test are largely attributable to this group.

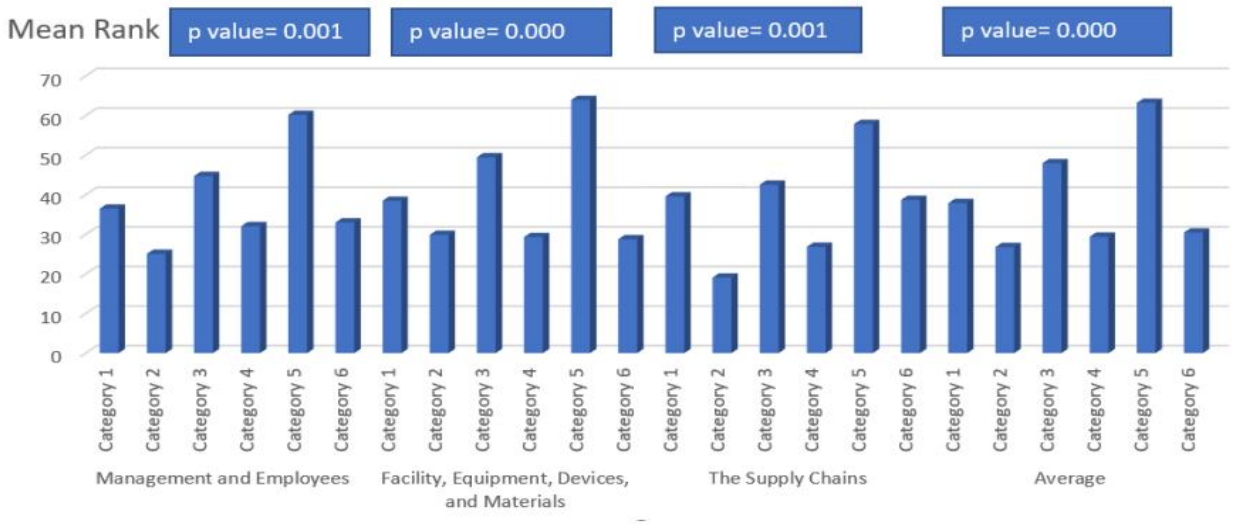

Figure 4.10: Distribution of Mean Ranks for CMP Implementation Levels by Company Category.

Chapter Five:

Discussion.

5.1 Introduction.

This chapter provides a discussion and interpretation of the findings from the study titled **(Assessment of Awareness, Implementation, and Barriers to Continuous Manufacturing Processes (CMP) Among Pharmaceutical Manufacturing Companies in Palestine)**. The main goal is to situate these findings within the Palestinian pharmaceutical industry, connect them to relevant theoretical and empirical literature and compare them with previous research, and identify practical implications that could guide future strategies for enhancing continuous manufacturing in this local context.

5.2 Discussion of Research Question One: Awareness of CMP.

Q1: What is the level of awareness regarding Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

The study findings indicate that pharmaceutical manufacturing companies in Palestine possess a strong awareness of Continuous Manufacturing Processes (CMP), with a mean score of (3.68), corresponding to (73.6%) and classified as high level on the study rating scale. However, a closer examination shows that this awareness is primarily operational, arising from hands on experience in the industry rather than from a strong technical or academic foundation, these findings are consistent with (Yu & Lee, 2018), who emphasized the need to raise awareness among regulatory agencies and manufacturers to transition CMP from theory to practice.

Notably, the highest-rated benefits of CMP include its capacity to improve product quality (mean = 4.10), distinguish itself from traditional batch processing (mean = 4.09), and enhance production efficiency (mean = 4.05). Despite these strengths, the data demonstrated notable gaps in both technical and academic competence. The lowest-rated areas were formal training (2.94), academic qualifications in the field (2.88), and exposure to CMP during undergraduate studies (2.60). These findings indicate a lack of institutional and educational support, suggesting a superficial understanding of the technology and its requirements.

To address this gap, it is essential to integrate CMP topics into academic curricula and offer specialized training programs that enhance both theoretical knowledge and practical skills. Pharmaceutical companies should invest in staff training and partner with academic institutions to create dedicated CMP courses to promote the sustainable adoption of this advanced manufacturing approach.

5.3 Discussion of Research Question Two: Implementation of CMP.

Q2: What is the level of implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

The implementation of Continuous Manufacturing Processes (CMP) in Palestinian pharmaceutical companies is moderate, with a mean score of (3.46) and a standard deviation of (0.688), indicating a partial implementation rate of (69.3%). Although there is a general interest in CMP, achieving full scale adoption remains a challenge. The analysis of implementation was organized into three main levels: **management and employees**, **facility, equipment, devices, and materials supply chains.** The following paragraphs provide a detailed discussion of the results for each level of implementation.

- ✓ **Management and Employees:** The overall score for this field is (3.35), indicating a moderate commitment to transitioning to CMP. Management demonstrates a moderate interest, scoring (3.54) for the statement, (Our management is interested in converting from batch manufacturing to CMP). However, there are noticeable gaps in employee readiness and the formation of specialized teams, reflected in a lower score of (3.14) for the statement, (Our management recruited experienced employees in CMP). This difference indicates that although management is interested in adopting CMP, effective practices, particularly in employee training, are still insufficient.

  These finding are consistent with (Markarian, 2021), which emphasizes that workforce readiness is a significant challenge, exacerbated by a shortage of specialized training programs. The connection underscores the necessity for pharmaceutical companies to invest in customized training initiatives to adequately prepare employees for the implementation of continuous manufacturing processes (CMP).

- ✓ **Facility, Equipment, Devices, and Materials**: This field demonstrates a moderate level of implementation, with an overall score of (3.53), particularly in ensuring that materials comply with CMP specifications (mean = 3.88). In contrast, facility layout and equipment suitability receive lower scores (mean = 3.09), suggesting that the physical infrastructure is not fully optimized for CMP. The substantial costs and complexities associated with upgrading facilities and acquiring specialized equipment likely pose significant barriers to complete implementation. These findings are consistent with Jennifer Markarian observation (2021), which emphasized that inadequate infrastructure, including outdated facility layouts and the high costs associated with upgrading to CMP compatible equipment, presents a significant obstacle for many pharmaceutical companies.
- ✓ **Supply Chains**: The supply chain demonstrates a moderate coordination with CMP, achieving a score of (3.57), which reflects a (71.5%) implementation rate. Items like Our

contracts with suppliers are suitable for CMP and Our suppliers have quality certificates in CMP were ranked moderately, demonstrating that pharmaceutical companies have made efforts to align supplier relationships with CMP requirements. However, logistical challenges remain, particularly regarding delivery dates, as evidenced by the moderate scores in Our supplier's delivery dates are suitable for CMP. These challenges indicate a need for enhanced coordination and reliability in the supply chain to fully meet CMP requirements. These findings are consistent with those reported by (United States Pharmacopeia, 2023), where logistical issues within pharmaceutical supply chains, especially the ability to meet the real-time demands of continuous production, remain a major barrier to successful implementation.

These implementation gaps are further addressed in the recommendations section, which presents targeted strategies to enhance CMP adoption in Palestine.

5.4 Discussion of Research Question Three: Barriers to CMP.

Q3: What is the extent of barriers to implementing Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine?

The study findings indicate that the observed barriers to implementing Continuous Manufacturing Processes (CMP) in Palestinian pharmaceutical companies are of moderate difficulty (66.7%), with an average score of (3.33). These barriers include **regulatory, financial, and human-related challenges,** all of which significantly impact the companies' ability to effectively adopt CMP.

- ✓ **Regulatory Barriers:** The study identified key regulatory barriers, particularly concerning continuous research and development and ongoing process optimization. The statements CMP involves extensive research and development (mean = 4.04) and (CMP requires extensive process optimization) with (mean = 4.02) received the highest mean scores. These findings indicate that Palestinian companies encounter significant challenges in harmonizing continuous manufacturing technologies with market demands and maintaining high-quality standards, necessitating considerable investment in R&D efforts.

These findings are consistent with similar regulatory and operational concerns noted in global literature. Hock et al. (2021) and Domokos et al. (2021) underscored the substantial upfront investments required for research and development, automation, and system integration, noting that these costs are significant barriers to adopting continuous manufacturing processes (CMP), particularly for smaller companies and those in developing economies (Domokos et al., 2021; Hock et al., 2021).

Similarly, Lee et al. (2015) emphasized the critical role of regulatory frameworks in either facilitating or hindering the shift to continuous manufacturing (CM). They noted that the FDA has worked to provide guidance and flexibility through initiatives like Quality by Design (QbD) and Process Analytical Technology (PAT), which enable real-time process optimization (Lee et al., 2015). Additionally, Borkar et al. (2017) addressed existing regulatory gaps and the necessity for harmonized guidelines to support the implementation of CM systems (Borkar et al., 2017).

- ✓ **Financial Barriers:** The financial obstacle of implementing CMP emerged as a significant obstacle. The statement (Adopting CMP with its underlying technologies is expensive)

received a mean rating of (3.75), making it one of the top-rated barriers. Furthermore, the costs associated with expanding physical space for CMP operations, which had a mean rating of (3.52), were also recognized as a major constraint. This illustrates the economic pressures companies face when planning for CMP integration.

These findings are consistent with previous literature that points to the significant capital investment needed for transitioning to continuous manufacturing systems. For example, Hock et al. (2021) underscored those high initial costs, particularly for automation and PAT technologies, pose a major challenge for pharmaceutical companies, especially in the generics sector (Hock et al., 2021). Similarly, Schaber et al. (2011) conducted a case study that demonstrated, through economic modeling, that while long-term savings are achievable, the transition to CM platforms necessitates heavy initial capital expenditures (Domokos et al., 2021). Furthermore, Rossi (2022) emphasized in his investment analysis that, despite the long-term financial advantages of continuous manufacturing, the transition requires a significant investment in infrastructure and process integration, which can stress companies with limited financial flexibility (Rossi, 2022). Thus, the financial barriers identified in this study are not only observed locally, but also reflect global concerns widely emphasized in pharmaceutical literature.

