9-8-2019

Drug shortage in Egypt: causes and mitigation measures

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A Thesis Submitted to
the Public Policy and Administration Department

in partial fulfillment of the requirements for the degree of
Master of Public Administration

By

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Fall 2019

Acknowledgement

First, I would like to thank the Yousef Jameel GAPP Public Leadership Program for granting me this golden opportunity, and for letting me be part of this incredible leaders' network.

Further, I would like to extend my deepest gratitude and appreciation to my supervisor Dr. Laila El Baradei for her guidance and persistent help along my research process. I consider myself lucky to have such an inspiring supervisor who has always been considerate and supportive.

Also, I would like to sincerely thank Dr. Ghada Barsoum and Dr. Khaled Abdel-Halim for their continuous support and constructive feedback since the early stages of the thesis and for accepting to serve on the committee. I am also grateful to all my professors who were the lights along my way through graduation.

I would like to thank all participants for their assistance and the time they allocated for the interviews to produce this research.

I must express my very profound gratitude to my brothers and friends for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis.

Finally, I dedicate this work to the soul of my mother who had always been a model of persistence and dedication in life, she taught me love and kindness, and inspired me to be strong and responsible. I also dedicate it to the soul of my father, who believed in me. This accomplishment would not have been possible without their valuable advices which I always remember. Thank you.

Above all, I thank Allah, the almighty for providing me this opportunity and granting me the capability to proceed successfully.

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ABSTRACT

Drug shortage is a worldwide problem, which gained the attention of many authorities in recent years including the Egyptian government. The problem has markedly increased in Egypt during the past few years and has had a significant negative impact on patient care with subsequent costly financial implications. Despite the importance of the drug shortage problem and its consequences on the health of Egyptians and society as a whole, only a few researchers have addressed the topic in Egypt. This qualitative study aims at filling the gap and providing a better understanding of the problem in the Egyptian context. To achieve the study objective, the root causes of the problem and the actions taken by the government to mitigate the problem are explored. In-depth, semi-structured interviews are carried out with different stakeholders including from government, industry, distributors, and pharmacies. The findings of this research revealed that the drug shortage is attributed to a myriad of interlinked causes. The most critical causes of drug shortages are as follows: the drug pricing constraints, the devaluation, economic changes, overdependence on the importation of production inputs, illegal distribution practices, excessive bureaucracy and complicated procedures, manufacturing problems, poor supply chain management, and scarcity of raw materials. The findings also show that although the government has exerted many efforts to tackle drug shortages, there is still a gap to be addressed. Based on experiences of other countries and according to the Egyptian context, solutions are proposed to help in mitigating drug shortages in Egypt which include enhancing the sustainability of the production of medicines by improving companies' profitability, improving collaboration between various stakeholders, developing a system for reporting and communication of drug shortage information, and modifying workflow within MoHP to avoid unnecessary delays.

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List of abbreviations

AIFA	Italian Medicines Agency
API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
CAPA	Central Administration for Pharmaceutical Affairs
CAPMAS	Central Agency for Public Mobilization and Statistics
CBE	Central Bank of Egypt
DSD	Drug Shortage Department
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGP	Egyptian Pound
EMA	European Medicine Agency
ERP	External Reference Pricing
EU	European Union
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FEDCOC	Federation of Egyptian Chambers of Commerce
FIP	International Pharmaceutical Federation
GMP	Good Manufacturing Practices
IDA	Industrial Development Authority
MOHP	Ministry of Health and Population
MNCs	Multinational Corporations
MSSC	Multi-Stakeholder Steering Committee
NODCAR	The National Organization for Drug Control and Research
NORCB	The National Organization for Research and Control of Biologics
OTC	Over-the-Counter
TGA	Australian Therapeutic Goods Administration
USD	United States Dollar
WHO	World Health Organization
MSII	Medicines Shortage Information Initiative

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Chapter one: Introduction

1.1. Study overview

Health is an essential human right, based on the Oslo declaration which states that "life is the most fundamental of human rights and that life and health are the most precious assets" (Mclnnes & Lee, 2012, p.66). A holistic approach and many tools are required to ensure the attainability of this right. Access to medicines is one of the basic tools to guarantee this right. However, guaranteeing the right to health for all individuals may not be attainable in many countries.

