An-Najah National University

Faculty of Graduate Studies

Identification and prioritization of barriers to implement quality by design (QbD) by the local pharmaceutical industry in Palestine: a consensual analytic hierarchy process approach

By

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Dedication

To my lovely parents

To my brothers and sisters

To my grandfather

To all home I love

Acknowledgment

وما توفيقي الا بالله عليه توكلت واليه أنيب هود- 88

Greeting goes to my supervisor Dr. Ramzi Shawahna for hi Sincere encouragement, helpful, and close supervisions which has invaluable for me through of all stages of this study. Thanks to go to my family with all my love especially my father, mother, brother and sisters, who provided me with psychological support and encouragement

الإقرار

أنا الموقع أدناه, مقدم الرسالة التي تحمل العنوان

Identification and prioritization of barriers to implement quality by design (QbD) by the local pharmaceutical industry in Palestine: a consensual analytic hierarchy process approach

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Declaration

The work provided in this thesis, unless otherwise referenced, is the researchers own work, and has not been submitted elsewhere for other degree or qualification.

Student Name: **اسم الطالب:**

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Abbreviations

Abbreviations	Meaning
AAPS	American Association of Pharmaceutical Scientists
AHP	Analytic hierarchy process approach
ANDAs	Abbreviated drug application
BLAs	Biological license application
CMA	Critical material attribute
CPOE	Computerized physician order entry
CPP	Critical process parameter
CQA	Critical quality attribute
CSF	Critical success factor
DoE	Design of experiment
FDA	Food and drug administration
FMEA	Failure mode effect analysis
FTA	Fault tree analysis
HACCP	Hazard analysis critical control point
HIS	Human information system
ICH	International conference on harmonization
IRB	Institutional review board
MOH	Ministry of health
NDAs	New drug application
PAT	Process analytic technology
QbD	Quality by design
QbT	Quality by testing
QRM	Quality risk management
QTPP	Quality target product profile
TQM	Total quality management
WHO	World health organization

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Abstract

Background: Despite the potential benefits of applying quality by design (QbD) articulated by quality experts and regulatory agencies, these benefits are not easy to achieve in practice. Many pharmaceutical industrial plants found it difficult to implement QbD successfully.

Objectives: The present study investigates and categorizes the barriers to a successful implementation of QbD in local pharmaceutical industry in Palestine. The purpose of this study is to understand QbD barriers and prioritize their relative importance by ranking them in the pharmaceutical industry.

Methods: The opinion generation round of the Delphi technique used to identify barriers to implement QbD by the local Palestinian pharmaceutical industry. Further two Delphi rounds were undertaken to achieve consensus on the potential barriers and successive Delphi rounds were conducted to prioritize and rank barriers using an analytic hierarchy process (AHP) approach.

Quality and value: The strength of this study is the development of a comprehensive model for the investigation and prioritization of barriers

that the pharmaceutical industry experiences when implementing a QbD program.

Ethical approval: Ethical approval obtained from the Institutional Review Board (IRB) of An-Najah National University. Participants provided verbal informed consent before taking part in this study.

Result: Of the 34 potential barriers presented to the panelists for voting, consensus was achieved on 15 (44.1%) statements that represent barriers impeding the implementation of QbD in generic development by the local pharmaceutical industry in Delphi round 01. Consensus was also achieved on further 14 (41.2%) statements that represent barriers impeding the implementation of QbD in generic development by the local pharmaceutical industry in Delphi round 02. In general, 15 barriers were related to resources, instruments, and personnel, 5 items were related to the regulatory process, and 9 items were related to decision making within the local pharmaceutical industry. Consensus was achieved to exclude 5 statements as barriers impeding the implementation of QbD in generic development by local pharmaceutical industry. These barriers ranked from the most barrier to least one by using AHP approach. In this study, about 62% of the panelists were male in gender, about 64% were 40 years old and above, about 10% had PhD degree, about 59% obtained their academic degree before the year 2000, about 85% were currently employed by the pharmaceutical industry, about 69% held positions in quality control, quality assurance, R&D, formulation and/or validation, about 80% had practical experience of 10 and more years, and about 69% had been trained

on QbD during their practical experience. The vast majority (about 97%) thought it was either of high or extremely high importance. However, when the panelists were asked to what extent they thought implementing QbD by the Palestinian pharmaceutical manufacturers was currently a priority, about 51% of the panelists thought it was either of high or extremely high importance.

Conclusion: Consensual techniques might be used in identifying and prioritizing barriers to implement QbD by local pharmaceutical industry. Further studies are needed to investigate ways to eliminate these barriers and promote the implementation of QbD in the manufacture of pharmaceutical products in Palestine.

Key words: *Quality by design (QbD); pharmaceutical industry; regulatory guidelines; drug development; generics; barriers, qualitative interviews*

Chapter One

Introduction

Pharmaceutical development has long been iterative and empirical focusing on the delivery of the pharmaceutical product to the next phase of the clinical studies [1]. During a workshop sponsored by the US Food and Drug Administration (FDA) and the American Association of Pharmaceutical Scientists (AAPS) in 2005, FDA deputy commissioner described the drug development process as “costly, wasteful, and encouraging industry to conduct more tests and file more data than needed to drug shortages, slower drug development, and intensive regulatory oversight” [2].

The concept of Quality by Design (QbD) has been proposed some 10 years ago with the objective of improving the manufacturing and safety of pharmaceutical products and to facilitate a flexible regulatory process [3]. QbD as opposed to quality by testing (QbT) might impact success of generic development, continuous development, clinical performance, and patient satisfaction. The concept of QbD has been articulated in the guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. Further, the concept was articulated in different related documents such as in Q8 Pharmaceutical development, along with ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality Systems [4, 5]. Subsequently, QbD was endorsed by regulatory agencies in US (the FDA)

and Europe (the European Medicines Agency (EMA)) [6]. In QbD approach, it is important to thoroughly understand the characteristics of a pharmaceutical product and the process of its manufacture. The impact of variability in raw materials and process on the critical quality attributes of the finished product must also be thoroughly understood. Similarly, the association between the critical quality attributes (CQAs) of the finished product and its clinical properties must also be understood. Lately, the QbD approach has been utilized extensively in pharmaceutical development. Today, it is widely regarded that implementing QbD might guarantee the development of high quality pharmaceutical products. However, little was reported on tangible improvements in productivity, competitiveness in the market, and /or financial returns on investment. To address those issues, the FDA established a pharmaceutical quality assessment system (PQAS) and outlined the agency's thinking in the article "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" [7]. The FDA designed the PQAS to encourage pharmaceutical manufacturers to adopt modern approaches for the development of pharmaceutical products that lead to a desired state of drug regulation, which would result in, according to Woodcock, "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight" [2]. To achieve the desired state, the concept of quality by design (QbD) was introduced. This led quality experts to claim that quality must be planned not tested in the first place because most of quality problems arise from poor planning [8].

Implementation of QbD approach in contemporary pharmaceutical industry has become a necessity [9]. During traditional pharmaceutical development approaches, the focus was to deliver the product to the next phase of clinical study, therefore, formulation design tended to be largely empirical [1]. Patient safety was ensured through the use of well-defined parameters governed by a changing control process. This has placed a considerable burden on the pharmaceutical industry, especially when changes to the parameters were required during the product's life cycle. A continuous innovation and improvement culture was not easily implementable. To ensure efficiency and facilitate regulatory decision, regulatory agencies tended to require a supplemental application for every manufacturing change [10]. This has increased the number of manufacturing supplement applications dramatically. For example, in 2007 there has been 5000 supplements submitted for the FDA for new drug applications (NDAs), biological license applications (BLAs) and abbreviated new drug applications (ANDAs) with focusing only on chemistry without taking other consideration of manufacturing such as engineering for both of original and supplements [1].

QbD can be described as a systematic approach to drug development that starts with predefined objectives and emphasizes product and process understanding and process control, all based on sound science and quality risk management [2, 7]. In QbD, a) the product is designed to meet patient needs and performance requirements, b) the process is designed to consistently meet product critical quality attributes, c) the impact of starting

raw materials and process parameters on product quality is understood, d) critical sources of process variability are identified and controlled with appropriate control strategies, and e) the process is continually monitored and updated to allow for consistent quality over time [11, 12]. Little was reported on failures to implement QbD in generic development. In Palestine, the concept of QbD is not applied by local pharmaceutical manufacturers in generic development. This makes one pose several questions like “is it important to apply the concept of QbD in generic development?”, “is implementing QbD in generic development in Palestine a priority?”, “why the concept of QbD is not being applied by local pharmaceutical manufacturers in generic development?”, and “what are the barriers hindering the implementation of QbD in generic development?”.

Despite the potential benefits of applying QbD articulated by quality experts and regulatory agencies, these benefits are not easy to achieve in practice. Many pharmaceutical industrial plants found it difficult to implement QbD successfully. It is not fully understood what barriers hinder the local pharmaceutical industry in Palestine from implementing QbD approach in the development of their branded generics.

Identifying barriers to implementing QbD by the local pharmaceutical industry in Palestine is a prerequisite step in eliminating this phenomenon and bridging the gaps in existing evidence-based drug development. The literature does not narrate intensively what are these barriers from experts’ viewpoint. Identifying and prioritizing barriers to implementing QbD in generic development could provide crucial information to quality managers

and decision makers in regulatory agencies, industry, education, and training sectors to intervene and design proper measures or interventions to eliminate these barriers.