- ✓ **Human-Related Barriers:** These barriers come from a lack of adequate experience and qualifications within the workforce. like (Our workers are not sufficiently qualified to operate CMP) with (mean = 3.05) and (Our workers are not sufficiently experienced in CMP) with (mean = 3.15) show a notable gap in employee readiness. These results underscore the urgent need for training and educational programs to provide the workforce with the technical skills necessary for effective operation and management of CMP systems. This connects with Jennifer Markarian's observation (2021) that the shortage of skilled personnel poses a significant challenge in the pharmaceutical industry. She emphasizes the importance of workforce training and retention to ensure efficient manufacturing processes. Our findings further support the necessity for training programs to address the skills gap in CMP implementation (Markarian, 2021).

- ✓ **Logistical Barriers:** Logistical challenges represent a significant obstacle. The statement (CMP requires complex logistical issues) with (mean = 3.14) reflects difficulties related to supply chain management and the availability of suitable materials and equipment for CMP operations. These concerns may hinder the efficient implementation of continuous processes This observation closely parallels the findings from the USP Workshop on Identifying and Addressing Barriers to Continuous Manufacturing Adoption (2023). The workshop highlighted the complexities of managing global supply chains and the need to establish resilient logistics networks. It pointed out that logistical challenges (especially in sourcing, equipment availability, and stakeholder coordination) pose significant obstacles to successful continuous manufacturing process (CMP) implementation. Consequently, the logistical barriers identified in our study reflect these broader, globally recognized challenges, which necessitate strategic planning and cross-sector collaboration to overcome (USP, 2023).

- ✓ **Minimal Perceived Barriers**: Conversely, the items that received the lowest mean scores were associated with time and operational complexity. For example, the statements (Adopting CMP is time-consuming) with (mean = 2.54) and (CMP system is complex to operate) with (mean = 2.85) were rated as the least concerning barriers. This suggests that companies do

not view time constraints or system complexity as significant obstacles when compared to financial and human-related challenges.

In summary, overcoming these barriers necessitates a coordinated approach that includes capacity building, regulatory facilitation, and financial support, which are explored further in the following recommendations.

5.5 Discussion of Research Question Four: Demographic Differences in Awareness.

Q4: Are there statistically significant differences in the awareness levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector, and company category)?

H_{01}A: There are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

The **Mann-Whitney U test** produced a (p-value of 0.704), which exceeds the significance threshold of 0.05 ($p > 0.05$). This indicates that the differences in awareness of continuous manufacturing processes (CMP) between those with Bachelor's and Master's degrees were not statistically significant. Hence, formal educational level alone may not play a crucial role in shaping employees' awareness of CMP. Instead, exposure to CMP concepts may rely more on on-the-job training, company-specific programs, or professional development courses than on academic qualifications. Additionally, the close proximity in mean ranks ((41.19) for Bachelor vs. (39.08) for Master) further supports the conclusion that both groups have similar levels of awareness.

H_{02}A: There are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

The **Kruskal-Walli's Test** yielded a (p-value of 0.020), which is below the significance threshold of 0.05 ($p < 0.05$). This indicates statistically significant differences in awareness of CMP across various specializations. Mean rank analysis showed that respondents with Chemistry backgrounds had the highest awareness (mean rank = 46.79), followed by those in the (Others) category with (mean rank = 45.70). In contrast, Pharmacy graduates exhibited the lowest awareness (mean rank = 31.37). This difference may be attributed to curricular variations; chemistry-related fields typically emphasize industrial processes and production technologies, potentially enhancing familiarity with modern manufacturing paradigms like CMP. Conversely, pharmacy programs in Palestine may prioritize clinical, formulation, and pharmacological content, limiting direct exposure to industrial manufacturing systems unless supplemented with additional training.

H_{03}A: There are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

The **Kruskal-Walli's Test** yielded a (p-value of 0.001), which is below the threshold of 0.05 ($p < 0.05$), indicating a statistically significant difference in awareness of CMP across job categories. The highest awareness was observed among supervisors (mean rank = 46.61) and management (46.20), followed by department heads (42.56). In contrast, employees categorized as "Others" demonstrated the lowest awareness (mean rank = 19.43). These findings reveal a hierarchical knowledge gradient within companies, where individuals in leadership and supervisory positions are more likely to engage with strategic innovations like CMP, often due to their roles in operational planning, regulatory compliance, or decision-making. Conversely, staff in support or administrative roles may have limited access to training or discussions on advanced manufacturing strategies.

H_{04}A: There are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

The **Kruskal-Walli's** test produced a (p-value of 0.390), which is above the significance threshold of 0.05 ($p > 0.05$). This indicates that no statistically significant differences in awareness of CMP are present based on years of experience. However, the mean ranks show a progressive trend: awareness increases with experience, rising from (33.64) for those with 5 years or less to (45.03) for individuals with 16 years or more. This suggests a potential experiential learning effect, where individuals gain knowledge over time through cumulative exposure, internal training, or professional networking. Nevertheless, the differences were not substantial enough to achieve statistical significance, likely due to limited sample sizes in certain experience groups or the influence of standardized internal training programs that reduce awareness gaps between junior and senior staff members.

H_{05}A: There are no statistically significant differences in awareness of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the company category.

The Kruskal-Walli's test yielded a **p-value of 0.166** ($P > 0.05$), indicating no statistically significant differences in awareness based on company. Although differences in mean ranks were observed such as higher awareness levels in Category 5 and lower levels in Category 6, the (p value of 0.166) suggests that these differences are not statistically significant. This lack of significance may be due to similarities in training opportunities, managerial priorities, or exposure to CMP practices across different company types. Additionally, unequal group sizes and limited samples in some categories may have diminished the statistical power necessary to detect significant differences. Thus, while company classification seems to influence awareness, it is not strong or consistent enough to result in statistically significant variations.

The analysis indicates that awareness of CMP varies significantly based on specialization and job title, while educational qualifications, years of experience, and company type do not exhibit statistically significant differences. These findings highlight the importance of professional roles and academic backgrounds in shaping awareness of innovative manufacturing practices.

5.6 Discussion of Research Question Five: Demographic Differences in Implementation.

Q5: Are there statistically significant differences in the implementation levels of CMP among respondents from pharmaceutical companies in Palestine based on demographic and professional variables (educational qualification, field of specialization, job title, years of experience in the pharmaceutical sector, and company category.)?

H_{01}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the qualification variable.

The **Mann-Whitney U test** was conducted to determine if there are significant differences in the implementation of Continuous Manufacturing Processes (CMP) between respondents with a Bachelor's degree and those with a Master's degree. The resulting (p-value of 0.967) exceeds the threshold of 0.05 ($p > 0.05$), indicating that there are no statistically significant differences in CMP implementation between the two groups.

The mean ranks for the Bachelor's group (40.43) and the Master's group (40.65) show only a minimal difference, reinforcing the conclusion that educational qualifications do not significantly impact the implementation of continuous manufacturing processes. This implies that on-the-job training and exposure to company specific programs may have a greater influence on CMP implementation than academic qualifications alone. It appears that hands on experience and professional development courses play a more critical role in the practical application of these processes than formal education.

H_{02}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the specialization variable.

The **Kruskal-Walli's test** was employed to evaluate differences in CMP implementation among the respondents' various academic specializations. A (p-value of 0.088) was obtained, which exceeds the threshold of 0.05 ($p > 0.05$), indicating no statistically significant differences in CMP implementation across the specializations. However, for the item concerning field facilities, equipment, and materials, the Kruskal-Walli's test produced a (p-value of 0.037). Consequently, mean ranks were analyzed to identify which group contributed to these observed differences.

Average mean ranks indicate that respondents with chemistry backgrounds have a higher level of CMP implementation (45.79) compared to those from pharmacy backgrounds (38.74). Although this difference is not statistically significant, it suggests that chemistry related fields may provide a deeper understanding of industrial processes, including modern manufacturing paradigms like CMP. In contrast, pharmacy curricula primarily focus on clinical and pharmacological content, which may limit exposure to industrial manufacturing unless supplemented by additional training or industry specific knowledge.

H_{03}I: There are no statistically significant differences (at p > 0.05) in Implementation of Continuous Manufacturing Processes (CMP) among pharmaceutical companies in Palestine based on the job category variable.

The Kruskal-Walli's Test yielded a (p-value of 0.036), which is below significance level of 0.05 ($p < 0.05$). This indicates that there are statistically significant differences in CMP implementation across different job categories.

The field-specific p-values indicated that the statistically significant differences in implementation were primarily related to management, facilities, equipment, and materials. In contrast, the supply chain subgroup did not demonstrate a statistically significant difference, as evidenced by a (p-value of 0.595).

This lack of significance may be attributed to the indirect role that supply chain personnel typically have in the core technical implementation of CMP. Their responsibilities often center on logistics and coordination, rather than direct involvement with manufacturing equipment or process design, which are the primary areas affected by CMP technologies.

The average mean ranks indicate that supervisors (46.67) and management (43.6) achieved the highest implementation scores, followed by department heads (40.31). In contrast, the "others" category had the lowest mean rank at (25.50). These findings illustrate a hierarchical knowledge gradient within pharmaceutical companies, suggesting that individuals in leadership positions are more likely to engage with strategic innovations like CMP. This engagement is likely due to their active roles in operational planning, regulatory compliance, and decision-making. Conversely, staff in support or administrative roles may have limited exposure to training or discussions about advanced manufacturing technologies.

H_{04}I: There are no statistically significant differences (at $p > 0.05$) in the implementation of continuous manufacturing processes (CMP) among pharmaceutical companies in Palestine based on years of experience in the pharmaceutical industry.