One of the main obstacles to achieving good health standards is the unavailability of medicines. Drug shortage is a global concern gaining the attention of all authorities as well as world organizations concerned with health issues. The World Health Organization WHO (2012) describes this phenomenon as an old complex global challenge. The importance of this issue emerges from its fatal consequences on health, livelihood and mortality rates. The psychological, economic, and medical challenges resulted from drug shortage cannot be underestimated. The psychological challenges arise from the frustration of parties involved in the process such as patients, nurses, physicians, pharmacists, distributers and regulatory bodies. On the other hand, economic challenges occur due to the increased medical and health cost to deliver patient care. This cost includes replacing the medicine with an alternative medical procedure or substituting the drug in shortage with a more expensive one. Furthermore, the medical challenges are the most substantial concern, because drug shortage may lead to deterioration of health and a shift from treatment to surgery (Abdulrahman et al., 2016). In addition, it may cause medication dosage errors, adverse effects and delays, or cancellation of urgent surgeries. Finally, drug shortage does not lead only to patients' inconvenience but it may also cause health hazards.

The importance of the problem encouraged many governments and scholars to determine the root causes behind the problem. The causes of drug shortages can be one or a combination of problems throughout the supply chain. For example, manufacturing problems and quality issues lead to delays, disruptions or ceasing of production (Dill & Ahn, 2014, Bogaert et al., 2015). Another example is raw material problems emerging from deterioration and unavailability of botanical and animal sources (Kaakeh et al., 2011). Poor supply chain management including forecasting, ordering, delivery, inventory practices leads to disruption in supply and drug shortage (Alruthia et al., 2018, Woodcock & Wosinska, 2013). Moreover, economic factors represented in low profit margins and inflexible fixed prices lead to a cessation in product manufacturing. Policies, regulations, and bureaucratic systems lead to further delays in production due to lengthy processes (Alruthia et al., 2016, Yang et al., 2016).

In response to the drug shortage problem, governments adopted many measures to tackle the problem and decrease its severity. The governments' responses include the introduction of new laws and legislation, developing strategies and protocols, establishing a steering committee to improve cooperation, improving notification and communication of drug shortages, and cooperating with pharmaceutical companies to overcome problems and speed up the procedures (Health Canada, 2017; Dill & Ahn, 2014; TGA, 2018; Donelle et al, 2018). By adopting such actions and measures, many countries have succeeded in decreasing the frequency and severity of drug shortages such as the U.S. which witnessed a tremendous decline in new shortages since the peak in shortages in 2011 (FDA, 2018).

Egypt has not been spared from the drug shortage problem. During the past few years, many shortages were reported. Numerous newspaper articles and news reports

(Abaza, 2013; Huseein, 2016; Morsy, 2018) discussed the drug shortage problem and described it as a crisis due to its severity and dire consequences on patient care.

Thus, this study is conducted to determine the root causes of the drug shortage problem in Egypt, which can allow for the proposal of more effective solutions to address the problem. To achieve the study objective, a conceptual framework has been developed based on reviewing previous studies and literature on the definition of drug shortages and the causes of the problem, and actions taken to mitigate drug shortages.

This study is performed using a qualitative exploratory research design to provide a better understanding of the drug shortage problem in Egypt. A non-probability purposive sampling technique is adopted to determine the key interviewees. The primary data is collected through conducting in-depth semi-structured interviews with different stakeholders: industry, distributors, pharmacies, regulatory bodies, and professional associations and civil society to understand the problem from different perspectives. The primary data is triangulated and validated using other secondary data obtained from publications, reports and published data.

The study investigates the government's definition of drug shortage to understand which cases the government considers a shortage. It determines the root causes of drug shortage in Egypt, highlighting the influence of recent economic changes on the pharmaceutical industry. Moreover, it explores the impact of current regulations and legislation on drug availability. Finally, government actions are examined to identify gaps and propose solutions.

1.2. Problem statement

After the revolution on 25th January 2011 in Egypt, political and economic instabilities led to many difficulties and challenges. These instabilities adversely affected

many sectors in the country including the pharmaceutical sector which lead to interrupted medicine supply. Drug shortage in Egypt gained much media attention after the 2011 revolution, and it was referred to as a crisis. Deya Abaza reported in Ahram Online (2013) that instances of stock-out of medicines had increased. For example, many hormonal drugs such as insulin and levothyroxine had disappeared from the market, and they do not have alternative drug products. Levothyroxine is a lifesaving maintenance drug used to treat hypothyroidism, and a sudden stoppage of taking it may cause withdrawal symptoms such as debilitating weight loss and muscle weakness. More seriously, insulin shortage can lead to severe health problems such as blindness, kidney failure, heart disease, stroke, and death due to high blood sugar. Such terrible consequences cause a drug shortage to be a serious and pressing problem facing our nation. In addition, a study conducted in Egypt by Abdelrahman et al. which started in January 2014 reported that more than half of the respondents faced difficulties in obtaining medicines causing case deterioration and shifting treatment to surgery (2016).