In order to design interventions to highlight barriers to implement QbD in the Palestinian pharmaceutical industry, identifying these barriers from experts' viewpoint is a priority. Obviously, it is more likely that stakeholders in the industry would respond and change their current practice to eliminate these barriers based on interventions designed on barriers they believe in rather than barriers that they would conflict with.

The present study conducted to investigate and categorize the barriers to a successful implementation of QbD in local pharmaceutical industry in Palestine. The purpose of this study is to understand QbD barriers and prioritize their relative importance by ranking them in the pharmaceutical industry.

This study will identify, prioritize and rank the barriers from the most important to the least important, which potentially shall allow managers and decision makers in pharmaceutical industry to decide which barriers they need to pay attention to and take care of for a successful implementation of QbD.

The strength of this study is the development of a comprehensive model for the investigation and prioritization of barriers that the pharmaceutical industry experiences when implementing a QbD program.

1.1 Traditional pharmaceutical development

Traditionally, pharmaceutical development and formulation design, as mentioned previously, was dependent upon empirical methods to reach the optimal dosage form. Patients' safety determined by using defined parameters and tight specifications that make barriers when changes occur to these parameters during life cycles of products. In addition, these tight specifications make barriers to the culture of continuous improvements [13]. Quality by testing (QbT) which was used in early stage of good manufacturing practice is not enough to completely assure the quality of finished products. In the QbT process, only the quality of the product is assured by the testing (raw material and drug substance, product manufacturing: in-process testing and end-product testing) and the quality is not guaranteed. While by the new vision of GMP that is now known as cGMP, adding new guidance as the integration of quality risk management (ICH Q9) and pharmaceutical development (ICH Q8), gave more room for improvement in the drug manufacturing and gave more flexibility. In addition, the cGMP enhanced quality, reduced cost, and time. Such guidance was issued because the regulatory authorities recognized that more controlling is needed on drug manufacturing to assure the quality of pharmaceutical products. Aiming to promote a maximally efficient, agile, and flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory. QbD which is a quality risk management based approach began with the recognition that increased

testing does not improve product quality, while enhanced quality can be assured by building quality into the product while in the design state. In order for quality to enhance, it must be built into the product. To achieve this goal, it is important to understand how formulation and manufacturing process variables influence product quality [5]. Table 1.1 compares the traditional approach (QbT) and QbD.

Table (1.1): Traditional approach (Quality by testing) Vs Quality by design [14]

Aspect	Minimal Current Traditional Approaches	Enhanced QbD Approaches
Pharmaceutical development	Empirical, random, focus on optimization	Systematic, mechanistic, multivariate experiments, focus on control strategy and robustness
Manufacturing process	Fixed	Adjustable within design space, managed by company's quality systems
Process control	Some in-process testing	Process analytical technology used, process operations tracked and trended
Product specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control strategy	Testing and inspection	Risked-based control strategy, real-time release possible
Lifecycle management	Reactive (problem-solving and corrective action)	Preventive action with continual improvement

To understand the most current thinking behind pharmaceutical development and regulatory expectations, one must understand the principles articulated in the international conference on harmonization (ICH) on different guidelines. These guidelines depend on the use of information and knowledge gathered during development studies, to provide a scientific rationale for the design of the manufacturing process

for a pharmaceutical product. These guidelines include ICH Q8, Q9 and Q10 [4].

1.2 ICH Q8. Pharmaceutical development

ICH Q8 was published in the federal register on May 22, 2006, as a guidance for pharmaceutical product development and regulatory expectations [15]. This guidance introduced the concept of QbD, which is a systematic approach to design a product of predefined quality and its production process to continually and consistently delivering intended performance of the final product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. According to ICH Q8, pharmaceutical development is a learning process, understanding is gained from design of experiments (DOE) (which is an integral part of QbD that aids in the planning, optimization and systematic screening of the parameters involved.), process analytical technology (PAT) and failure are discussed as a part of the life cycle in QbD [15]. ICH Q8 defines design space as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality, movement within design space not consider a change and does not need post approval change process. However, movement out of design space need a regulatory post

approval change process [16]. The design space depends upon the equipment, batch size and design principles [4].

1.3 ICH Q9. Quality risk management

1.3.1 Introduction

Risk management concept is widely used in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system. Risk is defined as the probability of the harm to be occur and the severity of this harm. The protection of the patient by managing the risk to quality should be considered of prime importance [17]. Risk Management is a systematic process for the assessment, control, communication and review of risks. It starts with identifying the possible risks associated with a product or with the process used to develop, manufacture, and distribute the product.

Each process and product associated with some risk; the reduction of this risk to zero level is not a realistic goal. The manufacturing of drugs and its components have some risk of quality; this risk is part from the overall risk. Therefore, it is important to keep the quality of drug during the life cycle of products. QRM must be applied to different areas in pharmaceutical industry as in process, materials, facilities, manufacturing, distribution, and patient [18].

1.3.2 Ssignificance of quality risk management

Implementation of risk based approach in pharmaceutical industry provides a consistent method, where improve decision making, reduce the number of threats or minimize their impact through the consistent use of the tools/methods and periodic review. Furthermore, which was easily associated with resource allocation and ensuring patient safety. Ultimately, applying risk management to pharmaceutical industry should be the output of the risk management supports the organization to meet the defined goals [18]. In addition to that, an effective quality risk management approach can further ensure and facilitate better and more informed decision, providing a proactive means to identify and control potential quality issues during development and manufacturing, leading to a high quality manufactured medicinal products provided for patient, also provide regulators with greater assurance of a company's ability to deal with potential risks, can beneficially affect the extent and level of direct regulatory oversight, and providing regulators with greater assurance of a company's ability to deal with potential risks. QRM obviate the communication between industry and regulatory authorities [17].

1.3.3 Approaches to Quality Risk Management

QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. Where two approaches were identified in implementing QRM in industry.

1. Proactively (Proactive): Where by this approach, identifies the threat exposure areas to mitigate the potential for loss, before the loss occurs.
2. Retrospectively (Reactive): Where by This approach investigates the threat exposure areas to identify the root cause for loss and its control, after the loss occurs.

1.3.4 General process of quality risk management

According to the following diagram which is shown in figure one. QRM is a systematic process, starting with assessment, controlling, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. One of the most element important is risk assessment.

1.3.4.1 Risk assessment

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of the harm. Risk assessment is one of the essential step require for ensuring the effective risk management. It reviews the materials, processes, equipment used, storage conditions and intended use of the product. Recognizing risk assessment, important for identification of critical quality attribute , which affect On quality of finished products, link between FDA and industry. In addition to, increase the communication and cooperation between R&D and manufacturing and other sites on the plant [19]. ICH guideline Q9 mentions some methods of risk assessment such as fishbone diagram whish used to

identify all potential variables as raw materials, compression parameters, and environmental parameters that affect on particular CQA. In addition to, Failure Mode Effects Analysis (FMEA), Failure Mode Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), Preliminary Hazard Analysis (PHA), Risk ranking and filtering and Supporting statistical tools. ICH Q9 also clarifies the concept of quality risk management and related concept as risk communication, risk control, risk evaluation, risk identification and risk reduction, that aim to decrease the probability of the occurrence of the harm and the severity of this harm. The benefits of risk assessment include importance of identifying and classifying of parameters on design space, necessary in process development and important in case of monitoring and improvement. Furthermore, risk assessment increases assurance of quality, where process variability identified and linked to CQA of products, so any changes in future within design space will be known without affect on quality of finished product [8]. The following diagram explain the process of quality risk management. Starting with risk assessment and finish with risk review.