The **Kruskal-Walli's test** produced a (p-value of 0.606**)**, which exceeds the threshold of 0.05 ($p > 0.05$), indicates that there are no statistically significant differences in CMP implementation based on years of experience in the pharmaceutical industry.

The average mean ranks indicate a clear trend in CMP implementation as years of experience increase: it rises from (34.32) for individuals with five years or less of experience to (41.59) for those with 16 years or more. This suggests a potential experiential learning effect, where individuals accumulate knowledge and skills over time through exposure to industry practices, internal training, or professional networking. However, the differences in ranks were not statistically significant, possibly due to limited sample sizes in some experience groups or the influence of standardized internal training programs, which may narrow the awareness gap between less experienced and more experienced employees.

H_{05}I: There are no statistically significant differences (at $p > 0.05$) in the implementation of continuous manufacturing processes (CMP) among pharmaceutical companies in Palestine based on the company category.

The Kruskal-Walli's test showed a p-value of 0.000, significantly lower than the standard significance level of 0.05 ($p < 0.05$). This indicates that statistically significant differences exist in the implementation of Continuous Manufacturing Processes (CMP) across different company categories.

The average mean ranks offer clear insight into the differences among the categories: Category 5 companies had the highest implementation rank (63.24), followed by Category 3 (48.00), while Category 2 scored the lowest (26.80). This notable contrast in ranks suggests that larger or more advanced companies may possess superior capabilities, infrastructure, or a stronger strategic orientation toward modern manufacturing innovations like CMP.

The significantly higher implementation rates in Category 5 companies may be due to their greater investment in technology, stronger regulatory involvement, and the presence of specialized quality and innovation teams. These companies usually focus on improving processes and following international standards, which are consistent with CMP principles.

These findings indicate that there is a structural variation within the Palestinian pharmaceutical sector, with significant differences in resource management, innovation capacity, and regulatory maturity among different company categories.

5.7 Integrated Analysis: Linking All Research Questions.

This section offers the analysis of the study findings by integrating the results from all three research questions: awareness, implementation, and barriers. The relationship between awareness, implementation, and barriers regarding Continuous Manufacturing Processes (CMP) in Palestinian pharmaceutical companies reveals a complex dynamic. Although awareness levels are generally high, this awareness tends to be primarily theoretical and superficial, driven more by knowledge of the benefits than by formal education or structured training. This suggests that while respondents acknowledge CMP as a valuable innovation, their understanding may lack practical or technical depth.

Implementation, however, exhibits a selective and uneven pattern. Companies often engage in partial adoption, typically limited to specific departments or stages, such as supply chain or quality control. This indicates an opportunistic approach rather than a systematic one. It suggests that the challenges to implementation arise not from a rejection of CMP, but from the structural limitations and contextual constraints faced by these companies.

The barriers identified by participants provide a clearer insight into the situation. These challenges are not mainly caused by personal hesitation or a lack of effort, but from issues at the organizational, technical, and legal levels. Key problems include outdated production systems, limited access to modern machinery, financial limitations, and unclear rules on how to shift from traditional batch production to continuous processes. Additionally the differences between different job positions and areas of work show a gap in knowledge and responsibility. Individuals in higher positions tend to have a greater understanding and involvement, whereas those in lower roles are often less involved.

The results indicate a gap between knowledge and action: simply being aware of CMP does not guarantee its implementation, as many challenges lie beyond individual control. To close this gap, it is essential to enhance education and training on CMP and address the broader issues hindering progress. This may require support from policymakers, improved equipment and facilities, and a clear national strategy for advancing medicine production.

5.8 Conclusion.

This chapter synthesizes the study findings by exploring the awareness, implementation, and barriers associated with Continuous Manufacturing Processes (CMP) in pharmaceutical companies in Palestine. The analysis indicates that while there is a relatively high general awareness of CMP, it is uneven and primarily conceptual, often lacking practical depth.

Implementation efforts exist but are limited, influenced more by institutional capacity and leadership priorities rather than by individual knowledge or experience. Additionally, barriers to CMP adoption are largely structural instead of attitudinal, highlighting the infrastructural limitations, regulatory gaps, and resource constraints.

The findings emphasize a crucial insight: awareness alone does not ensure successful implementation. Transitioning to effective and sustainable adoption of CMP requires more than just informed personnel; it necessitates systemic readiness, targeted investments, and supportive policies. Closing the gap between awareness and action is essential for enabling pharmaceutical companies in Palestine to stay aligned with global manufacturing innovations and enhance operational efficiency. These insights set the foundation for the final chapter, which presents actionable recommendations based on the study's findings.

8.9 Recommendations.

This study findings lead to several key recommendations aimed at improving awareness, implementation, and addressing barriers to Continuous Manufacturing Processes (CMP) in Palestinian pharmaceutical companies:

- ✓ **Enhanced Training Programs:** Due to the high awareness of CMP but its selective implementation, it is recommended that pharmaceutical companies develop training programs. These programs should emphasize practical elements of CMP, such as facility design, equipment optimization, and supply chain integration. This approach will ensure that employees at all levels possess the skills needed to effectively implement and sustain CMP practices.
- ✓ **Policy and Regulatory Support:** Policymakers in Palestine should focus on developing frameworks and regulations that encourage the adoption of advanced manufacturing technologies, such as CMP. By establishing clear guidelines for implementing these processes and providing financial incentives, they can motivate pharmaceutical companies to invest in and adopt these technologies.
- ✓ **Addressing Structural Barriers:** It is essential to eliminate the structural barriers identified in this study, including resource constraints and inadequate infrastructure. Companies should collaborate with government agencies, industry groups, and international organizations to obtain the resources and infrastructure needed to support CMP.
- ✓ **Promote Cross-Sector Collaboration:** Encouraging collaboration among pharmaceutical companies, academia, and industry experts can bridge knowledge gaps and facilitate the exchange of innovative manufacturing practices. Hosting regular industry forums, conferences, and partnerships with academic institutions will foster a culture of continuous learning and innovation.
- ✓ **Targeted Research on Barriers to CMP Adoption:** Further investigation is needed to identify the specific barriers to CMP adoption in Palestine, such as financial limitations,

regulatory issues, and a lack of qualified personnel. Gaining a clearer understanding of these challenges will enable more focused interventions.

These recommendations are designed to create a more supportive ecosystem for the adoption of CMP, thereby enhancing long-term innovation and competitiveness in Palestine's pharmaceutical sector.

5.10 Study Outcomes.

This study significantly enhances our understanding of Continuous Manufacturing Processes (CMP) in Palestine pharmaceutical industry. It offers valuable insights into the current awareness, implementation, and barriers that hinder widespread adoption of CMP.

- **Pioneering Insight into CMP in Palestine:** This study is among the first to explore the awareness and implementation of Continuous Manufacturing Processes (CMP) in Palestinian pharmaceutical companies. It identifies key areas of progress as well as those needing improvement, establishing a clear baseline for future research and action. Moreover, the study suggests that subsequent research could investigate how cultural and regional factors affect the adoption of innovative manufacturing processes in developing economies.
- **Identification of Key Barriers:** A significant outcome of this study is the identification of key barriers to CMP adoption, including structural challenges and limited infrastructure. These barriers highlight specific areas for policymakers and business leaders to target in order to accelerate CMP adoption. Additionally, further exploration is needed on how smaller companies can overcome these challenges through strategic partnerships or government support.
- **Impact on Policy and Practice:** This study findings are expected to shape policy discussion regarding pharmaceutical manufacturing practices in Palestine. By identifying gaps in implementation and awareness, it lays the foundation for policy interventions and practical recommendations aimed at enhancing the pharmaceutical manufacturing sector. Policymakers are also encouraged to take international best practices into account when developing regulations that support advanced manufacturing systems like CMP, ensuring these regulations are tailored to local conditions.
- **Contributions to Global Discussions on CMP:** This research enhances the existing literature on Continuous Manufacturing Processes (CMP) by offering insights from a developing country perspective. It expands our understanding of how advanced manufacturing processes can be effectively integrated into various industrial contexts, especially in resource limited regions.
- **Future Research Directions:** This study also opens doors for future research, especially regarding how CMP can be tailored to various company sizes, resources, and market conditions. Investigating the long-term effects of CMP on product quality, regulatory compliance, and production costs will be essential for advancing the field. Additionally, this research will provide valuable insights for other countries facing similar challenges, offering a realistic perspective on the opportunities and obstacles associated with adopting CMP technologies in developing regions.

5.11: Limitations.

- **Sample Size and Response Rate:** A significant limitation of this study is its small sample size, which may hinder the generalization of the findings to the broader pharmaceutical industry in Palestine. Future research should focus on including a larger number of companies from various regions.
- **Survey Completion Issues:** Some companies did not fully complete the survey, which could impact the accuracy of the data. Future research might explore alternative methods, such as case studies, for a more in-depth understanding. Additionally, extending deadlines or sending reminders could help improve survey completion rates.
- **Generalization of Results:** This study provides valuable insights; however, the findings may not represent the perspectives of all pharmaceutical companies in Palestine. Therefore, caution is advised when generalizing these results. Future research should include a wider variety of companies to gain a more understanding of the factors influencing CMP adoption.

References.