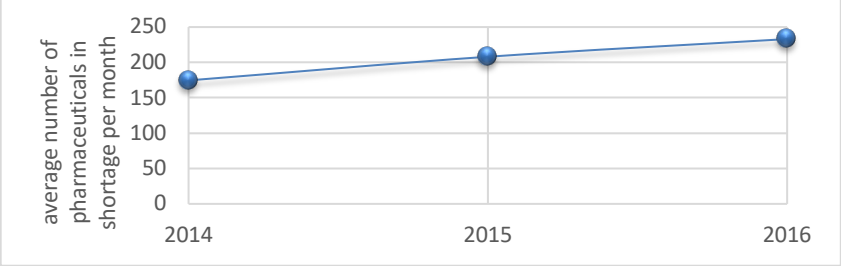
Unfortunately, the situation has become more complicated when the shortage of foreign currency hit the country which impeded the importation of raw materials and Active Pharmaceutical Ingredients (APIs) needed for local production (El Agroudy & Mokhtar, 2015). In this regard, Hayat Hussein (2016) stated that the dollar crisis resulted in increasing the number of pharmaceuticals in shortage. Besides, she mentioned that some patients are forced to buy more expensive alternatives due to the unavailability of the cheaper ones. On the other hand, other patients could not find the medications and live with the disease and its pain.

In an attempt to overcome the shortage of foreign currency and the subsequent emergence of the black market, the Central Bank of Egypt has decided to float the Egyptian

Pound in 2016. The EGP to USD exchange rate became 17.42 compared to 8.63 before floatation (CBE, 2019) which lead to an increase in the prices of all commodities. Given that medicines are subjected to a compulsory pricing system in Egypt, pharmaceutical companies could not increase the price of medicines to cope with the increase in costs. Thus, companies reacted to Egypt's difficult economic circumstances by downsizing or ceasing the production of some drug products due to rigid pricing constraints, so the crisis had escalated (Gaballa & Knecht, 2016). Furthermore, an article in Egypt Independent added that life-saving pharmaceuticals such as those used in the treatment of leukemia, cancer, kidney failure, diabetes, blood clotting, hormones, and muscle atrophy are in shortage (Hussien, 2016). All these types of medicine are very critical for patients, any disturbance in their supply results in many health hazards and potentially death in many cases. Indeed, having cancer or other critical diseases is hard enough without unnecessary impediments such as drug shortages.

The dramatic increase in the number of drugs in shortage is evident from the data published on the official website of the Central Administration for Pharmaceutical Affairs (CAPA). A monthly bulletin for drug shortages is issued by CAPA, only bulletins from 2014, 2015 and 2016 were published. By comparing the average number of pharmaceuticals in shortage per month during the three years, an increase in numbers can be identified, as shown in Figure 1.

Figure 1 Increase in number of pharmaceuticals in shortage in Egypt



Source: developed by the researcher, http://www.eda.mohp.gov.eg/Articles.aspx?id=134

Despite that the data of drug shortages has not been published since the crises was at its peak at the end of 2016, the media continued to report on prominent cases of drug shortages as they emerge.

On the other hand, as a result of shortage of life-saving drugs and essential medicines a black market has emerged where the prices of medicines were tripled. Al-Masry Al-Youm (2017) reported that patients were forced to obtain their medicines from the black market to avoid dire consequences of stopping their medication. For example, anticoagulants are used to help prevent blood clots and stop having them for a while increase the risk of developing blood clots. Thus, patients resorted to buying their medication from the black market at higher prices to avoid severe implications of the formation of a blood clot. However, obtaining medicines from the black market is disastrous because these medicines may be expired, contaminated or fake which increases the risk of health hazards.

In response, the government has taken many actions and corrective measures to overcome the problem. However, the Egyptian market still frequently suffers from stock-outs and shortage. In 2018, Ahmed Morsy explained in his article "drug shortage crisis hit the Egyptian market again" that patients and pharmacists were facing problems when purchasing essential medicines (Morsy, 2018). He also added that, despite a temporary improvement in the situation after the hard currency became more available and the economic environment became more stable, it worsened again.

Drug shortages not only do affect the health of the individual but they also impact society. According to WHO (2002), economic growth is highly linked to health because good health leads to higher labor productivity. Consequently, negative impacts of drug shortage on health can hinder economic growth.