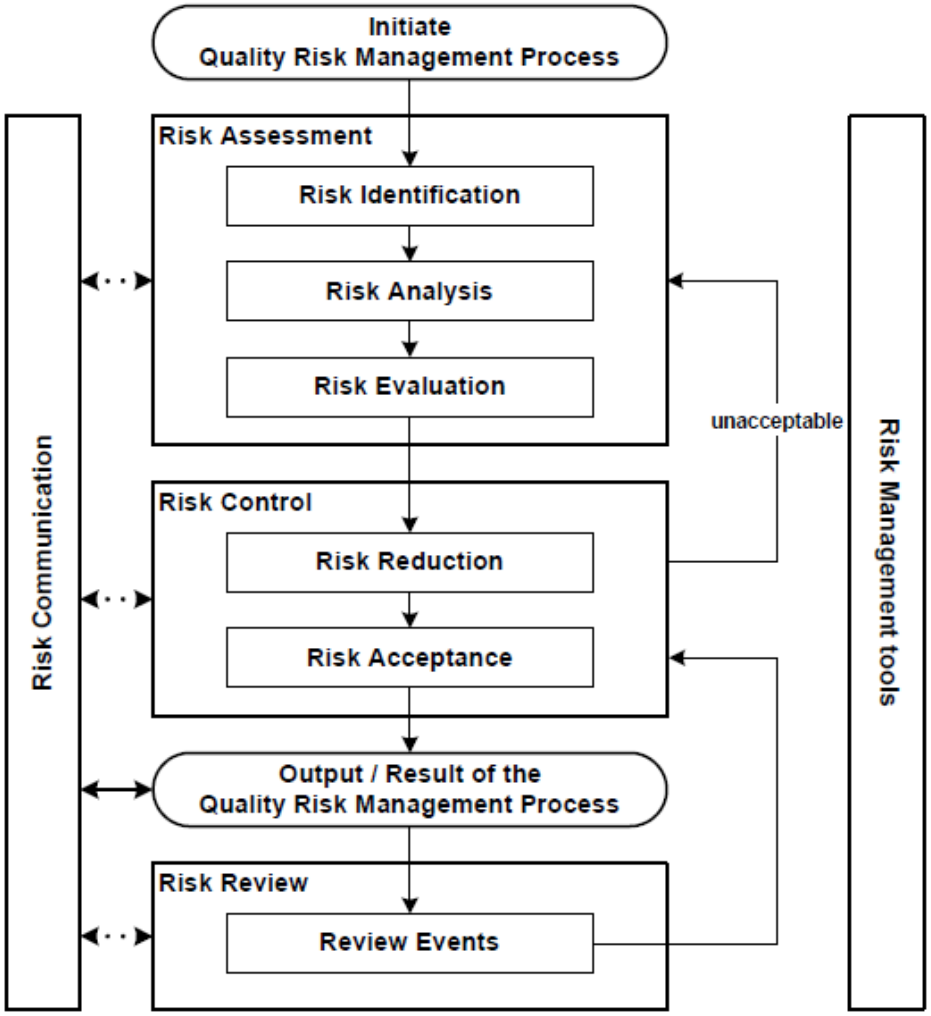

Figure (1.1) : Overview of a typical quality risk management process [19].

1.4 ICH Q10 Pharmaceutical Quality System

This guideline describes the stages of drug manufacturing from development stage till to product discontinuation by passing on technology transfer and commercial manufacturing according to the figure (1.2). In conjunction with ICH Q8 and ICH Q9 reach to desired state as described in figure (1.3).

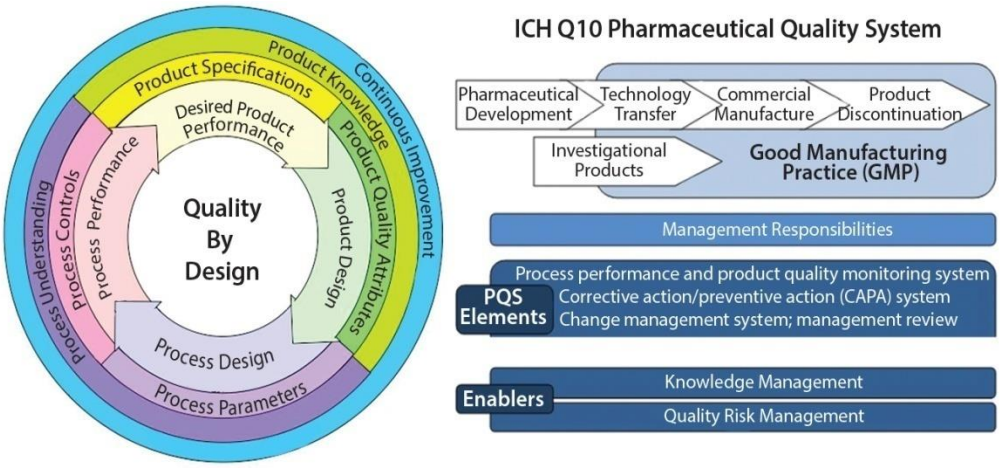

Figure (1.2) : Quality by design embraces an integrated science and risk-based approach with continuous improvement for the entire product life cycle; PQS = pharmaceutical quality system [20].

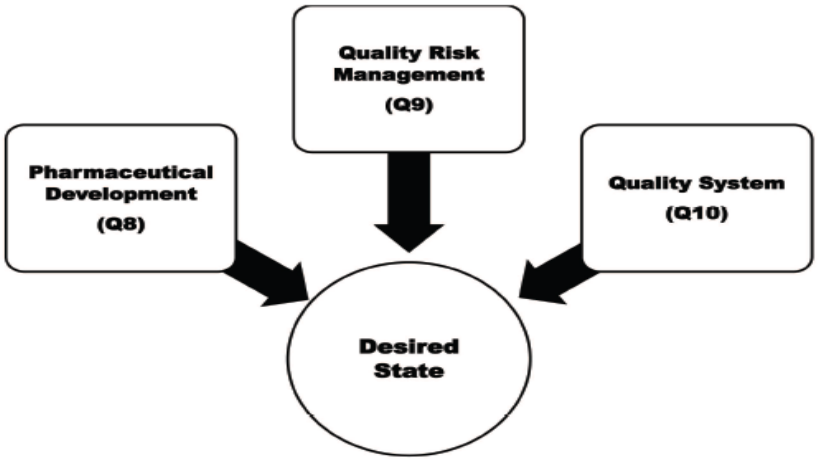

Figure (1.3) : Quality attributes governing quality of desired product [21]**.**

1.5 Elements of QbD

1.5.1 Quality target product profile

Quality by design approach composed by different elements starting with identification of quality target product profile (QTPP), which mean prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to evolve the desired quality and thus

the safety and efficacy of a drug product is realized . QTPP for generic product determined from reference listed drug because the generic must be as brand, identical in the dose strength, route of administration, safety, efficacy and intended use [22]. According to ICH QTPP form the basis of QbD and the basis for drug development. ICH Q8 describe the QTPP as prospective summary of the quality characteristic must be available in the drug product to assure the safety and efficacy of this product.

1.5.2 Critical Quality Attribute

All the characteristic as physical, chemical, biological and microbiological that must be within the range to assure the quality of finished products, these characteristic included for drug substance, excepients, intermediates and drug product. For example, CQAs for solid oral dosage form consist those aspects affect on quality of finished products such as purity, potency, stability and drug release. Further More, addition aspects added to include aerodynamic properties for inhaled dosage form, adhesive prosperities for transdermal patches and specific aspect for each dosage form [23]. QRM approach is a very important aspect providing the most important information that links materials attributes and process parameters that affect on CQA of products, used also for prioritization the list of CQA for subsequent evaluation. By using this concept in addition to experiments, identify their effect or impact on the quality of finished products where

- Definition of critical is varied
- Most of the applications of CQA attributes related

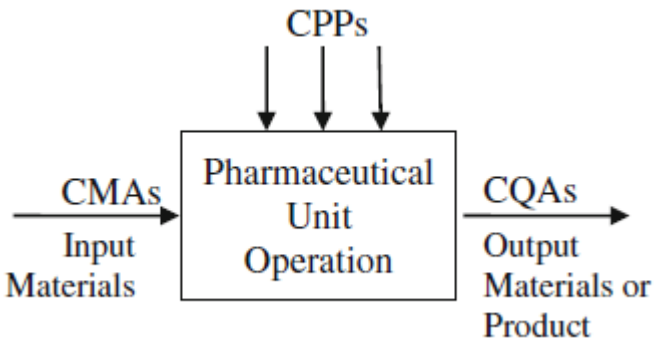

Figure (1.4) : Link input critical material attributes and critical process parameter to output critical quality attributes [4].

1.5.3 Design space

That defined according to ICH Q8 the multidimensional and interaction of input variables for example, material attributes and process parameters that have been demonstrated to provide assurance of quality. Working within a design space doesn't meaning a change and doesn’t need a post approval changes. However, out of design space means a change and need post approval changes. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. In contrast, in case of traditional pharmaceutical development the knowledge is limited, so any changes need new data and new post approval changes and supplement. After Q8 implementation, an influence of factors is explored, creating knowledge, and risk analysis of impact of change is possible. Leading to increase the understanding of the product life cycles including material attributes, process controls and robustness of drug manufacturing [24]. To achieve this flexibility, different tools must be used as design of

experiments, process analytical technology (PAT) and quality risk management approach, which use as prioritizing tool and ranking if a new study needed to gather important knowledge.

1.5.4 Control strategy

How in-process controls and the controls of input materials (drug substance and excipients), the container closure system, intermediates, and end products contribute to the final product quality. Depending on understanding of product, formulation, process and controlling of critical quality attributes [23]. The aim of control strategy to assure that product of required quality manufacture in a consistent manner.

Examples of control strategy elements.

- Controlling of input materials as drug substance, excipients, primary packaging materials by understanding there effect on product quality.
- Product specifications.
- Controls for unit operations that have an impact on product quality for example (drying on degradation, particle size distribution on dissolution).
- In process or real time release testing
- A monitoring program (full product testing at regular intervals) .

A very important thing must be considered in control strategy, where a very good knowledge of manufacturing process to put specifications, more meaningful sampling for drug product testing, and strong experience in putting release time specifications [8].

1.5.5 Process Analytical Technology

The application of PAT may be part of the control strategy [25]. This tool use to assure that the process still within established design space and continuous monitoring for CMAs, CPPs, and CQAs. In-process testing, CMAs, or CQAs can also be measured online or in line with PAT. This tool is more effective than end product testing used by traditional methods for failure detection. PAT is a system for designing analyzing and controlling of manufacture through timely measurement (during processing) of critical quality of raw material and in process materials to assure the best quality of finished products [15]. Change from lab-based end-product quality testing to better formulation and process design, leading potentially to more in-line (where sample analysis while it part from process stream), online (while the sample is analyzed and may return to the stream) or at-line testing (where the sample is removed and analyzed close to the process stream) [15, 26]. PAT along with DoE and risk assessment are tools used to implement the concept of QbD. In order to use PAT tool four key components are needed as

1. Multivariate data acquisition and analysis
2. Process analytical chemistry tools
3. Process monitoring and control
4. Continuous process optimization and knowledge management.