- Abdalla, H. (2021). The production of solid dose pharmaceutical tablets: A shift towards continuous manufacturing (Undergraduate honors thesis, California State University, Long Beach). Scholar Works. https://scholarworks.calstate.edu/downloads/st74cx430.
- Abu Rjeila, M. (2019). Enhancing Competitiveness and Increasing the Market Share of National Products in Palestine: The Pharmaceutical Sector. Palestine Economic Policy Research Institute (MAS). Retrieved from https://library.mas.ps/Records/IndexToPrint?libId=1&recordNo=23094.
- Adamo, A., Beingessner, R. L., Behnam, M., Chen, J., Jamison, T. F., Jensen, K. F., Monbaliu, J.-C. M., Myerson, A. S., Revalor, E. M., Snead, D. R., Stelzer, T., Weeranoppanant, N., Wong, S. Y., & Zhang, P. (2016). On-demand continuous-flow production of pharmaceuticals in a compact reconfigurable system. Science, 352(6288), 61–67. https://doi.org/10.1126/science.aaf1337.
- Ahmad, S. (2020). Tablets manufacturing [PowerPoint slides]. Glocal University. https://www.glocaluniversity.edu.in/files/eContent/eBpharm/Pharmacetics%201%20tablet%20Manufacturing%20PPT.pdf.
- Allen, L. V., Popovich, N. G., & Ansel, H. C. (2014). Ansel's pharmaceutical dosage forms and drug delivery systems (10th ed.). Lippincott Williams & Wilkins.
- Allison, G., Cain, Y. T., Cooney, C., Garcia, T., Bizjak, T. G., Holte, O., Jagota, N., Komas, B., Korakianiti, E., Kourti, D., Madurawe, R., Morefield, E., Montgomery, F., Nasr, M., Randolph, W., Robert, J.-L., Rudd, D., & Zezza, D. (2015). Regulatory and quality considerations for continuous manufacturing: May 20–21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences, 104(3), 803–812. https://doi.org/10.1002/jps.24324.
- American Chemical Society. (2005). ACS GCI Pharmaceutical Roundtable. https://www.acs.org/content/acs/en/greenchemistry/industryroundtables/pharmaceutical.html.
- Badman, C., & Trout, B. L. (2015). Achieving continuous manufacturing. Journal of Pharmaceutical Sciences, 104(3), 779–780. https://doi.org/10.1002/jps.24246.
- Badman, C., Cooney, C. L., Florence, A., Konstantinov, K., Krumme, M., Mascia, S., Nasr, M., & Trout, B. L. (2019). Why we need continuous pharmaceutical manufacturing and how to make it happen. Journal of Pharmaceutical Sciences, 108(11), 3521–3523. https://doi.org/10.1016/j.xphs.2019.07.016.
- Baxendale, I. R., Braatz, R. D., Hodnett, B. K., Jensen, K. F., Johnson, M. D., Sharratt, P., Sherlock, J.-P., & Florence, A. J. (2015). Achieving continuous manufacturing: Technologies and approaches for synthesis, workup, and isolation of drug substance—May 20–21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences, 104(3), 781–791. https://doi.org/10.1002/jps.24252.
- Baxendale, I.R., Braatz, R.D., Hodnett, B.K., Jensen, K.F., Johnson, M.D., Sharratt, P., Sherlock, J.-P., & Florence, A.J. (2015). Achieving continuous manufacturing: Technologies and approaches for synthesis, workup, and isolation of drug substance. Journal of Pharmaceutical Sciences, 104(5), 781–791. https://doi.org/10.1002/jps.24252.
- Borkar, T. S., Jadhav, S. S., & Patil, K. D. (2017). Regulatory and quality considerations for continuous manufacturing. International Journal of Pharmaceutics, 528(1), 1–9. https://doi.org/10.1016/j.ijpharm.2017.03.053.

- Byrn, S., Futran, M., Thomas, H., Jayjock, E., Maron, N., Meyer, R. F., Myerson, A. S., Thien, M. P., & Trout, B. L. (2015). Achieving continuous manufacturing for final dosage formation: Challenges and how to meet them—May 20–21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences, 104(3), 792–802. https://doi.org/10.1002/jps.24247.
- Chatterjee, S., Dr. (2012, January). FDA perspective on continuous manufacturing. Speech presented at IFPAC Annual Meeting, Baltimore. Retrieved from https://www.fda.gov/files/about%20fda/published/FDA-Perspective-on-Continuous-Manufacturing--Sharmista-Chatterjee--Ph.D.--January-22--2012--IFPAC-AnnualMeeting.pdf.
- Chaudhary, S. (2021, July 7). The impact of COVID-19 on pharmaceuticals: Current challenges and future directions. LinkedIn. https://www.linkedin.com/pulse/impact-covid-19-pharmaceuticals-current-challenges-future-chaudhary.
- Chauhan, G., & Gupta, V. (2019, April). Developments and challenges: Adapting continuous manufacturing for pharmaceuticals. AAPS Newsmagazine. https://www.aapsnewsmagazine.org/articles/2019/apr19/cover-story-apr19.
- DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics, 47*, 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.
- Domokos, A., Nagy, B., Szilágyi, B., Marosi, G., & Nagy, Z. K. (2021). Integrated continuous pharmaceutical technologies—A review. *Organic Process Research & Development, 25*(8), 1426–1446. https://doi.org/10.1021/acs.oprd.1c00040
- Food and Drug Administration. (2019). Drug shortages: Root causes and potential solutions (FDA Off. Doc.). Retrieved from https://www.fda.gov/media/131089/download.
- Food and Drug Administration. (2019). FDA statement on FDA's modern approach to advanced pharmaceutical manufacturing. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-modern-approach-advanced-pharmaceutical-manufacturing.
- Food and Drug Administration. (2004). Guidance for industry changes to an approved NDA or ANDA (FDA Off. Doc. No. 1–40). https://www.fda.gov/media/71846/download.
- Food and Drug Administration. (2004). Guidance for Industry PAT: A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. U.S. Department of Health and Human Services.
- Food and Drug Administration. (2019). Quality Considerations for Continuous Manufacturing: Guidance for Industry. U.S. Department of Health and Human Services.
- Food and Drug Administration. (2018). Report on drug shortages for calendar year 2018 (FDA Off. Doc.). Retrieved from https://www.fda.gov/media/131089/download.
- General Kinematics. (2021, January 5). *The differences between batch processing and continuous flow processing*. https://www.generalkinematics.com/blog/batch-processing-vs-continuous-flow/.
- Hock, S. C., Siang, T. K., & Wah, C. L. (2021). Continuous manufacturing versus batch manufacturing: Benefits, opportunities and challenges for manufacturers and regulators. *GaBI Journal, 10*(1), 44–56. https://doi.org/10.5639/gabij.2021.1001.004.
- International Council for Harmonization. (2018). *ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products.* Retrieved from http://www.ich.org (accessed February 19, 2020).

- International Council for Harmonization (ICH). (2023). *ICH guideline Q13 on continuous manufacturing of drug substances and drug products*. European Medicines Agency (EMA). https://www.ema.europa.eu/en/ich-guideline-q13-continuous-manufacturing-drug-substances-and-drug-products-scientific-guideline.
- Jolliffe, H. G., & Gerogiorgis, D. I. (2015). Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen. *Chemical Engineering Research and Design, 97*, 175–191. https://doi.org/10.1016/j.cherd.2014.12.005.
- Kane, A. (2017). Key parameters to be optimized in the development and manufacturing of oral solid-dosage forms. *Pharmaceutical Technology, 41*(4).
- Kanetkar, A. (2020, December 17). *The importance of continually evolving solid dosage forms*. European Pharmaceutical Review. https://www.europeanpharmaceuticalreview.com/article/117391/the-importance-of-continually-evolving-solid-dosage-forms/.
- Lee, S. L. (2019). Quality considerations for continuous manufacturing: Guidance for industry (Rep.). Silver Spring, MD: Center for Drug Evaluation and Research. https://www.fda.gov/media/121314/download.
- Lee, S. L., O'Connor, T. F., Yang, X., Cruz, C. N., Chatterjee, S., Madurawe, R. D., Moore, C. M. V., Yu, L. X., & Woodcock, J. (2015). Modernizing pharmaceutical manufacturing: From batch to continuous production. Journal of Pharmaceutical Innovation, 10(3), 191–199. https://doi.org/10.1007/s12247-015-9215-8.
- Lee, Sau. (2017, May 17). Modernizing the way drugs are made: A transition to continuous. U.S. Food and Drug Administration (FDA). Retrieved from https://www.fda.gov/drugs/news-events-human-drugs/modernizing-way-drugs-are-made-transition-continuous-manufacturing.
- Markarian, J. (2021, November 2). Meeting supply and training challenges. Pharmaceutical Technology, 45(11), 30–32. https://www.pharmtech.com/view/meeting-supply-and-training-challenges.
- Mascia, S., Heider, P. L., Zhang, H., Lakerveld, R., Benyahia, B., Barton, P. I., Braatz, R. D., Cooney, C. L., Evans, J. M. B., Jamison, T. F., Jensen, K. F., Myerson, A. S., & Trout, B. L. (2013). End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation. Angewandte Chemie, 125(45), 12585–12589. https://doi.org/10.1002/ange.201305429.
- Massey, S. (2019, May 8). Making the switch: Continuous manufacturing vs. batch processing of pharmaceuticals. X talks. https://xtalks.com/continuous-and-batchmanufacturing-pharmaceuticals/
- McKenzie, P., Kiang, S., Tom, J., Rubin, A. E., & Futran, M. (2006). Can pharmaceutical process development become high tech? AIChE Journal, 52(12), 3990–3994. https://doi.org/10.1002/aic.11022.
- McLaughlin, S. (2019, May 31). Continuous manufacturing vs batch manufacturing in the pharmaceutical industry. SL Controls. https://slcontrols.com/us/continuous-manufacturing-vs-batch-manufacturing-in-the-pharmaceutical-industry/.
- Mihokovic, N. (2017). Continuous manufacturing - EMA perspective and experience. Presented at Engineering Conferences International. Retrieved from https://dc.engconfintl.org/cgi/viewcontent.cgi?article=1033&context=biomanufact_iii.
- Ministry of National Economy (MONE) & Palestinian Central Bureau of Statistics (PCBS). (2020). Impact of Coronavirus (COVID-19) pandemic on economic/business establishments

during (5/3/2020 – 31/5/2020). Palestinian Central Bureau of Statistics. Retrieved from https://www.pcbs.gov.ps/portals/_pcbs/PressRelease/Press_En_14-11-2020-covid-est-en.pdf.