It can be concluded that numerous drug shortages and frequent disturbances in the supply of essential medicines and life-saving drugs have hit the pharmaceutical market in Egypt over the past few years. Economic changes, scarcity of hard currency, the devaluation, and drug pricing constraints have negatively influenced the availability of medicines. As a result of shortages of critical drugs, the black market has emerged which complicated the problem. Drug shortages lead to costly financial implications. Importantly, they have dire consequences on health as they lead to clinical complications, dosage errors, adverse effects, health deterioration, or even death.

The drastic effect of drug shortages on Egyptians' health and livelihood may adversely affect their performance and productivity. Broader reaching effects of a loss of productivity include an impact on economic prosperity. Thus, the drug shortage problem not only deprives citizens of obtaining their rights to health, but it can also affect society as a whole.

Being working in the pharmaceutical field allows the researcher to witness the problem. Once a shortage is resolved, another emerges which creates burdens on healthcare providers and patients and their families. These repeated shortages threaten public health by creating barriers to optimal care. Thus, this research is conducted in an attempt to help understanding the phenomenon in Egypt and in finding relevant and effective solutions for this pressing and complicated problem.

1.3. The significance of the study

Drug shortage is increasingly becoming a serious problem facing many countries. The importance of this issue emerges from its dire consequences on the most valuable asset people have, which is "health". Seeing the drug shortages as one of the fundamental factors hampering the delivery of adequate health care services triggers the analysis of the problem

by many health authorities, world organizations, and scholars. However, previous work has mainly focused on discussing causes of drug shortages based on the experiences of developed countries such as the United States and Europe (Dill & Ahn, 2014; Bogaert et al., 2015; Woodcock & Wosinska, 2013; Fox et al., 2018). Few researchers have addressed the problem in developing countries and specifically in the Arab world and Egypt which have a different political, economic, and legislative context that may lead to different analysis and causes of the problem. Thus, this study seeks to provide a better understanding of the drug shortage problem according to the Egyptian context, especially after the devaluation and economic changes. This is achieved by exploring the root causes contributing to the problem because only when such causes are clearly identified can solutions be found. In addition, the study attempts to investigate the actions taken by the Egyptian government to solve this problem so gaps can be identified and more effective solutions can be proposed.

1.4. Research Questions

The key question this study will attempt to answer is:

How and to what extent can the government of Egypt mitigate the drug shortage problem?

Sub-questions include:

a- How does government define drug shortage? And in which situations are medications considered to be in a shortage?

b- What are the causes of drug shortage in Egypt?

- What government policies and regulations may contribute to drug shortages?
- How did economic changes during the last few years affect drug availability, and to what extent were pharmaceutical manufacturers able to cope with these changes?

c- What are the regulations and measures taken by the Egyptian government to mitigate and prevent drug shortages?

d- What can be done to reduce the likelihood, severity and duration of drug shortage?

1.5. Structure of the paper

The paper is divided into six chapters, first chapter introduces the topic, determines the significance of the study and ends by illustrating the research questions. The second chapter offers a detailed review of the literature including determination of drug shortage definitions, illustration of the root causes of drug shortages in different countries, exploration of the experiences of other countries in tackling the problem. The third chapter presents the concepts that guide the understanding in the study and how they are applied into the Egyptian context plus the operational definitions. Moreover, it describes the research methodology by giving details on the overall research design and strategy, sample selection, data collection and data analysis techniques. Ethical considerations, study limitations and delimitations are also elaborated in the third chapter. The fourth chapter discusses the structure of the pharmaceutical market in Egypt and the regulatory framework. It provides an analysis of the pharmaceutical market in Egypt covering a historical overview, the market structure and the economic environment. In addition, it illustrates the structure of the regulatory agencies, and it sheds light on the main laws and Ministerial Decrees regulating pharmaceuticals in Egypt. In the fifth chapter, the findings of the field work are presented and thoroughly analyzed to determine the main causes of dug shortage and the actions have been taken by the government to mitigate the problem. Conclusion and proposed solutions are outlined in the sixth chapter.

Chapter Two: Literature review

The information provided in this section is gathered from different resources. These resources include peer reviewed articles, reports issued by different competent authorities such as the European Medicine Agency (EMA), Health Canada, and the Food and Drug Administration (FDA). In addition, reports and articles from international organizations were reviewed, such as, reports of International Pharmaceutical Federation (FIP) and World Health Organization (WHO). Most of these articles and reports were published over the last decade.