The following diagram explain the QbD elements and their relationship.

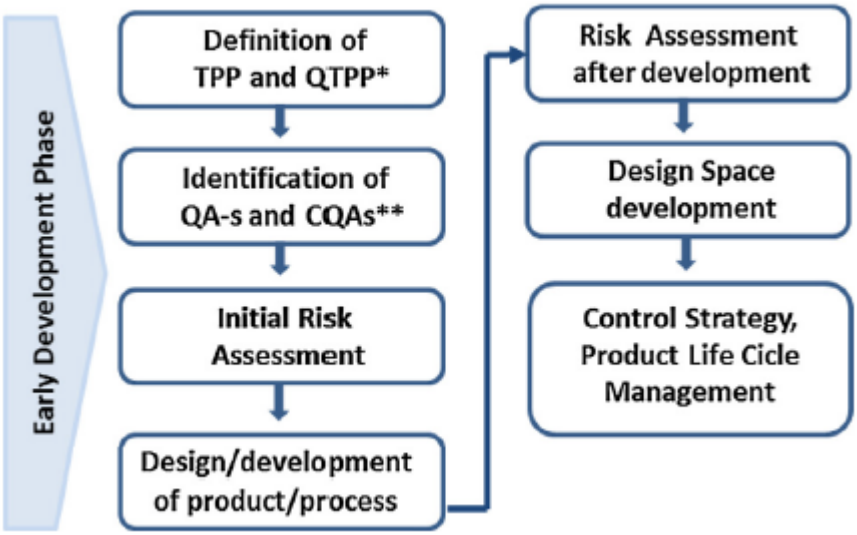

Figure (1.5): Roadmap of quality by design elements [27].

1.6 Gap in the literature

To the best of our knowledge, identification and prioritization of barriers to implement QbD by the local pharmaceutical industry in Palestine were not studied before, and therefore, currently little information is available on this topic.

1.7 Objectives

1.7.1 General objectives

The general aim of this study is to identify and prioritize the barriers to implementing QbD by local pharmaceutical industry in Palestine. Identifying and prioritizing these barriers might be the first step to tackle these barriers and enhance the quality of pharmaceuticals manufactured in Palestine.

1.7.2 Specific objectives

1. To investigate and categorize the QbD barriers faces the implementation of QbD in Palestinian pharmaceutical industry.
2. Identifying these barriers from experts' viewpoint.
3. To prioritize the relative importance of these QbD barriers which could serve as invaluable lesson to those service industries that are planning to implement QbD in the process of its implementation.
4. Identifying barriers to implementing QbD by the local pharmaceutical industry in Palestine is a prerequisite step in eliminating this phenomenon and bridging the gaps in existing evidence-based drug development.

1.8 Significance of this study

To the best our knowledge, there are limited data about QbD and its implementation in our local pharmaceutical industry in Palestine. The strength of this study is the development of a comprehensive model for the investigation and prioritization of barriers that the pharmaceutical industry experiences when implementing a QbD program. Therefore, this study provides baseline data and information about QbD in Palestine, this study is the first of its type in Palestine. Such information is highly required in pharmaceutical company, as such information might make the implementation of QbD in Palestine more easy, encourage the local companies to integrate the concept of QbD. This might enhance the quality of pharmaceutical products provided for patients.

Chapter Two

Literature review

2.1 Studies on quality attributes

Observational exploratory qualitative studies were conducted to increase the quality of health care provided for patients and to improve the efficiency and safety of health care services. For example, a study carried out by Rad et al as a survey to implementation of total quality management (TQM) in health care organization in Iran. The objective of this research was to investigate the success of TQM and barriers to its successful implementation in health care services organizations in Isfahan province, Iran [28]. The study correlated barriers to TQM and identified the dimensions of the problem. In this study, human resource, strategic and structural problems were the most important obstacles and barriers to TQM. The results could be very useful for developing a model of TQM that can be implemented easily, effectively, efficiently and successfully in a cross-cultural context. The authors attempted to investigate the success of TQM and its implementation barriers in health care services organizations. The importance of this study is postulated to help organizations in planning better TQM designs, researchers also will be able to use this research results for developing quality management theory and construct a model for choosing and implementing a culturally suitable TQM approach to avoid some of these problems. Health care managers will be able to use the results to evaluate their TQM implementation so as to target improvement

areas. This research provides useful insight into the organization that uses TQM as an organization development program [28]. In another example, Ahmadian et al attempted to prioritize the barriers to successful implementation of hospital information systems (HIS). HIS are often implemented to enhance the quality of care, as well as to improve the efficiency and safety of health care services. In this study barriers were identified and prioritized from most to the least important. This study was supposed to help policy makers to decide what to do when planning for HIS utilization [29]. Another study carried out by Hoonakker and co-worker. The authors aimed in this study to investigate the barriers that prevent or limit the implementation of quality management in construction industry. In this article they discussed the problems of defining quality in the construction industry, examined possible benefits of implementing quality, and looked at barriers to quality implementation in construction. By using data collected during interviews with contractors and data from questionnaire surveys. Results show that contractors do understand the potential benefits of quality implementation but there are also many barriers to implementation. They describe recent developments that might help to overcome the barriers. One of the most barriers they found is changing the culture in construction industry. Lessons from manufacturing and services industries have shown that implementing quality management programs require a thorough understanding of organizational culture and the changes needed in order for quality to become a state of mind of organizational members [30]. In addition to, with other qualitative study

carried out to identification and overcoming the barriers of implementation of quality related issues as the study conducted by Poon et al in which computerized physician order entry (CPOE) implementation in hospitals was proposed to decrease the medication errors and improve the quality services provided for patients. This study explain in summary CPOE implementation is a difficult process, punctuated by uncertainties, risks, and organizational barriers. Strategies identified by study informants to overcome these barriers offer hope to hospitals that are willing to take on this challenge. Although widespread adoption will take time, they believe that policymakers have many opportunities to speed the nationwide adoption of this proven patient-safety intervention. These findings highlight several policy levers to speed the adoption of this important patient safety technology [31]. Several qualitative and exploratory studies were used to explain, discus and integration of quality attributes in different services and industries. In case of our study, despite the fact that the critical success factors (CSFs) responsible for a successful implementation of QbD in pharmaceutical industry have helped to achieve the desired results, where Patient safety and product efficacy are focused and improving the scientific understanding of pharmaceutical process and methods, also involves in product design and process development. Moreover, robustness of product manufacturing. In addition to, improve post approval change management.[32]. However, implementing QbD is not free from barriers and it is not fully understood what barriers hinder the local pharmaceutical

industry in Palestine from implementing QbD approach in the development of their branded generics.

2.2 Benefits of QbD implementation

According to the study carried out by Kourti and Davis on 2012 the importance of QbD implementation include reduce batch failure, increase robustness of product manufacturing, reduce variability of pharmaceutical products. Furthermore, enhance root cause analysis and post approval change management, while without good product and process understanding, the ability to efficiently scale-up and conduct root cause analysis is limited and requires the generation of additional data sets on the proposed larger scale [33]. Also several studies were done to prove the importance of QbD implementation, for example a study carried out in August 2011 the statistical analysis for response of 193 professionals from biopharmaceutical manufacturing company were 85% of respondent recognize that QbD improve process understanding and 65% of respondent recognized that QbD improved connections to quality outcomes. However, 50% of participant found that up-front cost of QbD and poor understanding of return on investment are barriers to implement QbD [34]. Another study conducted by the QbD and Product Performance Focus Group of AAPS in 2012 as a survey formed from three parts, a majority of respondents reported high frequency of utilization of several tools and most QbD elements outlined in ICH Q8 as QTPP, Quality risk management are used, where specialists from academia, agency and industry take part in this

study talked about the implementation of QbD asses as positive impact on the patients health and improve internal process such as knowledge management and decision making within pharmaceutical company [35]. Furthermore, in case of complex dosage form using QbD concept give many benefits. For example, in case of oral disintegrated film coated tablet, by controlling a lot of variables that affect on quality of finished products, as a study conducted in USA by Sonal Mazumder and coworker for studying the impact of formulation and process variables on product quality of oral disintegrating films by using quality by design approach [36].

Chapter Three

Methods

3.1 Study design

This was an observational exploratory qualitative study among different stakeholders in the Palestinian local pharmaceutical industry using the Delphi technique and the Analytic Hierarchy Process [37-41]. Consensus on potential barriers impeding the implementation of QbD by local pharmaceutical industry in generic development was investigated using a modified Delphi technique. Since its inception, the Delphi technique has emerged as a powerful tool in exploring the views and opinions of experts on a certain concept and in achieving formal consensus on issues lacking formal consensus among experts [37-41]. The modified Delphi technique combines qualitative and quantitative approaches in achieving consensus among panelists in a panel composed for the objective of achieving consensus on what barriers impede local pharmaceutical industry from implementing QbD in generic development. This technique employs iterative rounds among a panel in which the panelists with prior knowledge of the subject being investigated make private and independent votes of either agreement or disagreement on a series of presented statements or items. The iterative rounds are repeated until a consensus is achieved among the panelists on the basis of predefined consensus. A common practice in this technique that panelists are fed back with summaries of their own voting, statistics of the votes other panelists, and summaries of

their comments on each statement or item. The objective of this feedback is to allow the panelists to reconsider their votes in view of the votes and/or comments of other panelists. Normally, the Delphi technique would employ more than one round in the majority of the panels. The Delphi technique demonstrates certain advantages over other formal consensus techniques like round-table meetings, focused, and nominal groups. The merits of the Delphi technique include saving costs of gathering the panelists in one place, overcoming geographical distances and need to travel, preserving the anonymity of the panelists, and inability of a panelist or a group of panelists to dominate the discussion and voting process [37-41].