- Nasr, M. M., Krumme, M., Matsuda, Y., Trout, B. L., Badman, C., Mascia, S., Cooney, C. L., Jensen, K. D., Florence, A., Johnston, C., Konstantinov, K., & Lee, S. L. (2017). Regulatory perspectives on continuous pharmaceutical manufacturing: Moving from theory to practice: September 26–27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals. Journal of Pharmaceutical Sciences, 106(11), 3199–3206. https://doi.org/10.1016/j.xphs.2017.06.015
- Nepveux, K., Sherlock, J.P., Futran, M., Thien, M., & Krumme, M. (2015). How development and manufacturing will need to be structured-heads of development/manufacturing. Journal of Pharmaceutical Sciences, 104(5), 850–864. https://doi.org/10.1002/jps.24286.
- Niazi. (2010, September 30). Operations involved in tablet manufacturing. Dotty. Retrieved May 5, 2021, from http://niazipharmaceuticalinfo.blogspot.com/2010/09/operations-involved-intablet.html.
- People's Dispatch. (2023). The pharmaceutical landscape in occupied Palestine. Peoples Dispatch. Retrieved from https://peoplesdispatch.org/2023/12/30/the-pharmaceutical-landscape-in-occupied-palestine/
- Phys.org. (2019, May 1). Drug companies warm up to continuous manufacturing. https://phys.org/news/2019-05-drug-companies.html.
- Plumb, K. (2005). Continuous processing in the pharmaceutical industry: Changing the mind set. Chemical Engineering Research and Design, 83(6), 730–738.
- Poechlauer, P., Manley, J., Broxterman, R., Gregertsen, B., & Ridemark, M. (2012). Continuous processing in the manufacture of active pharmaceutical ingredients and finished dosage forms: An industry perspective. Organic Process Research & Development, 16(9), 1586–1590. https://doi.org/10.1021/op300159y.
- Poechlauer, P., Colberg, J., Fisher, E., Jansen, M., Johnson, M. D., Koenig, S. G., Lawler, M., Laporte, T., Manley, J., Martin, B., & O'Kearney-McMullan, A. (2013). Pharmaceutical Roundtable Study Demonstrates the Value of Continuous Manufacturing in the Design of Greener Processes. Organic Process Research & Development, 17(12), 1472–1478. https://doi.org/10.1021/op400245s.
- Rana, A., & Hari Kumar, S. (2013). Manufacturing defects of tablets – A review. *Journal of Drug Delivery and Therapeutics, 3*(6), 200–206. https://doi.org/10.22270/jddt.v3i6.72.
- Rantanen, J., & Khinast, J. (2015). The future of pharmaceutical manufacturing sciences. *Journal of Pharmaceutical Sciences, 104*(11), 3612–3638. https://doi.org/10.1002/jps.24594.
- Rogers, A. J., Hashemi, A., & Ierapetritou, M. G. (2013, August 19). *Modeling of particulate processes for the continuous manufacture of solid-based pharmaceutical dosage forms*. Processes, 1(2), 67–78. https://www.mdpi.com/2227-9717/1/2/67.
- Rossi, C. V. (2022). A comparative investment analysis of batch versus continuous pharmaceutical manufacturing technologies. *Journal of Pharmaceutical Innovation, 17*(6), 1373–1391. https://doi.org/10.1007/s12247-021-09612-y.
- Schaber, S. D., Gerogiorgis, D. I., Ramachandran, R., Evans, J. M. B., Barton, P. I., & Trout, B. L. (2011). Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study. Industrial & Engineering Chemistry Research, 50(17), 10083–10092. https://doi.org/10.1021/ie2006752.

- Select USA. (2014). Biopharmaceutical industry spotlight. SelectUSA.gov. https://www.selectusa.gov/pharmaceutical-and-biotech-industries-united-states.
- Shah, B. (2011). Dosage forms, routes of administration, and dispensing medications. In Navigate course manager: The 21st century pharmacy technician (pp. 79–112). Jones & Bartlett
- Shah, N. (2004). Pharmaceutical supply chains: Key issues and strategies for optimization. Computers & Chemical Engineering, 28(6), 929–941. https://doi.org/10.1016/j.compchemeng.2003.09.022.
- Simon, L. L., Kiss, A. A., Cornevin, J., & Gani, R. (2019). Process engineering advances in pharmaceutical and chemical industries: Digital process design, advanced rectification, and continuous filtration. Current Opinion in Chemical Engineering, 25, 114–121. https://doi.org/10.1016/j.coche.2019.02.005.
- Simon, L. L., Pataki, H., Marosi, G., Meemken, F., Hungerbühler, K., Baiker, A., ... & Litster, J. D. (2015). Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review. Organic Process Research & Development, 19, 3–62. https://doi.org/10.1021/op500261y.
- Srai, J. S., Badman, C., Krumme, M., Futran, M., & Johnston, C. (2015). Future supply chains enabled by continuous processing—Opportunities and challenges. Journal of Pharmaceutical Sciences, 104(3), 840–849. https://doi.org/10.1002/jps.24343.
- Srai, J. S., Harrington, T., Alinaghian, L., & Phillips, M. (2015). Evaluating the potential for the continuous processing of pharmaceutical products - A supply network perspective. Chemical Engineering and Processing: Process Intensification, 97, 248–258. https://doi.org/10.1016/j.cep.2015.07.018.
- Su, Q., Ganesh, S., Moreno, M., Bommireddy, Y., Gonzalez, M., Reklaitis, G. V., & Nagy, Z. K. (2019). A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing. Computers & Chemical Engineering, 125, 216–231. https://doi.org/10.1016/j.compchemeng.2019.03.001.
- Suresh, P., & Basu, P.K. (2008). Improving pharmaceutical product development and manufacturing: Impact on cost of drug development and cost of goods sold of pharmaceuticals. Journal of Pharmaceutical Innovation, 3(4), 175–187. https://doi.org/10.1007/s12247-008-9043-1.
- Tężyk, M., Milanowski, B., Ernst, A., & Lulek, J. (2016). Recent progress in continuous and semicontinuous processing of solid oral dosage forms: A review. Drug Development and Industrial Pharmacy, 42(8), 1195–1214. https://doi.org/10.3109/03639045.2015.1122607.
- Thomas Publishing Company. (2021, May 5). The pharmaceutical manufacturing process: Steps, tools and considerations. Thomasnet. https://www.thomasnet.com/articles/chemicals/the-pharmaceutical-manufacturing-process-steps-tools-and-considerations/.
- Tovey, G. (2018). Pharmaceutical formulation: The science and technology of dosage forms. Royal Society of Chemistry.
- United States Pharmacopeia (USP). (2023). USP Workshop on Identifying and Addressing Barriers to Continuous Manufacturing Adoption. Retrieved from https://www.usp.org/events-training/workshops/usp-workshop-on-identifying-and-addressing-barriers-to-continuous-manufacturing-adoption.

- U.S. Food and Drug Administration, Center for Drug Evaluation and Research. (2021). Drug recalls. Retrieved May 5, 2021, from https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls.
- Vanhoorne, V., & Vervaet, C. (2020). Recent progress in continuous manufacturing of oral solid dosage forms. International Journal of Pharmaceutics, 579, 119157. https://doi.org/10.1016/j.ijpharm.2020.119157.
- Vanhoorne, V., & Vervaet, C. (2020). Recent progress in continuous manufacturing of oral solid dosage forms. *International Journal of Pharmaceutics, 579*, 119194. https://doi.org/10.1016/j.ijpharm.2020.119194.
- Vervaet, C., & Remon, J. P. (2005). Continuous granulation in the pharmaceutical industry. Chemical Engineering Science, 60(14), 3949–3957. https://doi.org/10.1016/j.ces.2004.10.005.
- Wilson Tool. (n.d.). *How to make solid dose pharmaceutical tablets*. Retrieved May 5, 2021, from https://www.wilsontool.com/en-us/news/technical-articles/tableting/how-to-make-solid-dose-pharmaceutical-tablets.
- Yu, L. X. (2008). Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 25(4), 781–791. https://doi.org/10.1007/s11095-007-9511-1.
- Yu, L. X., & Lee, S. L. (2018). Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving From Theory to Practice. Journal of Pharmaceutical Sciences, 107(5), 1235–1240. https://doi.org/10.1016/j.xphs.2017.11.014.
- Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. The AAPS Journal, 16(4), 771–783. https://doi.org/10.1208/s12248-014-9598-3

Appendix.

Appendix A: Questionnaire.

The complete version of questionnaire used in this study is provided below.

Part One: Demographic and General Information:

1- Country of origin of your industry: .....

2-Qualification:

- o Ph.D. degree
- o Master degree
- o Bachelor's degree
- o Diploma degree

3- Specialization:

- o Pharmacy
- o Chemical engineering
- o Industrial engineering
- o Mechanical engineering
- o Biology
- o Chemistry
- o Others (please specify).....

4-Job title:

- o Consultant
- o Director
- o Manager
- o Section Head
- o Supervisor
- o Others (please specify) .....

5- Years of experience in the pharmaceutical industry sector: ..... years

6- Type of the production line/s (you can choose more than one choice):

- o Solid dosage forms
- o Liquid dosage forms
- o Semisolid dosage forms
- o Injectable dosage forms
- o Others (please specify) .....

Part Two: Continuous Manufacturing Process (CMP)

Please indicate (by placing a check mark (√) in the corresponding box) your extent of agreement for each of the following statements **according to the current awareness and practices in your pharmaceutical manufacturing company**.