Drug shortage is universally perceived as a public health problem (WHO, 2012). Numerous studies have been conducted in many countries in an attempt to find the root causes of the problem and try to find solutions to mitigate and prevent this problem. This literature review is divided mainly into three themes: drug shortage definition, causes of drug shortage and handling drug shortages. The first theme presents the definitions of drug shortage from different perspectives. Causes of drug shortage as the second theme is divided into six subthemes: causes related to the regulatory framework, causes related to the manufacturing, causes related to the distribution and supply problems, causes related to consumption, economic causes, and natural disasters. The final theme of handling drug shortages shows the experiences of the United States (US), the European Union (EU), Canada, Australia, and Brazil in mitigating drug shortages.

2.1. Drug shortage Definition

Drug shortage does not have a common definition because this problem involves many stakeholders with different perspectives. From the manufacturers' perspective, drug shortage is described as a shortage in raw material or a sustained problem in the manufacturing processes (Awad et al., 2016). Along with this definition, the European

Federation of Pharmaceutical Industries and Associations (EFPIA) describes potential drug shortage as "the occurrence of internal or external situations (single or in a combination of both), which could result in an interruption of supplies of a medicinal product, if not properly addressed and controlled'' (EFPIA, 2013, p.2). These definitions consider a drug shortage at the supply level without taking into consideration the demand side. This may refer to the fact that manufacturers are more concerned with the issues related to manufacturing process and their ability to tackle and deal with such issues.

On the other hand, healthcare providers define drug shortage as any change in supply that may potentially affect patient care and consequently their safety (Mayers et al., 2012). On the same hand, the American Society of Health-System Pharmacists (ASHP) defines it as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent" (Fox et al., 2009, p.1400). In a similar vein, FIP (2013) states that a drug shortage is "a drug supply issue requiring a change. It impacts patient care and requires the use of an alternative agent" (p.4). Generally, healthcare providers and professional organizations focus more on how a drug shortage could affect the ability of healthcare providers to deliver adequate services to patients. Also, they are concerned with the negative impacts that drug shortage has on patients.

In addition, competent authorities in different countries have various definitions for drug shortage. For example, Food and Drug Administration FDA defines drug shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA regulated drug is inadequate to meet the current or projected demand at the user level" (Para. 6). In addition, Health Canada (2017) describes it as "a situation in which an authorization holder for a drug is unable to meet the demand for the drug. Drug shortages

can include temporary disruptions or permanent discontinuances in the production and supply of a drug" (Para. 1). Moreover, Australian Therapeutic Goods Administration (TGA) considers a drug shortage "when the supply of a medicine is not likely to meet the normal or projected consumer demand for the medicine within Australia for a period of time" (Para. 2). Furthermore, the Italian Medicines Agency (AIFA) states that drug shortage occurs "when a medicinal product is not available or commercially unavailable all over the country and the market authorization holder does not assure appropriate and continued supply to meet the patients' needs". It may be concluded that the common idea between these definitions is that the authorities do not consider a drug shortage as long as there is no demand for this drug. In other words, if there is a supply problem resulted in the unavailability of certain medications at the pharmacy level, and there is no demand for this medication at the patient level, there is no shortage. However, some differences can be identified between these definitions. For instance, FDA definition considers a medication to be in shortage only when it does not have any alternatives, whereas other definitions do not include this element.

Briefly, it can be said that the remarkable differences between drug shortage definitions are because of the diversity of stakeholders. Each party defines drug shortages in a way consistent with their roles, responsibilities, and expectations. In the case of competent authorities who are responsible for ensuring the availability of medications to patients, they consider drug shortage when there is a failure to meet a demand for certain medications at the user level. In contrast, manufacturers focus on the supply side, and they define a shortage as a situation where there are interruptions in the supply of medication due to encountered problems. However, some differences may arise within the same group of stakeholders, according to the role of each group and the context of each country.

2.2. Main causes of drug shortage

Drug shortage is a multifaceted problem, its causes are wide-reaching and complex. Many studies have been conducted in numerous countries to manifest these reasons. The causes are mainly linked to defects and failures in different points across the supply chain. Thus, the drug shortage may be a result of issues related to the manufacturing processes, distribution, or consumption. Additionally, some studies argued that economic aspects, drug pricing policies, regulatory framework, and natural disasters could adversely influence drug availability. Many of these causes were found to be common among different countries.