3.2 Identifying barriers to implementing QbD

To identify barriers to implementation of QbD approach in the manufacture of generics in the local Palestinian pharmaceutical industry, we approached and interviewed eight key contacts in the field who held managerial positions in the local pharmaceutical industry. The key contacts were approached and selected based on their extensive experience in the field as demonstrated by long experience (> 10 years) in pharmaceutical industry holding different precedent positions at different hierarchies. Multiple in-depth interviews were conducted with the key contacts on different occasions with open-ended questions included what barriers impede the implementation of QbD in the local pharmaceutical industry in Palestine. The objective of this step was to explore potential barriers from the perspectives of those in the upper hierarchy. The key contacts were

encouraged to list all potential barriers they thought impeded the pharmaceutical industry in Palestine from implementing the concept of QbD in generic development. In many occasions during the interviews, the interviewers evoked barriers mentioned by other key contacts. The evoked barriers served as prompts and helped the interviewee to brain-storm and provide more potential barriers. The objective of this step was to allow interviewees to “hitchhike” or follow up on other key contacts as another way of generating ideas and mentioning additional barriers. The barriers mentioned by the key contacts were noted and compiled. We then conducted an extensive literature review to collected potential barriers to implementation of QbD in the pharmaceutical industry in general. These barriers along with others barriers mentioned by the interviewee key contacts were compiled into a questionnaire. The questionnaire was piloted for clarity and understandability.

After exploring the views and opinions of the key contacts on what impede the implementation of QbD by local pharmaceutical industry in manufacturing generics, the Delphi technique was employed to achieve consensus among the panelists on what barriers impede the implementation of QbD by local pharmaceutical industry in manufacturing generics.

3.3 The panelists

In this study, a purposive sampling technique was employed to recruit panelists with prior knowledge of the subject being investigated. The panelists were recruited from local pharmaceutical industry, regulatory

agency, and universities through personal contacts in the field. The selection process ensured recruiting panelists who had extensive experience and rich in information on generic development and the accompanying regulatory process. Attention was paid to this step as it is one of the most critical steps in the Delphi technique. The inclusion criteria were as follows: 1) possession of an academic qualification at least equivalent to a bachelor of science (BSc) in pharmaceutical sciences or related sciences, 2) employed by a local pharmaceutical industry manufacturing generics or regulatory agency, 3) held a managerial or decision making position within a local pharmaceutical industry or regulatory agency, and 4) possession of a practical experience related to generic development of more than 5 years. The panelists were approached in person and invited to participate in the study. Objectives and design of the study were explained to potential participants before their consent to participate was obtained. In this study, a total of 39 panelists were included in the panel. The panel size used in this study was in the range of the panels composed to achieve consensus on issues lacking consensus in healthcare. It is noteworthy mentioning that generally there is no consensus on optimal panel size to be used in a Delphi technique. No incentives were offered to any panelist in compensation to their participation in the current study.

3.4 The study tool for the Delphi technique rounds

The questionnaire used in this study collected the sociodemographic and experience characteristics relevant to the panelists. Panelists were requested

to provide their gender, age, academic qualifications, year of obtaining the academic degree, employment history, positions held, and practical experience in years. Panelists were also asked if they had taken courses on QbD during their academic degree programs and if they had taken a training on QbD during their practical experience. To explore the views and opinions of the panelists on the importance and priority of implementing QbD in local pharmaceutical industry, the panelists were requested to express the degree to which they think implementing QbD by the Palestinian pharmaceutical manufacturers in generic development was important and a priority on a scale of 5 ranging from extremely low to extremely high.

The panelists were also provided with 34 statements representing potential barriers impeding the implementation of QbD by the Palestinian pharmaceutical manufacturers in generic development and panelists were requested to express the degree to which they agree or disagree with the provided statement, i.e. if they agree or disagree that the statement represented a real barrier impeding the implementation of QbD in generic development. The panelists expressed the degree to which they agree or disagree with the provided statements on a Likert scale of 1-9.

3.5 The modified Delphi technique

To achieve consensus on what barriers impede the implementation of QbD in the local pharmaceutical industry in Palestine, we used a two-round

Delphi technique among a panel of 39 panelists with extensive experience in generic development.

3.5.1 The Delphi round 01

In Delphi round 01, the questionnaire was hand-delivered to the 39 panelists and panelists were requested to provide their sociodemographic and experience details. The panelists expressed their views and opinions on the importance and priority of implementing QbD by local pharmaceutical industry in generic development and voted on each statement representing potential barrier impeding the implementation of QbD by local pharmaceutical industry in generic development. When a panelist votes 1-3 on a statement, this meant that the panelist was of the opinion that the potential barrier does not impede the local pharmaceutical industry from implementing the concept of QbD in generic development. When a panelist votes 7-9 on a statement, this meant that the panelist was of the opinion that the potential barrier impeded the pharmaceutical industry from implementing the concept of QbD in generic development. When a panelist votes 4-6 on a statement, this meant that the panelist could not decide whether the potential barrier impeded the pharmaceutical industry from implementing the concept of QbD in generic development or not. The panelists were encouraged to add comments to justify and/or to qualify their votes on each statement.

3.5.1.1 Analysis of the votes in Delphi round 01

Votes of the panelists in the Delphi round 01 were entered into an Excel Sheet (Microsoft Excel 2013) and their descriptive statistics were generated. Statistics like 1st quartile (Q1), median (Q2), 3rd quartile (Q3), and interquartile range (IQR) for each statement were generated separately. In this study, consensus was defined as in previous studies conducted to achieve consensus on issues lacking formal consensus in healthcare. Briefly, a statement was considered barriers when the median score of the votes was 7-9 and the IQR was 0-2. A statement was not considered as a barrier when the median score of the votes was 1-3 and the IQR was 0-2. A statement was considered equivocal when the median score was 4-6 or the IQR was larger than 2. All equivocal statements were included in a second iterative Delphi round.

3.5.2 The Delphi round 02

Statements that were considered equivocal as per the consensus definition were included in a revised questionnaire along with summaries of the median score, IQR, and comments made by the panelists in the Delphi round 01. The panelists were also reminded of their own previous votes and asked if they wished to reconsider their votes in view of the votes and comments of the other panelists. The votes obtained in the Delphi round 02 were analyzed using the same criteria of consensus used in the Delphi round 01.

3.6 Relative importance weight scores of the barriers

In this study, we used the Analytical Hierarch Process (AHP) to generate relative importance weight scores of the barriers on which consensus was achieved in the Delphi technique. The objective of this process was to hierarchies the barriers in order of their relative importance. The AHP has evolved as one of the most commonly used multi-criteria decision analysis technique in healthcare. The AHP has certain merits over other multi-criteria decision analysis techniques. These merits include suitability to use in small group settings and providing accessible procedure to address and make a decision in complex matters with multiple criteria. The AHP makes use of pairwise comparisons to hierarchies items in order of their priority or importance. In this study, barriers were organized into categories and 8 panelists were recruited and requested to make the pairwise comparisons between categories and items within categories on a scale of 1-9. When a category was given higher score this indicated a higher priority or importance score is given to that category compared to other categories. Similarly, a higher score given to one item in a category indicated a higher priority or importance of that item compared to the other items within the category. In this study, matrices in spreadsheets were used to compute the relative importance scores as percentages for categories and for items with the categories separately. The formula used in the matrices and the spreadsheets were originally developed by Saaty. Importance scores (%) for all categories sum to 100% and importance scores (%) for all items within a category sum to 100% [42].

3.7 Statistical analysis

Votes of the panelists were considered when calculating the importance weights (%) when their consistency ratios were below 0.1. Votes were entered and analyzed into GraphPad Prism 6.0 for Windows (GraphPad Software). One-way analysis of variance (ANOVA) with Bonferroni post hoc tests were used to evaluate differences in importance weights (%) between categories and items within the same category. Statistical significance was considered when the p was < 0.05.

3.8 Ethical approval

This study received approval from the Institutional Review Board of An-Najah National University, Nablus. The approval number was (40 September /2016). All panelists provided verbal consents before taking part in this study. Votes of the panelists weighed equally in the analysis. The Delphi technique is a semi-anonymous technique in which the identity of the panelist is known to the investigator and not to the rest of the panel members. During the study, the identity of each panelist remained confidential to the rest of the panelists.

Chapter Four

Results

4.1 Interviews with the key contacts and barriers evoked by the interviewees

During the interviews with the key contacts many themes and potential barriers were evoked by the interviewees. A list of these themes and potential barriers are listed in Table 1.