	Dimensions and Items	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
	CMP Awareness					
1	I recognize the difference between the continuous manufacturing process (CMP) and traditional batch manufacturing.					
2	I knew about the CMP through my work.					
3	I learned about the CMP through my undergraduate study.					
4	I learned about the CMP through self-learning.					
5	I received training in the field of CMP.					
6	I received qualifications in the CMP field.					
7	I am knowledgeable about CMP.					
8	I realize the benefits of adopting CMP compared to traditional batch manufacturing processes.					
9	CMP reduces the cost of production compared to traditional batch manufacturing processes.					
10	CMP provides greater control over manufacturing processes than traditional batch manufacturing processes.					
11	CMP reduces the amount of space required compared to traditional batch manufacturing processes.					
12	CMP improves production efficiency compared to traditional batch manufacturing processes.					
13	CMP improves product quality more than traditional batch manufacturing processes.					
14	The company management is aware of CMP's requirements.					
15	Our management is aware of the benefits of CMP.					
16	I know about CMP through the international guidelines.					
17	Our management is aware of the continuous manufacturing principles.					
18	CMP reduces the waste of raw materials more than traditional batch manufacturing processes.					
19	We are aware of the new technology used in CMP.					

20	We are aware of process analytical techniques (PAT) used in CMP.					
Dimensions and Items		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
21	CMP is used to develop new formulations more than traditional batch manufacturing processes.					
22	Capital expenditures in CMP are less than those in the batch process.					
23	The CMP is more flexible than the traditional batch process.					
CMP Implementation						
A. Management and Employees						
1	Our management is interested in converting from batch manufacturing to CMP.					
2	Our management is committed to implementing CMP.					
3	Our management attracted qualified employees in CMP.					
4	Our management recruited experienced employees in CMP.					
5	Our workers were trained in CMP.					
6	Our management seeks to invest in the CMP.					
7	Our management is dedicated to a specialized skills development training program in CMP.					
8	We have a specialized team in the company to study the requirements for CMP implementation.					
9	Our management constantly seeks to apply the CMP.					
10	The company exploits process analytical techniques (PAT) used in CMP.					
11	Our workers can handle CMP operations effectively.					
12	Our workers can solve CMP problems effectively.					
B. Facility, Equipment, Devices, and Materials						
1	Our facility layout is designed for the CMP.					
2	Our facility layout can be adjusted to operate the CMP.					
3	We have all the necessary machines and equipment for CMP.					
4	Our machines and equipment are suitable for CMP.					
5	Our machines and equipment are arranged to be used sequentially according to CMP.					
6	Our machines and equipment cleaning times are suitable for CMP.					
7	We have the required infrastructure for the CMP.					
8	Our machines and equipment can be adjusted to suit the CMP.					

9	Our machines and equipment can be rearranged sequentially according to CMP.					
	Dimensions and Items	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
10	We use the necessary manufacturing materials for CMP.					
11	We ensure the specifications of materials used in CMP.					
12	We have qualified warehouses to store materials needed for the CMP.					
13	We verify the packaging materials used in CMP according to the required guidelines.					
14	All of our products can be produced through the CMP.					
C. The Supply Chains						
1	Our contracts with suppliers are suitable for the CMP.					
2	Our suppliers have quality certificates in CMP.					
3	Our suppliers' delivery dates are suitable for CMP.					

Part Three: Barriers to CMP Implementation:

Please indicate (by placing a check mark (√) in the corresponding box) your extent of agreement for each of the following statements that may hinder CMP implementation **(compared to the traditional batch process)**.

	Dimensions and Items	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Barriers to CMP Implementation						
1	Adopting the CMP with its underlying technologies is expensive.					
2	Lack of top management commitment to CMP.					
3	Adopting the CMP is time-consuming.					
4	Adopting the CMP with its underlying technologies is difficult.					
5	Adopting the CMP is not worth it.					
6	The CMP is not flexible.					
7	The CMP poses quality management challenges.					
8	Our workers are not sufficiently qualified to operate the CMP.					
9	Our workers are not sufficiently experienced in the CMP.					
10	Lack of awareness of the CMP and its benefits.					
11	The CMP system is complex to operate.					

12	The CMP requires complex logistic issues.					
	Dimensions and Items	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
13	The CMP requires more physical space than the batch process.					
14	Limited availability of the CMP-compatible resources, technologies, and materials.					
15	The CMP requires more control and evaluation processes.					
16	The CMP involves extensive research and development.					
17	The CMP encounters complex regulatory approvals.					
18	The CMP requires continuous validation and monitoring.					
19	The CMP requires extensive process optimization.					

Appendix B: **Official Letter for Coordinating Company Visits.**

This letter template was provided to Jerusalem Company and is the same for all companies in the study, with only the company name modified as necessary.

Al-Quds University
Faculty of Pharmacy

جـامعة القـدس
كليـة الصيدلـة

التاريخ: 2024/8/19

حضرة السادة مصنع (القدس لصناعة الأدوية)

تحية طيبة و بعد,

أرجو السماح للطالبة عبير ناصر, تخصص تكنولوجيا تطبيقية وصناعية /مسار تصنيع ادوية في جامعة القدس/ ابو ديس بإجراء استبيان مختصر وذلك ضمن بحث رسالة ماجستير بعنوان:

Assessment of the awareness,implementation and barriers to continuous manufacturing processes among pharmaceutical manufacturing companies in palestine

تحت إشراف الدكتور طارق الجعبة . حيث يهدف الاستبيان الى قياس مدى تطبيق ممارسات التصنيع المستمر و تقييم الاداء من ناحية الوقت التكلفة والمرونة

نؤكد لكم أن جميع المعلومات المقدمة من حضرتكم ستعامل بسرية و مهنية تامة وستستخدم فقط للأغراض الأكاديمية ونتعهد بعدم نشر النتائج الا بعد اخذ موافقة مسبقة منكم
مرفق مختصر البحث و نموذج الاستبيان ادناه

مع خالص الشكر والتقدير

د.طارق الجعبة
نائب عميد كلية الصيدلة جامعة القدس /ابو ديس

كلية الصيدلة
Faculty of Pharmacy

Prof. Dr. Ahmad Amro.

Appendix C: Frequency Tables for Demographic Variables.

The table below displays the frequency distribution of the demographic characteristics of the study participants. It includes variables such as company, educational qualifications, field of specialization, job category, years of experience in the pharmaceutical industry, and type of production line.

In this table, n represents the number of valid responses for each category, and the percentage (%) shows the valid distribution of responses within each variable. This format facilitates a clear understanding of the sample composition while maintaining the clarity and comparability of the data. Appendix (C) provides a detailed breakdown of these frequencies, offering contextual background on the participants' profiles in the study.

Table C 1: Frequency Distribution of Demographic Variables.

Variables	Category	n (%)
Company	**Jerusalem company (JPC)**	**5 (6.3%)**
	Palolea company	**5 (6.3%)**
	Alison company	**10 (12.5%)**
	Birzeit Company (BPC)	**14 (17.5%)**
	Pharmacare company (PLC)	**19 (23.8%)**
	Beit Jala company (BJP)	**27 (33.8%)**
Qualification	**Master degree**	**26 (32.5%)**
	Bachelor's degree	**54 (67.5%)**
Specialization	**Pharmacy**	**31 (38.8%)**
	Chemist	**25 (31.3%)**
	Others	**24 (30%)**
Jop category	**Management and above**	**20 (25%)**
	Department heads	**18 (22.5)**
	Supervisor	**27 (33.8)**
	Others	**15 (18.8)**
Years of experience in the pharmaceutical industry sector	**5 years and less**	**14 (17.5%)**
	From 6-10 years	**19 (23.8)**
	From 11-15 years	**13 (16.3)**

	16 years and more	**34 (42.5)**
Type of production line	**Solid dosage form**	**65 (27%)**
	Liquid dosage form	**71(33.6%)**
	Semi-solid dosage form	**56 (23.2%)**
	Injectable dosage form	**39 (16.2%)**

Appendix D: Frequency Tables for Responses to Survey Items Based on the Five-Point Likert Scale.

This table presents the frequency and percentage of responses for each item on the questionnaire, organized using a 5-point Likert scale: 5 = Strongly Agree, 4 = Agree, 3 = Neutral, 2 = Disagree, 1 = Strongly Disagree. The distribution illustrates the general tendency of participants' opinions across the study items.

Table D1: Frequency Distribution for Responses to Survey.

CMP Awareness		
Variables	**Category**	**n (%)**
I recognize the difference between the continuous manufacturing process (CMP) (and traditional batch manufacturing.	**Strongly Agree**	**24 (30%)**
	Agree	**44 (55%)**
	Neutral	**8 (10%)**
	Disagree	**3 (3.8%)**
	Strongly Disagree	**1 (1.3%)**
I knew about the CMP through my work.	**Strongly Agree**	**19 (23.8%)**
	Agree	**42 (52.5%)**
	Neutral	**8 (10 %)**
	Disagree	**9 (11.3%)**
	Strongly Disagree	**2 (2.5%)**

I learned about the CMP through my undergraduate study.	**Strongly Agree**	**3 (3.8%)**
	Agree	**14 (17.5%)**
	Neutral	**25 (31.3%)**
	Disagree	**24 (30%)**
	Strongly Disagree	**14 (17.5%)**
I learned about the CMP through self-learning	**Strongly Agree**	**10 (12.5%)**
	Agree	**29 (36.3%)**
	Neutral	**18 (22.5%)**
	Disagree	**21 (26.3%)**
	Strongly Disagree	**2 (2.5%)**
I received training in the field of CMP.	**Strongly Agree**	**10 (12.5%)**
	Agree	**18 (22.5%)**
	Neutral	**16 (20%)**
	Disagree	**29 (36.3%)**
	Strongly Disagree	**7 (8.8%)**
I received qualifications in the CMP field.	**Strongly Agree**	**6 (7.5%)**
	Agree	**21 (26.3%)**
	Neutral	**18 (22.5%)**
	Disagree	**27 (33.8%)**
	Strongly Disagree	**8 (10%)**
I am knowledgeable about CMP.	**Strongly Agree**	**11 (13.8%)**
	Agree	**46 (57.5%)**
	Neutral	**10 (12.5%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**6 (7.5%)**
I realize the benefits of adopting CMP compared to traditional batch manufacturing processes.	**Strongly Agree**	**19 (23.8%)**
	Agree	**43 (53.8%)**