2.2.1. Causes related to regulatory framework

Bureaucracy and tough regulations and procedures may cause many delays which is very crucial in case of medicines as these delays may lead to health hazards. Awad et al. (2016) assumed that the most significant cause of drug shortages in Jordan is the regulatory and legislative procedures including the long process for new drug approval, the unfair pricing mechanism and the lack of coordination between different entities. On the other hand, the absence of deterrent sanctions may encourage companies to violate rules that may lead to a shortage of medicines. For example, in Saudi Arabia, all pharmaceutical companies must keep reserves of their products, and if they do not, they are penalized for non-compliance (Alruthia et al., 2018). However, the level of penalty and the law enforcement are not adequate to deter companies from violating laws and regulation. In addition, slow and lengthy process to receive government approval for lot release and other processes may lead to unavailability of medicines in market. Not only did studies performed in developing countries show the negative impact of regulations on drug availability, but also studies performed in developed countries demonstrated the same

results. Heiskane et al. (2017) argued that European tightened rules and regulations which are formulated by national authorities lead to drug shortages. Additionally, a study conducted in the EU revealed that non-compliance with the regulatory standards is a major cause of drug shortage (Bogaert et al., 2015). In accordance, the ASHP mentioned that the process adopted by FDA to ensure manufacturers` compliance with current Good Manufacturing Practices GMP is lengthy, especially with limited resources to duly inspect the manufacturing site.

Furthermore, pricing regulations may remarkably affect drug shortages because of reference pricing or low-profit margin (Bogaert et al., 2015), this aspect will be dealt with in more detail in the next subsection. Therefore, business decisions may be unfavorably influenced by legislation and policies, resulting in drug shortages. In addition to pricing regulations, tendering and procurement policies may adversely impact drug availability. As suggested by Bogaert et al, tendering policies that allow only a sole supplier to be awarded the tender may lead to drug shortage (2015). Besides, Legislation supporting parallel importation may cause drug shortages (Birgli, 2013). For instance, in the EU, wholesalers purchase medicines from low-income countries where prices are low and sell them in another Member State with higher prices (Bogaert et al., 2015). Thus, the availability of medicines in low-income countries may be negatively affected.

Overall, we can see that regulations and rules are a double-edged sword. They are mainly formulated to control the pharmaceutical market and to protect patients, but in fact, they may lead to the unavailability of medicines. Bureaucracy and delays in obtaining approvals from regulatory authority may significantly lead to drug shortages. Pricing policies may negatively affect the economic aspects of the pharmaceutical industry which result in low-profit margin and a halt in production. Other regulations may influence drug

distribution such as tendering regulations and parallel trade. Thus, regulations and rules must strike a fine balance to control and monitor pharmaceuticals and to protect patients without negatively affecting the availability of medicines.

2.2.2. Economic causes

Markowski (2012) argued that the "ultimate cause" of drug shortages from an economic viewpoint is inadequate profits because the incentive for manufacturers to provide products is earning profits. The US Department of Health and Human Services studied the economic effect on drug shortages, and it found that shortages have been substantially noticed in drugs whose prices and volume of sales were declining. As a consequence, manufacturers, usually, decide to shift from shrinking lines of business to growing ones (as cited in Markowski, 2012). This also was evident by many studies conducted in different countries showing that low profits affect the level of drug shortages (Alruthia et al., 2016; Yang et al., 2016; Awad et al., 2016). In other words, manufacturers that have lower profits prefer to shift to other drugs hitting higher profits regardless of the negative impacts on the market and patients.

As reported by Markowski, a low-profit margin is considered as an economic driver of quality problems because manufacturers will invest less in the expensive production processes required to comply with GMP (2012). Similarly, Dill & Ahn argued that the absence of market recognition to quality products results in insufficient quality investments (2014). That is to say, companies tend to adopt a reactive approach for quality management rather than a proactive one. Thus, the sustainability of production can be affected because companies wait until problems are identified before taking actions. Another relevant point is that economic aspects influence inventory practices because some pharmaceutical entities prefer low inventory levels to cut costs by eliminating surplus production and

inventory costs. Consequently, the probability of stock-outs increases as a slight increase in demand or a modest disruption in supply will cause a shortage (Woodcock & Wosinska, 2013; Bogaert et al., 2015).

Drug Pricing policies

Pricing policies adopted by countries may negatively influence companies' profitability which lead to ceasing of production. For example, Bogaert et al. (2015) contended that Reference Pricing (RP) significantly affect drug shortages. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies defines reference price as "the practice of using the price of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a particular country" (WHO, 2013). This means that manufacturers will prefer getting their products out of the low-priced markets to avoid low prices in other countries, so Reference Pricing most probably affects the access to medicines in low-income countries.

In this context, WHO (2015) emphasized the importance of ensuring that paid prices are appropriate to encourage quality products and to guarantee a continuous supply. Thus, economic aspects are an essential cause of drug shortages, and the price component is crucial because it determines the profit margin and the company's ability to maintain the production of a high-quality drug.