Table 1: Themes and potential barriers evoked by the key contacts during the multiple interviews

#	Theme/potential barrier
	Barriers related to technicality, resources, instruments, and personnel
1	In QbD-based product development, there are many variables that need to be controlled. Having an in-depth understanding of the nature of these variables and how they can impact the performance of the finished product limits implementing the concept of QbD in generic development.
2	In QbD-based product developments analytical methods need to be developed and multiple tests need to be performed. The difficulty of developing suitable analytical methods and the amount of testing needed hinders implementing the concept of QbD in generic development.
3	QbD-based product developments require hiring highly qualified personnel. Highly qualified personnel are difficult to find and hire.
4	In QbD-based product developments, there is a need for data management systems for tracking and controlling operations. Resources allocated for such systems are scarce and hence this hinders implementing the concept of QbD in generic development.
5	QbD-based product developments require using different equipment by the R&D department. The availability and difficulty of procuring various equipment hinders implementing

#	**Theme/potential barrier**
	QbD in generic development.
6	QbD-based product development requires more equipment to be procured to the production department. The availability and difficulty of procuring various equipment hinders implementing QbD in generic development.
7	In QbD-based product developments, materials like active pharmaceutical ingredients, excipients, and packaging materials need to be procured from different suppliers. This might increase costs and thus hinders implementing QbD in generic development.
8	Qualified trainers on QbD are difficult to find or hire. This hinders implementing QbD in generic development.
9	Manufacturers of generics do not have sufficient access to resources for assessment of different processes in QbD-based developments. Limited availability and access to resources hinders implementing QbD in generic development.
10	Manufacturers are familiar with the many regulatory processes and follow on steps in traditional development. Little is known on regulatory processes and follow on steps in QbD-based developments. Lack of knowledge of these processes and follow on steps hinders implementing QbD in generic development.
11	There are costs incumbent upon the manufacturers to train staff on QbD-based development. These incumbent costs hinder implementing QbD in generic development.
12	Training on QbD based developments is costly time-wise. In competitive environment, time constraints hinder implementing QbD in generic development.
13	In QbD-based developments there is a need to procure and use software packages to facilitate the process. Availability and access to these software packages hinder implementing QbD in generic development.
14	Software packages used in QbD-based developments are often not user-friendly and require training. Availability of qualified trainers and the costs related to training hinder implementing QbD in generic development.
15	In QbD-based development, there is a need to use many software packages. Acquiring adequate command on all required software packages takes time, efforts, and costs which hinder implementing QbD in generic development.
	Barriers related to the regulatory process

#	**Theme/potential barrier**
1	The organizational culture within local regulatory agencies does not encourage implementing QbD in generic development.
2	QbD-based developments imply testing processes before implementing them. Manufacturers are concerned that this testing may slow down the development of the final product and thus hinder implementing QbD in generic development.
3	Local regulatory agencies do not have adequate access to and command on resources to assess and evaluate the different processes in QbD-based developments. Lack of access and command hinder implementing QbD in generic development.
4	Implementing QbD-based developments requires a lot of resources, costs, efforts, and training. Therefore, local regulatory agencies need to incentivize the industry to encourage implementing QbD in generic development. Lack of incentives hinder implementing QbD in generic development.
5	Manufacturers believe that implementing QbD slows down the time taken to fill an abbreviated new drug application (ANDA) to local regulatory agencies. This believe hinders implementing QbD in generic development.
	Barriers related to decision making within the local pharmaceutical industry
1	The organizational culture within the local generic pharmaceutical industry does not encourage implementing QbD-based development. The current organizational culture hinders implementing QbD in generic development.
2	Local pharmaceutical industry manufacture a large number of generic products. Implementing QbD-based developments on a large number of products would be difficult. The time, efforts, training, and/or costs needed to implement QbD-based developments on a large number of products hinder implementing QbD in generic development.
3	The top management within the local pharmaceutical industry lack adequate knowledge of quality risk management. Lack of adequate knowledge of the attributes of quality risk management hinders implementing QbD in generic development.
4	The concept of QbD in general is not well understood within the local pharmaceutical industry. Lack of understanding on the concepts behind QbD and QbD-based development hinder implementing QbD in generic development.
5	The top management within the local pharmaceutical industry lack adequate knowledge of critical quality attributes. Lack of

#	**Theme/potential barrier**
	adequate knowledge of the critical quality attributes hinders implementing QbD in generic development.
6	The top management within the local pharmaceutical industry is not familiar with the equipment required for implementing QbD-based developments and this hinders implementing QbD in generic development.
7	Implementing QbD-based developments necessitates implementing new measures for inspection, quality assurance, review and scale-up. Lack of knowledge of and familiarity with these measures hinder implementing QbD in generic development.
8	Implementing QbD-based development requires training for the personnel. Reluctance of the top management to facilitate training the personnel hinders implementing QbD in generic development.
9	Manufacturers believe documentation in QbD-based developments is more complicated and requires more time, training and allocation of resources than in traditional developments. This belief hinders implementing QbD in generic development.
10	Decision makers within the local pharmaceutical industry believe that implementing QbD might increase the price of the finished pharmaceutical products and that would negatively impact their market share.
11	Decision makers within the local pharmaceutical industry believe that implementing QbD-based developments would increase the quantity of unnecessary information filed to regulatory agencies and this might delay the review and approval process.
	Barriers related to the concept of QbD
1	The concept of QbD was originally conceived for pharmaceutical companies developing innovative pharmaceutical products. Because local pharmaceutical companies make generic copies of these innovative products after the expiry of their patent, QbD-based developments are not needed in generic development.
2	Because local pharmaceutical industry obtains already developed and tested formula after the expiry of a patented innovative pharmaceutical product to make a generic copy, real development within the local pharmaceutical industry is rare. Therefore, QbD-based developments are not implemented in

#	Theme/potential barrier
	generic developments.
3	The concept of QbD was originally conceived for big multi-national pharmaceutical companies. Because local pharmaceutical companies are comparatively small, they are not be interested in QbD-based developments.

4.2 The sociodemographic and experience details of the panelists

Responses were obtained from all participants in both rounds. In this study, about 62% of the panelists were male in gender, about 64% were 40 years old and above, about 10% had PhD degree, about 59% obtained their academic degree before the year 2000, about 85% were currently employed by the pharmaceutical industry, about 69% held positions in quality control, quality assurance, GMP, R&D, formulation and/or validation, about 80% had practical experience of 10 and more years, and about 69% had been trained on QbD during their practical experience. The detailed characteristics of the panelists are shown in Table 2.

Table 2: Sociodemographic and experience details of the panelists who took part in this study (*n = 39*)

Characteristic	**N**		**%**
Gender			
Male	24		61.5
Female	15		38.5
Age (years)			
< 40	14		35.9
≥ 40	25		64.1
Academic qualifications			
BSc	18		46.2
MSc	17		43.6
PhD	4		10.3
Year of obtaining degree			
Before 1990	10		25.6
1990-2000	13		33.3
After 2000	16		41.0
Employer			
Pharmaceutical industry	33		84.6
Regulatory agency	4		10.3
University	2		5.1
Position			
Quality control or assurance manager/GMP	15		38.5
R&D/Formulation/Validation	12		30.8
Production/Project manager/Registration	12		30.8
Experience (years)			
< 10	8		20.5
≥ 10	31		79.5
Had a course on QbD during academic degree program			
Yes	5		12.8
No	34		87.2
Had a training on QbD during practical experience			
Yes	27		69.2
No	12		30.8

BSc: Bachelor of Science, MSc: Master of Science, PhD: Doctor of Science, QbD: Quality by design, GMP: good manufacturing practices, R&D: research and development

4.3 Opinions of the panelists on the importance and priority of QbD in generic development

When the panelists were asked to what extent they thought that implementing QbD by the Palestinian pharmaceutical manufacturers in generic development was important, the vast majority (about 97%) thought it was either of high or extremely high importance. However, when the panelists were asked to what extent they thought implementing QbD by the Palestinian pharmaceutical manufacturers was currently a priority, about 51% of the panelists thought it was either of high or extremely high importance. The detailed distribution of the responses of the panelists are shown in Table 3.

Table 3: Opinions of the panelists on the importance and priority of implementing QbD by local pharmaceutical industry

To what extent do you think implementing QbD by the Palestinian pharmaceutical manufacturers in generic development is important?			
	N		**%**
Extremely low	0		0.0
Low	0		0.0
Intermediate	1		2.6
High	13		33.3
Extremely high	25		64.1
To what extent do you think implementing QbD by the Palestinian pharmaceutical manufacturers is currently a priority?			
	N		**%**
Extremely low priority	0		0.0
Low priority	4		10.3
Intermediate priority	15		38.5
High priority	14		35.9
Extremely high priority	6		15.4

4.4 Barriers impeding the implementation of QbD in generic development by the local pharmaceutical industry

Of the 34 potential barriers presented to the panelists for voting, consensus was achieved on 15 (44.1%) statements that represent barriers impeding the implementation of QbD in generic development by the local pharmaceutical industry in Delphi round 01. Consensus was also achieved on further 14 (41.2%) statements that represent barriers impeding the implementation of QbD in generic development by the local pharmaceutical industry in Delphi round 02. In general, 15 barriers were related to resources, instruments, and personnel, 5 items were related to the regulatory process, and 9 items were related to decision making within the

local pharmaceutical industry. Statements on which consensus was achieved in both Delphi rounds 01 and 02 are shown in Table 4.