	Neutral	8 (10%)
	Disagree	8 (10%)
	Strongly Disagree	2 (2.5%)
CMP reduces the cost of production compared to traditional batch manufacturing processes.	Strongly Agree	16 (20%)
	Agree	44 (55%)
	Neutral	16 (20%)
	Disagree	3 (3.8%)
	Strongly Disagree	1 (1.3%)
CMP provides greater control over manufacturing processes than traditional batch manufacturing processes.	Strongly Agree	21 (26.3%)
	Agree	42 (52.5%)
	Neutral	12 (15%)
	Disagree	4 (5%)
	Strongly Disagree	1 (1.3%)
CMP reduces the amount of space required compared to traditional batch manufacturing processes.	Strongly Agree	18 (22.5%)
	Agree	42 (52.5%)
	Neutral	14 (17.5%)
	Disagree	4 (5%)
	Strongly Disagree	2 (2.5%)
CMP improves production efficiency compared to traditional batch manufacturing processes.	Strongly Agree	25 (31.3%)
	Agree	37 (46.5%)
	Neutral	15 (18.8%)
	Disagree	3 (3.8%)
	Strongly Disagree	0 (0%)
CMP improves product quality more than traditional batch manufacturing processes.	Strongly Agree	24 (30%)
	Agree	41 (51.2%)
	Neutral	14 (17.5%)
	Disagree	1 (1.3%)

	Strongly Disagree	**0 (0%)**
The company management is aware of CMP's requirements.	**Strongly Agree**	**21 (21.3%)**
	Agree	**39(48.8%)**
	Neutral	**17 (21.3%)**
	Disagree	**2 (25%)**
	Strongly Disagree	**1 (1.3%)**
Our management is aware of the benefits of CMP.	**Strongly Agree**	**26 (32.5%)**
	Agree	**37 (46.3%)**
	Neutral	**12 (15%)**
	Disagree	**4 (5%)**
	Strongly Disagree	**1 (1.3%)**
I know about CMP through the international guidelines	**Strongly Agree**	**9 (11.3%)**
	Agree	**35 (43.8%)**
	Neutral	**27 (33.8%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**2 (2.5%)**
Our management is aware of the continuous manufacturing principles	**Strongly Agree**	**16 (20%)**
	Agree	**41 (51.2%)**
	Neutral	**20 (25%)**
	Disagree	**2 (2.5%)**
	Strongly Disagree	**1 (1.3%)**
CMP reduces the waste of raw materials more than traditional batch manufacturing processes.	**Strongly Agree**	**27 (33.8%)**
	Agree	**31 (38.8%)**
	Neutral	**17 (21.3%)**
	Disagree	**4 (5%)**
	Strongly Disagree	**1 (1.3%)**
We are aware of the new technology used in	**Strongly Agree**	**18 (22.5%)**

CMP.	**Agree**	**39 (48.8%)**
	Neutral	**13 (16.3%)**
	Disagree	**8 (10%)**
	Strongly Disagree	**2 (2.5%)**
We are aware of process analytical techniques (PAT) used in CMP.	**Strongly Agree**	**15 (18.8%)**
	Agree	**33 (41.3%)**
	Neutral	**21 (26.3%)**
	Disagree	**9 (11.3%)**
	Strongly Disagree	**2 (2.5%)**
CMP is used to develop new formulations more than traditional batch manufacturing processes.	**Strongly Agree**	**14 (17.5%)**
	Agree	**37 (46.3%)**
	Neutral	**24 (30%)**
	Disagree	**2 (2.5%)**
	Strongly Disagree	**2 (3.8%)**
Capital expenditures in CMP are less than those in the batch process.	**Strongly Agree**	**11 (13.8%)**
	Agree	**33 (41.3%)**
	Neutral	**24 (30%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**5 (6.3%)**
The CMP is more flexible than the traditional batch process.	**Strongly Agree**	**15 (18.8%)**
	Agree	**37 (46.3%)**
	Neutral	**23 (28.7%)**
	Disagree	**3 (3.8%)**
	Strongly Disagree	**2 (2.5%)**
CMP Implementation		
A. Management and Employees		
Our management is interested in converting	**Strongly Agree**	**9 (11.3%)**

from batch manufacturing to CMP.	**Agree**	**35 (43.8%)**
	Neutral	**28 (35%)**
	Disagree	**6 (7.5%)**
	Strongly Disagree	**2 (2.5%)**
Our management is committed to implementing CMP.	**Strongly Agree**	**7 (8.8%)**
	Agree	**32 (40%)**
	Neutral	**32 (40%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**2 (2.5%)**
Our management attracted qualified (employees in CMP.	**Strongly Agree**	**10 (12.5%)**
	Agree	**23 (28.7%)**
	Neutral	**34 (42.5%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**6 (7.5%)**
Our management recruited experienced employees in CMP.	**Strongly Agree**	**6 (7.5%)**
	Agree	**22 (27.5%)**
	Neutral	**35 (43.8%)**
	Disagree	**11 (13.8%)**
	Strongly Disagree	**6 (7.5%)**
Our workers were trained in CMP.	**Strongly Agree**	**8 (10%)**
	Agree	**27 (33.8%)**
	Neutral	**26 (32.8%)**
	Disagree	**13 (16.3%)**
	Strongly Disagree	**6 (7.5%)**
Our management seeks to invest in the CMP.	**Strongly Agree**	**7 (8.8%)**
	Agree	**36 (45%)**
	Neutral	**25 (31.3%)**

	Disagree	9 (11.3%)
	Strongly Disagree	3 (3.8%)
Our management is dedicated to a specialized skills development training program in CMP.	Strongly Agree	7 (8.8%)
	Agree	30 (37.5%)
	Neutral	32 (40%)
	Disagree	8 (10%)
	Strongly Disagree	3 (3.8%)
We have a specialized team in the company to study the requirements for CMP implementation. (لدينا فريق متخصص في الشركة لدراسة متطلبات تنفيذ (CMP))	Strongly Agree	7 (8.8%)
	Agree	30 (37.5%)
	Neutral	32 (40%)
	Disagree	8 (10%)
	Strongly Disagree	4 (5%)
Our management constantly seeks to apply the CMP.	Strongly Agree	12 (15%)
	Agree	26 (32.5%)
	Neutral	35 (43.8%)
	Disagree	12(15%)
	Strongly Disagree	4 (5%)
The company exploits process analytical techniques (PAT) used in CMP.	Strongly Agree	12 (15%)
	Agree	26 (32.5%)
	Neutral	30 (37.5%)
	Disagree	9 (11.3%)
	Strongly Disagree	2 (2.5%)
Our workers can handle CMP operations effectively.	Strongly Agree	10 (12.5%)
	Agree	28 (35%)
	Neutral	31 (38.8%)
	Disagree	10 (12.5%)
	Strongly Disagree	2 (2.5%)

Our workers can solve CMP problems effectively.	**Strongly Agree**	**6 (7.5%)**
	Agree	**36 (54%)**
	Neutral	**28 (35%)**
	Disagree	**8 (10%)**
	Strongly Disagree	**2 (2.5%)**
B. Facility, Equipment, Devices, and Materials		
Our facility layout is designed for the CMP.	**Strongly Agree**	**6 (7.5%)**
	Agree	**23 (28.7%)**
	Neutral	**28 (35%)**
	Disagree	**18 (22.5%)**
	Strongly Disagree	**5 (6.3%)**
Our facility layout can be adjusted to operate the CMP.	**Strongly Agree**	**6 (7.5%)**
	Agree	**42 (52.5%)**
	Neutral	**25 (31.3%)**
	Disagree	**5 (6.3%)**
	Strongly Disagree	**2 (2.5%)**
We have all the necessary machines and equipment for CMP.	**Strongly Agree**	**9 (11.3%)**
	Agree	**22 (27.5%)**
	Neutral	**26 (32.5%)**
	Disagree	**18 (22.5%)**
	Strongly Disagree	**5 (6.3%)**
Our machines and equipment are suitable for CMP.	**Strongly Agree**	**10 (12.5%)**
	Agree	**26 (32.5%)**
	Neutral	**26 (32.5%)**
	Disagree	**14 (17.5%)**
	Strongly Disagree	**4 (5%)**

Our machines and equipment are arranged to be used sequentially according to CMP.	**Strongly Agree**	**8 (10%)**
	Agree	**28 (35%)**
	Neutral	**26 (32.5%)**
	Disagree	**14 (17.5%)**
	Strongly Disagree	**4 (5%)**
Our machines and equipment cleaning times are suitable for CMP.	**Strongly Agree**	**9 (11.3%)**
	Agree	**37 (46.3%)**
	Neutral	**24 (30%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**3 (3.8%)**
We have the required infrastructure for the CMP.	**Strongly Agree**	**6 (7.5%)**
	Agree	**31 (38.8%)**
	Neutral	**32 (40%)**
	Disagree	**9 (11.3%)**
	Strongly Disagree	**2 (2.5%)**
Our machines and equipment can be adjusted to suit the CMP.	**Strongly Agree**	**10 (12.5%)**
	Agree	**38 (47.5%)**
	Neutral	**27 (33.8%)**
	Disagree	**4 (5%)**
	Strongly Disagree	**1 (1.3%)**
Our machines and equipment can be rearranged sequentially according to CMP.	**Strongly Agree**	**11 (13.8%)**
	Agree	**34 (42.5%)**
	Neutral	**31 (38.8%)**
	Disagree	**3 (3.8%)**
	Strongly Disagree	**1 (1.3%)**
We use the necessary manufacturing materials for CMP.	**Strongly Agree**	**13 (16.3%)**
	Agree	**41 (51.2%)**