2.2.3. Causes related to manufacturing process

Manufacturing problems and quality issues are the most discussed causes in literature by scholars. Bogaert et al. (2015) identified manufacturing problems as one of the determinants of drug shortage. He described the manufacturing problem as any problem related to either: production of raw material, or production of the finished product, or due

to limited manufacturing capacity that cannot cover the needs, or due to non-compliance with regulatory standards leading to production ceasing till adjusting the manufacturing process to comply with GMP.

2.2.3.1. Manufacturing quality issues

It is important to shed light on the meaning of quality issues as it is considered one of the major causes leading to a shortage. According to Dill and Ahn (2014), quality issues range from low-risk issues such as mistakes related to secondary packaging to high-risk issues such as sterility problems, unexpected chemical reaction, exceeding the limits of impurities or formation of a new one, or degradation. All these quality issues require modification and remediation in the manufacturing process which consume a long time, consequently leading to significant interruption in production and drug shortage.

FDA reported that drug shortages in US are mainly due to quality manufacturing issues, and other issues related to delays in production and limited capacity (2018). In accordance, Fox et al. (2018) assumed that many production delays arise from quality problems. Moreover, companies may stop production upon government request due to non-compliance with regulatory standards or GMP rules (Yang et al., 2016; Bogaert et al., 2015; Reis & Perini, 2008). Companies may need a long time to implement the corrective measures to resume production leading to supply shortfalls and market gap. Other quality issues and manufacturing problems that are related to unforeseeable and uncontrollable events such as fires and disasters may lead to production halting (Dill & Ahn, 2014).

Conversely, a study performed in a developing country showed a different perspective. Awad et al. (2016) contended that manufacturing problems and other related issues were not significantly contributing to drug shortage in Jordan because pharmaceutical manufacturers do not directly distribute medicines to hospitals and because

the raw materials are purchased from international suppliers and other substitutes can be easily found in the market. However, in the researcher's opinion, more explanations should be provided because the two reasons provided by the author did not discuss the manufacturing problems related to the quality.

To sum up, according to many scholars, manufacturing problems and quality issues are considered one of the substantial reasons behind drug shortage. Quality issues, problems related to uncontrollable factors, and non-compliance with the regulatory standards result in delays in production or ceasing of the production.

2.2.3.2. Limited manufacturing capacity

Because of capacity constraints, many pharmaceutical companies tend to discontinue the production of older products, which are essential for patients, and replace them with other products (Woodcock & Wosinska, 2013, ASHP, 2009). This replacement may lead to a direct shortage of these essential older products. In addition, many manufacturers are already operating with their full capacity so if there is a tiny increase in demand, manufacturers will not be able to increase their production to make up the gap (Dill & Ahn, 2014; Jensen et al., 2002).

Another significant point is the rationalization and consolidation of the pharmaceutical industry which increased the probability of drug shortage. Rationalization means a fewer number of manufacturers as well as production lines. Companies tend to manufacture many drug products on the same production line so any problem encountered by the manufacturer may lead to a major disruption in the market for many products (Bogaert, 2015). Increasingly, pharmaceutical companies obtain production inputs through multiple traders outside their own continent which increases the vulnerability to drug shortages (Bogaert et al., 2015). Similarly, a study conducted in Saudi Arabia revealed that

overdependence on imported pharmaceuticals, especially biologics, radiopharmaceuticals, and chemotherapy, leads to drug shortage (Abdelrahman et al., 2016).

Accordingly, limited manufacturing capacity can be a driver of many business decisions to cease the production of some types of drugs. Furthermore, limited number of production lines and manufacturers may result in a significant shortage if the production stopped for any reason. Significantly, increased dependence on overseas drug manufacturers increases the risk of drug shortages. Thus, capacity constraints result in delays, supply disruptions, and inability to cope with increased demand.

2.2.3.3. Raw material issues

Disruptions in the supply of raw materials are frequently reported as a cause for drug shortages. It is considered more problematic when there is only one supplier for a particular active ingredient (Fox et al., 2018). Besides, substandard raw materials are a major concern leading to the majority of raw material shortages in the US as the importation of Chinese raw materials has been shrunk to fifty percent (Awad et al., 2016). The reasons behind the shortage of raw materials can also be due to the contamination of botanical sources of raw material or due to climate changes (Kaakeh et al., 2011). Additionally, the animal sources may be influenced by prevalent diseases which affect the production of raw materials. It is also important to highlight that delays in shipping of active pharmaceutical ingredients or other components may substantially lead to delays in the production and supply disruptions (Dill & Ahn, 2014).