Relative weight scores of the barriers

Issues related to resources, instruments, and personnel received higher weight scores (51.7%) followed by issues related to the regulatory process (38.9%), and issues related to decision making within the local pharmaceutical industry. The detailed relative weight scores of each category and items within the categories are shown in Table 4.

Table 4: Factors on which consensus was achieved by the panelist to include them as barriers hindering the implementation of QbD by local pharmaceutical industry

#	Item	Round	Relative weight scores (%)	
			Mean	**SD**
	Barriers related to technicality, resources, instruments, and personnel		**51.7**	**22.8**
1	Identifying and understanding all variables that need to be controlled.	1	13.3	0.5
2	Development of analytical methods and testing.	1	12.3	2.5
3	Finding and hiring qualified personnel.	1	9.9	3.4
4	Need for data management systems for tracking and controlling different operations.	1	9.0	6.4
5	Availability and difficulty of procuring various equipment for the R&D department.	2	8.9	1.0
6	Availability and difficulty of procuring various equipment for the production department.	2	7.9	2.4
7	Availability and difficulty of procuring active pharmaceutical ingredients, excipients, and packaging materials from different suppliers.	1	7.8	1.4
8	Availability and difficulty to hire qualified trainers.	1	4.7	1.7
9	Availability and accessibility to sufficient resources for assessment of different processes during QbD-based developments.	2	6.4	1.5
10	Insufficient knowledge of the regulatory processes and follow on steps during QbD-based developments.	2	5.4	1.1
11	Costs related to training on QbD based development.	2	4.2	1.3

#	Item	Round	Relative weight scores (%)	
			Mean	**SD**
12	Time needed for training on QbD-based development.	1	3.4	1.2
13	Availability and access to software packages used in QbD-based development.	2	2.5	0.5
14	Availability and costs of training on software packages used in QbD-based development.	2	2.2	0.3
15	Acquiring adequate command on the many software packages required in QbD-based development.	2	2.0	0.2
	Barriers related to the regulatory process		**38.9**	**20.3**
1	Organizational culture within local regulatory agencies.	1	35.8	4.0
2	Testing processes before implementing them in QbD-based development.	1	21.7	8.4
3	Local regulatory agencies lack adequate access and command to and command on resources.	1	18.1	9.1
4	Lack of incentives offered to local pharmaceutical industry for implementing QbD-based developments.	2	13.8	6.1
5	The belief that implementing QbD slows down the time taken to fill an abbreviated new drug application (ANDA).	2	10.6	3.9
	Barriers related to decision making within the local pharmaceutical industry		**9.4**	**2.5**
1	Organizational culture within the local the pharmaceutical industry.	1	18.9	7.1
2	The need to implement QbD-based developments on a large number of generic products.	1	16.6	5.3
3	Lack of knowledge of quality risk management at the decision makers' level.	1	15.0	5.4

#	Item	Round	Relative weight scores (%)	
			Mean	SD
4	Lack of understanding of the QbD and QbD-based development in general within the local pharmaceutical industry.	1	14.0	3.6
5	Lack of knowledge of critical quality attributes at the decision makers' level.	2	8.8	2.2
6	Lack of familiarity of the equipment needed to implement QbD-based development at the decision makers' level.	2	6.4	2.9
7	Lack of knowledge of and familiarity with new measures for inspection, quality assurance, review and scale-up needed in QbD-based developments.	2	6.1	1.1
8	Reluctance of the top management to facilitate training the personnel on QbD-based development.	1	5.9	2.6
9	The belief that documentation in QbD-based development is more complicated and labor intensive than in traditional development.	2	8.3	2.4

4.5 Issues not considered barriers to implementing QbD in generic development by local pharmaceutical industry

Of the 34 statements presented to the panelists for voting, consensus was achieved to exclude 5 statements as barriers impeding the implementation of QbD in generic development by local pharmaceutical industry. The details of these statements are shown in Table 5.

Table 5: Factors on which consensus was achieved by the panelist to exclude them as barriers hindering the implementation of QbD by local pharmaceutical industry

#	Barrier	Round
1	The concept of QbD was originally conceived for big multi-national pharmaceutical companies.	1
2	Local pharmaceutical industry obtains already developed and tested formulas, therefore, QbD-based developments are not implemented in generic developments.	1
3	QbD-based developments are not needed in generic development.	1
4	The belief of implementing QbD would increase the price of finished products and decrease their market share.	1
5	Implementing QbD-based developments would increase the quantity of unnecessary information filed to regulatory agencies and delay the review and approval process.	1

Chapter Five

Discussion

In this study, we sought consensus on barriers to implementing the QbD approach in the development of generics in the Palestinian pharmaceutical industry among a panel of stakeholders. We also sought to prioritize these barriers in order of their importance. To the best of our knowledge, this is the first study in which such barriers are identified and prioritized using a formal consensus technique and a multi-criteria decision analysis technique. Barriers to implementing QbD in generic development were not identified or prioritized before. In this consensual study, 29 barriers in 3 categories were identified and prioritized in order of their importance. This list of barriers should serve as a guidance for regulatory agencies, pharmaceutical industry, trainers, educators, and other stakeholders when designing measures and interventions to facilitate implementing QbD in generic development by the local pharmaceutical industry.

In this study, a purposive sampling technique was followed to recruit the panelists. This non probability sampling technique has long been viewed as biased. However, other probability sampling technique are not suitable for recruiting panelists who are rich in information on the subject being investigated in the Delphi rounds. Moreover, the diversity of the panelists included in this study add more strength and validity to the findings. The panel included participants from both genders, different qualifying academic degrees, employment history, hierarchical positions, experience

years, and training. Obtaining responses from all panelists in both rounds is an asset which adds strength and validity to this study.

Barriers to implementing QbD in generic development were not investigated before and currently there are no gold standards in identifying barriers to implementing QbD in generic development. Therefore, regulatory agencies, educators, trainers, industrialists and other stakeholders are left wondering what could be the barriers hindering the implementation of QbD in generic development. In absence of gold standards, it has been argued that consensual technique might provide views from inside the industry exploring the nature of these barriers. Consensual techniques also provide means to promote transparency, reduce bias, add validity, and strength when judgmental approaches are followed to develop concepts, in this case, identify which barriers hinder implementing QbD in generic development. We believe that the list of barriers identified in this study might appeal to stakeholders in regulatory agencies, educators, trainers, industrialists interested in designing measures and interventions to promote the implementation of QbD in generic development.

Interestingly in this study, the vast majority of the panelists thought that implementing QbD in generic development was important. However, about 49% of the panelists thought implementing QbD in generic development was currently of low or intermediate priority within the pharmaceutical industry.

Barriers related to technicality, resources, instruments, and personnel received comparatively higher relative weight scores. Probably, generic manufacturers need to allocate more resources and invest on research and development in order to optimize control over all variables that need to be controlled for successful implementation of QbD-based developments. In-depth understanding of all variables that need to be controlled and optimizing analytical techniques might facilitate implementing QbD in generic development.

5.1 Limitations of the study

Limitations related to AHP methods itself, the scale of relative importance utilized in AHP is based on a conceptual approach used to identify which barriers take precedence. In addition to, there are chances of bias while giving relative weight age of different factors. [43]. Also Delphi technique used requires time/participant commitment. Further More, No guidelines for determining consensus, sample size and sampling techniques used in this type of study. Moreover, the sample size of the panel was relatively small. A larger panel size would have an impact of the items included in the list. However, the number of panelists included was in the range used in previous studies. A larger panel size might have also increased the number of rounds needed to achieve consensus**.**

5.2 Conclusion

This article identifies and prioritizes the barriers that prevent the implementation of QbD in local pharmaceutical industry in Palestine according to opinion of experts from pharmaceutical industry, university, and regulatory authority (MOH). Ranking the barriers, from the most important to the least important, which will allow managers and practitioners in the pharmaceutical industry to decide which barriers they need to pay attention to and work on for a successful implementation of QbD. This list may serve as a guidance for other studies. Presenting of QbD barriers in AHP-based model and categorizing barriers is a new effort in the area of QbD.