	Neutral	**25 (31.3%)**
	Disagree	**1 (1.3%)**
	Strongly Disagree	**0 (0%)**
We ensure the specifications of materials used in CMP.	**Strongly Agree**	**15 (18.8%)**
	Agree	**41 (51.2%)**
	Neutral	**23 (28.7%)**
	Disagree	**1 (1.3%)**
	Strongly Disagree	**0 (0%)**
We have qualified warehouses to store materials needed for the CMP.	**Strongly Agree**	**17 (21.3%)**
	Agree	**35 (43.8%)**
	Neutral	**17 (21.3%)**
	Disagree	**11 (13.8%)**
	Strongly Disagree	**0 (0%)**
We verify the packaging materials used in CMP according to the required guidelines.	**Strongly Agree**	**15 (18.8%)**
	Agree	**34 (42.5%)**
	Neutral	**24 (30%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**0 (0%)**
All of our products can be produced through the CMP.	**Strongly Agree**	**16 (20%)**
	Agree	**34 (42.5%)**
	Neutral	**26 (32.5%)**
	Disagree	**4 (5%)**
	Strongly Disagree	**0 (0%)**
C. The Supply Chains		
Our contracts with suppliers are suitable for the CMP.	**Strongly Agree**	**10 (12.5%)**
	Agree	**35 (43.8%)**
	Neutral	**32 (40%)**

	Disagree	3 (3.8%)
	Strongly Disagree	0 (0%)
Our suppliers have quality certificates in CMP.	Strongly Agree	12 (15%)
	Agree	24 (30%)
	Neutral	39 (48.8%)
	Disagree	5 (6.3%)
	Strongly Disagree	0 (0%)
Our suppliers' delivery dates are suitable for CMP.	Strongly Agree	6 (7.5%)
	Agree	33 (41.3%)
	Neutral	39 (48.8%)
	Disagree	2 (2.5%)
	Strongly Disagree	0 (0 %)
Barriers to CMP Implementation		
Adopting the CMP with its underlying technologies is expensive.	Strongly Agree	16 (20%)
	Agree	37 (46%)
	Neutral	20 (25%)
	Disagree	5 (6.3%)
	Strongly Disagree	2(5%)
Lack of top management commitment to CMP.	Strongly Agree	5 (6.3%)
	Agree	15 (18.8%)
	Neutral	34 (42.5%)
	Disagree	23 (28.7%)
	Strongly Disagree	5 (6.3%)
Adopting the CMP is time-consuming.	Strongly Agree	3 (3.8%)
	Agree	9 (11.3%)
	Neutral	24 (30%)
	Disagree	36 (45%)

	Strongly Disagree	**8 (10%)**
Adopting the CMP with its underlying technologies is difficult.	**Strongly Agree**	**7 (8.8%)**
	Agree	**23 (28.7%)**
	Neutral	**25 (31.3%)**
	Disagree	**20 (25%)**
	Strongly Disagree	**5 (6.3%)**
Adopting the CMP is not worth it.	**Strongly Agree**	**7 (8.8%)**
	Agree	**12 (15%)**
	Neutral	**27 (33.8%)**
	Disagree	**26 (32.5%)**
	Strongly Disagree	**8 (10%)**
The CMP is not flexible.	**Strongly Agree**	**8 (10%)**
	Agree	**12 (15%)**
	Neutral	**27 (33.8%)**
	Disagree	**27 (33.8%)**
	Strongly Disagree	**6 (7.5%)**
The CMP poses quality management challenges.	**Strongly Agree**	**9 (11.3%)**
	Agree	**31 (38.8%)**
	Neutral	**19 (23.8%)**
	Disagree	**18 (22.5%)**
	Strongly Disagree	**3 (3.8%)**
Our workers are not sufficiently qualified to operate the CMP.	**Strongly Agree**	**8 (10%)**
	Agree	**23 (28.7%)**
	Neutral	**19 (23.8%)**
	Disagree	**25 (31.3%)**
	Strongly Disagree	**5 (6.3%)**
Our workers are not sufficiently	**Strongly Agree**	**6 (7.5%)**

experienced in the CMP.	**Agree**	**27 (33.8%)**
	Neutral	**25 (31.3%)**
	Disagree	**17 (21.3%)**
	Strongly Disagree	**5 (6.3%)**
Lack of awareness of the CMP and its benefits.	**Strongly Agree**	**7 (8.8%)**
	Agree	**28 (35%)**
	Neutral	**26 (32.5%)**
	Disagree	**17 (21.3%)**
	Strongly Disagree	**2 (2.5%)**
The CMP system is complex to operate.	**Strongly Agree**	**5 (6.3%)**
	Agree	**14 (17.5%)**
	Neutral	**30 (37.5)**
	Disagree	**26 (32.5%)**
	Strongly Disagree	**5 (6.3%)**
The CMP requires complex logistic issues.	**Strongly Agree**	**8 (10%)**
	Agree	**20 (25%)**
	Neutral	**30 (37.5%)**
	Disagree	**19(23.8%)**
	Strongly Disagree	**3 (3.8%)**
The CMP requires more physical space than the batch process.	**Strongly Agree**	**5 (6.3%)**
	Agree	**41 (51.2%)**
	Neutral	**26 (32.5%)**
	Disagree	**7 (8.8%)**
	Strongly Disagree	**1 (1.3%)**
Limited availability of the CMP-compatible resources, technologies, and materials.	**Strongly Agree**	**3 (3.8%)**
	Agree	**40 (50%)**
	Neutral	**26 (32.5%)**

	Disagree	**11 (13.8%)**
	Strongly Disagree	**0 (0%)**
The CMP requires more control and evaluation processes.	**Strongly Agree**	**13 (16.3%)**
	Agree	**45 (56.3%)**
	Neutral	**13 (16.3%)**
	Disagree	**8 (10%)**
	Strongly Disagree	**1 (1.3%)**
The CMP involves extensive research and development.	**Strongly Agree**	**19 (23.8%)**
	Agree	**45 (56.3%)**
	Neutral	**16 (20%)**
	Disagree	**0 (0%)**
	Strongly Disagree	**0 (0%)**
The CMP encounters complex regulatory approvals.	**Strongly Agree**	**10 (12.5%)**
	Agree	**38 (74.5%)**
	Neutral	**27 (33.8%)**
	Disagree	**5 (6.3%)**
	Strongly Disagree	**0 (0%)**
The CMP requires continuous validation and monitoring.	**Strongly Agree**	**19 (23.8%)**
	Agree	**44 (55%)**
	Neutral	**13 (16.3%)**
	Disagree	**4 (5%)**
	Strongly Disagree	**0 (0%)**
The CMP requires extensive process optimization.	**Strongly Agree**	**21 (26.3%)**
	Agree	**42 52.5(%)**
	Neutral	**15 (18.8%)**
	Disagree	**2 (2.5%)**
	Strongly Disagree	**0 (0%)**

العنوان: تقييم الوعي وتطبيق عمليات التصنيع المستمر (CMP) والمعيقات المرتبطة بها في فلسطين :دراسة مقطعية .(2024)

إعداد: عبير محمد حسين أعمر. **المشرف: الدكتور طارق الجعبة.**

الملخص.

أجريت هذه الدراسة بهدف تقييم مستوى الوعي وتطبيق عمليات التصنيع المستمر(CMP) إضافةً إلى التعرف على المعيقات المرتبطة بتبني هذه العمليات في مصانع الأدوية الفلسطينية, ورغم الأهمية المتزايدة لهذا القطاع في دعم الصحة العامة وتعزيز الاقتصاد الوطني، إلا أن معظم المصانع ما زالت تعتمد على طرق التصنيع التقليدية (الإنتاج على دفعات)، مما يؤدي إلى تحديات تتعلق بالكفاءة وجودة المنتج والاستجابة لحاجات السوق, من هنا جاءت أهمية التصنيع المستمر كبديل عالمي واعد، لما يوفره من مزايا تتعلق بخفض التكاليف وتحسين جودة العمليات والإنتاج.

قمنا بإجراء دراسة مقطعية شملت ست شركات أدوية فلسطينية، واستخدمنا فيها الاستبيان والمقابلات كأدوات رئيسية لجمع البيانات ,تم تقديم الاستبيان من قبل الدكتور محمد أبو عصب، الذي ساهم في تقديم الأداة الرئيسية للبحث، وشارك فيها 80 مستجيبًا من كوادر تلك الشركات, أظهرت النتائج مستوى عالٍ من الوعي بمتوسط عام قدره (3.68) أي ما يعادل (73.6%)، ومستوى متوسط من التطبيق بمتوسط عام (3.46)أي ما يعادل (69.3%)، بالإضافة إلى وجود معيقات متوسطة بمتوسط عام (3.33) يعادل (66.7%).

تبين من خلال النتائج أن من أبرز التحديات التي تواجه تبني هذا النوع من التصنيع: محدودية الموارد المالية، وغياب الوضوح التنظيمي، وضعف التأهيل والتدريب للعاملين, كما كشفت التحليلات الإحصائية عن وجود فروق في الوعي والتطبيق ترتبط ببعض الخصائص الديموغرافية للمستجيبين.

نوصي في هذه الدراسة بضرورة تحسين البنية التحتية، وتطوير الإطار التنظيمي، وتوفير برامج تدريبية متخصصة لدعم التحول نحو التصنيع المستمر، بما يعزز تنافسية واستدامة قطاع الأدوية في فلسطين.

الكلمات المفتاحية: التصنيع المستمر، صناعة الأدوية، فلسطين، الوعي، التطبيق، المعيقات، تحسين العمليات.