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Appendix

1. Gender: □ Male □ Female
2. Age (years): …….....
3. Qualifications: □ Bachelor of Science □ Master of Science, □ BSc Pharm, □ MSc Pharm, □ PhD, Other (please mention): …….
4. When did you graduate with the first degree? ……
5. Employer? □ Pharmaceutical industry □ University □ Regulatory agency (MoH) □Other (please mention): …….
6. Current position? ……..
7. Previous positions? …….
8. Experience in years? ……
9. Have you had lectures or courses on QbD during your academic programs?□ Yes □ No
10. Have you had training on QbD during your work experience? □ Yes □ No
11. Please express the extent to which you think implementing QbD by the Palestinian pharmaceutical manufacturers is a priority on a scale of 5 (1 indicates low priority and 5 indicates a high priority)? □ 1□ 2 □ 3□ 4 □ 5
12. Please express the extent to which you think implementing QbD by the Palestinian pharmaceutical manufacturers in generic development is important?on a scale of 5 (1 indicates low importance and 5 indicates a high importance)? □ 1 □ 2 □ 3 □ 4 □ 5

Please indicate the level of your disagreement or agreement with the following statements on a scale of 9 (1-3 indicates disagreement, 4-6 indicates in between, and 7-9 indicates agreement)

		درجات عدم الموافقة		درجات الحياد				درجات الموافقة		
		لا اتفق وبشدة مع هذا الأمر	لا اتفق بدرجة متوسطة مع هذا الأمر	لا اتفق مع هذا الأمر	محايد مع الميل لعدم الموافقة مع هذا الأمر	محايد	محايد مع الميل للموافقة مع هذا الأمر	اتفق مع هذا الأمر	اتفق بدرجة متوسطة مع هذا الأمر	اتفق وبشدة مع هذا الأمر
1	Although the implementation of QbD is encouraged by regulatory agencies, still it is not mandatory for generic development	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
2	We manufacture a large number of products, implementing QbD on a large number of products would be difficult	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
3	QbD is more appealing to companies manufacturing few products	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
4	Documentation in QbD is more complicated than in traditional process and requires more time, training and resource allocation	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
5	Generic manufacturers takes already developed and tested formula from another company, therefore, real development is rare and QbD is not needed	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
6	Culture within the generic pharmaceutical industry need to change to facilitate the	1	2	3	4	5	6	7	8	9

	implementation of QbD									
		تعليق (اختياري):								
7	Culture within the regulatory agencies need to change to facilitate the implementation of QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
8	Manufacturers do not have sufficient access to resources for assessment of different processes in QbD-based developments	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
9	Regulatory agencies do not have sufficient access to resources for assessment of different processes in QbD-based developments	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
10	QbD requires implementation of new measures for inspection and review	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
11	In traditional development approach, there are different regulatory processes, follow-on, ..etc, we do not know how these regulatory practices will be for QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
12	QbD might increase the price of the finished products	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
13	The concept of QbD was conceived for big pharma	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
14	Implementation of QbD slows down the time for filing an ANDA to the regulatory authorities	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								

15	Implementation of QbD slows down the time taken by the regulatory authorities to review an ANDA	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
16	Implementation of QbD slows down the time taken by the regulatory authorities to approve an ANDA	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
17	Implementation of QbD increases the quantity of unnecessary information to the regulatory authorities and this might create an obstacle for regulatory officers to review and approve our ANDA	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
18	Implementation of QbD requires a lot of software programs	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
19	The software programs are not user friendly and require training	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
20	Qualified trainers on these software packages are difficult to find or hire	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
21	Implementation of QbD requires a lot of training for the personal	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
22	Qualified trainers on QbD are difficult to find or hire	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
23	Training on QbD costs a lot	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
24	Training on QbD takes a lot of time	1	2	3	4	5	6	7	8	9

		تعليق (اختياري):								
25	The concept of QbD is not well understood within our company	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
26	The concept of QbD does not apply to the development of generics	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
27	Manufacturers are not familiar with the equipment required for implementation of QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
28	Manufacturers lack essential knowledge of critical quality attributes required in QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
29	Manufacturers lack essential knowledge of quality risk management	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
30	More instrumentations are needed to implement the concept of QbD in our company	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
31	More tests and analysis are needed to implement QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
32	Many variables need to be controlled in QbD-based product developments	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
33	Data management systems for tracking and controlling operations are needed in QbD	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								

34	Materials like active ingredients, excipients, packaging materials need to be procured from different suppliers in QbD which might increase the costs	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
35	QbD requires hiring more personal for the R&D department	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
36	QbD requires procuring more equipment for the R&D department	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								
37	QbD implies that processes should be tested which slows down the development of the final product and increases the production costs	1	2	3	4	5	6	7	8	9
		تعليق (اختياري):								

We would be thankful if you would you like to add more barriers preventing or slowing down the implementation of QbD in generic development by the Palestinian pharmaceutical industry?

جامعة النجاح الوطنية

كلية الدراسات العليا

تحديد وترتيب أولويات الحواجز التي تحول دون تطبيق الجودة حسب التصميم (QbD) من قبل الصناعة الدوائية المحلية في فلسطين: تحليل توافقي نهج التسلسل الهرمي

اعداد

عبد الفتاح نشأت عبد الفتاح منصور

اشراف

د.رمزي شواهنه

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في العلوم الصيدلانية، كلية الدراسات العليا، فلسطين، نابلس.

2019

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إشراف

د.رمزي شواهنه

الملخص

الخلفية: على الرغم من الفوائد المحتملة لتطبيق مفهوم جودة التصميم (QbD) التي تم توضيحها من قبل خبراء الجودة والهيئات التنظيمية ، إلا أن هذه الفوائد ليست سهلة التنفيذ عمليًا. حيث وجدت العديد من المنشآت الصناعية الصيدلانية صعوبة في تنفيذ هذا المفهوم بنجاح.

الأهداف: تبحث هذه الدراسة وتصنف العوائق التي تحول دون نجاح تنفيذ مفهوم جودة التصميم (QbD) في صناعة الأدوية المحلية في فلسطين. الغرض من هذه الدراسة هو فهم حواجز تطبيق مفهوم جودة التصميم (QbD) وتحديد أولوياتها النسبية من خلال تصنيفها في صناعة المستحضرات الصيدلانية.

الطرق: استخدم جولة استفتاء الرأي لتقنية دلفي لتحديد العوائق التي تحول دون تطبيق مفهوم جودة التصميم (QbD) من قبل الصناعة الدوائية الفلسطينية المحلية. بالإضافة إلى ذلك ، تم إجراء جولتين من دلفي لتحقيق إجماع حول العوائق المحتملة ، وأجريت جولات دلفي المتتالية لتحديد الأولويات وتصنيفها باستخدام نهج عملية تحليل هرمي توافقي (Analytic hierarchy process approach).

الجودة والقيمة: إن قوة هذه الدراسة هي تطوير نموذج شامل للتحقيق وتحديد الأولويات من العوائق التي تواجهها صناعة الأدوية في فلسطين عند تنفيذ برنامج جودة التصميم (QbD).

الموافقة الأخلاقية: الموافقة الأخلاقية التي تم الحصول عليها من مجلس المراجعة المؤسسية (IRB) من جامعة النجاح الوطنية. حيث يقدم المشاركون موافقة مستنيرة لفظية قبل المشاركة في هذه الدراسة.

النتيجة: من ال 34 عائق المحتملة التي عرضت على المشاركين في الدراسة في الجولة الأولى من استفتاء الرأي (Delphi) تم التوصل إلى توافق في الآراء بشأن 15 من هذه العوائق أي بنسبة (44.1٪) حيث تمثل هذه الحواجز عوائق في تنفيذ مفهوم جودة التصميم (QbD) في الصناعة الدوائية المحلية في فلسطين من وجهة نظر المشاركين في الدراسة وكانت النتائج في جولة استفتاء الرأي الثانية (Delphi) حيث تم الاتفاق على 14 من العوائق أي بنسبة (41.2٪) تمثل عوائق تعيق في تنفيذ مفهوم جودة التصميم (QbD) في التطوير العام من قبل الصناعة الدوائية المحلية في فلسطين. وتم استبعاد 5 عوائق حيث تم الإجماع على أنها لا تعيق تطبيق مفهوم جودة التصميم (QbD) في الصناعة الدوائية المحلية في فلسطين من وجهة نظر المشاركين في الدراسة. صنفت العوائق التي تم الإجماع عليها في الجولتين إلي 15 عائق يتعلق بالموارد والأدوات والموظفين و5 عوائق متعلقة بالعملية التنظيمية و 9 عوائق تتعلق باتخاذ القرارات في صناعة المستحضرات الصيدلانية المحلية. ثم تم تصنيف هذه العوائق من الأكثر إلي الأقل باستخدام نهج تحليلي توافقي هرمي (Analytic hierarchy process approach). في هذه الدراسة ، كان حوالي 62٪ من المشاركين من الذكور ، ونحو 64٪ 40 سنة وأكثر ، وحوالي10٪ لديهم درجة الدكتوراه ، وحوالي 59٪ حصلوا على درجة جامعية قبل عام 2000 ، حوالي 85٪ يعملون حاليا في الصناعة الدوائية و حوالي 69٪ من المشاركين يحتلون مناصب مختلفة في مصانع الادويه كمراقبة الجودة وضمان الجودة و ممارسة التصنيع الجيد (GMP) والبحث والتطوير (R&D) ، حوالي 80٪ لديهم خبرة عملية لمدة تزيد عن 10 سنوات ، وبنسبة 69٪ حصلوا على تدريب على مفهوم QbD خلال حياتهم العملية. 97٪ بأغلبية المشاركين صوتوا على أهمية تطبيق مفهوم QbD في الصناعة الدوائية المحلية في فلسطين ومع ذلك عندما سئل المشاركين في الدراسة إلى أي مدى اعتقدوا أن تنفيذ QbD من قبل الشركات المصنعة للأدوية الفلسطينية يمثل أولوية حاليًا، اعتقد 51٪ من المشاركين أن أولوية تطبيقه ذو أهمية كبيره .

الخلاصة: يمكن استخدام التقنيات التوافقية أو الإجماع في تحديد وإعطاء الأولوية للعوائق التي تحول دون تطبيق مفهوم جودة التصميم من قبل الصناعة الدوائية المحلية. هناك حاجة إلى مزيد من

الدراسات لدراسة سبل القضاء على هذه العوائق وتعزيز تنفيذ مفهوم جودة التصميم في تصنيع المنتجات الصيدلانية في فلسطين.