Generally, we can see that the manufacturing of raw material may face the same quality issues as those encountered in producing the finished drug products. In addition, the contamination of sources of raw materials exacerbates the problem and may lead to a

global prolonged shortage. Furthermore, delays in the importation of raw materials is another factor of production interruptions and drug shortage.

It is clear from the above that many studies showed that drug shortage is significantly associated with manufacturing problems. Manufacturing quality issues, manufacturing capacity constraints, and raw material issues are the main factors affecting the manufacturing process leading to production disruptions and drug shortage.

2.2.4. Causes related to distribution and supply problem

The supply chain involves all steps to move medicines from pharmaceutical manufacturers to the patient. Any failure at any point across the supply chain influences the availability of medicines (Yang et al., 2016). The distribution of medicines is a major contributor to drug shortage, especially if there is only one company monopolizing the market. Furthermore, management of the supply chain at the national level is highlighted by WHO (2015) as a significant problem that should be overcome to reduce stock-outs. This matches well with a study conducted by Awad et al. (2016) that revealed that lack of automation and poor communication system between central and regional warehouses and hospitals leads to poor inventory management. The absence of real-time data that trace product flows results in improper distribution; overstock in one place and stock out at the other (WHO, 2015). In addition, Awad et al. (2016) assumed that lack of skilled personnel in the supply chain management leads to improper forecasting of needs which results in temporary shortages of some products, these findings concur well with that of Alruthia et al. (2018). Thus, any defects in the management of supply chain starting from forecasting of needs to drug dispensing result in supply disruptions and shortages.

Due to economic issues, some inventory practices are adopted to reduce expenses such as just-in-time inventory and low inventory levels (Birgli, 2013). These practices increase the risk of shortages if any minimal disruption takes place (Woodcock & Wosinska, 2013; Bogaert et al, 2015; ASHP, 2009). Thus, the economic aspects seem to be interrelated to distribution and supply problems.

Furthermore, as reported by WHO, tendering and procurement policies are considered one of the potential causes of stock-outs (2015). For example, Bogaert et al. (2015) explained that, in Europe, tenders are exclusively awarded to a bidder of the lowest offered price. Thus, other companies may decide to be out of the market and cease production. Thereafter, if the sole supplier cannot cope with the demand for any reason, other companies will not be able to compensate for this shortfall. Similarly, Alruthia et al. (2018) stated that a poor governmental procurement system that does not cope with the changes in the market is one of the reasons of drug shortage.

Other practices of wholesalers and pharmacies that may affect drug availability are stockpiling and hoarding of huge quantities of medicines based on rumors of imminent shortage or price increase (ASHP, 2009; Alruthia et al., 2018). Stockpiling leads to artificial drug shortages or worsen an existing shortage. Besides, the development of gray-market or nontraditional distributors, who obtain drugs in short supply to resell them to end-users with higher prices, exacerbates the problem. Additionally, parallel distribution is deemed to be another cause of drug shortage (Birgli, 2013). Bogaert et al (2015) pointed out that parallel trade is a controversial issue, some stakeholders consider it as one of the main causes of drug shortages because distributors purchase medicines from low-priced countries and sold to higher-income countries at higher prices. In contrast, opponents argued that pharmacies can buy directly from companies so they can still obtain medicines.

However, even if pharmacies can buy drugs directly from the company, the total amount manufactured for this country might be adversely affected leading to drug shortages. It can be concluded that some distributors' practices may negatively affect drug availability.

In summary, poor supply chain management due to improper forecasting, procurement systems, inadequate delivery mechanisms, and poor inventory practices are considered to be a substantial cause of drug shortfalls. In addition to poor supply chain management, wholesalers and distributors practices such as stockpiling of medicines, grey-markets, and parallel trade result in a short supply of medicines.

2.2.5. Causes related to consumption

2.2.5.1. Increased demand

The demand of medicines may increase due to expanded use of drug, disease outbreaks and epidemic conditions (Fox et al., 2009; Lyengar et al., 2016; Reis & Perini, 2008). Unfortunately, manufacturers occasionally cannot cover this increased demand. In other words, any unexpected conditions resulting in increased demand for particular drugs without having the manufacturing ability to meet this increase will most probably lead to drug shortages. In addition, demand may increase due to a shortage of a similar product. For example, if a company with a high market share encountered any problem in production, the demand for other similar medicines produced by other companies will increase. However, other competitors may not have the capacity to ramp up the production or to deviate from their manufacturing schedules, so they cannot compensate for this shortage (Fox et al., 2009; Jensen et al., 2002). That is to say, each company sets its production plan according to its manufacturing capacity and marketplace demands. Accordingly, if any sudden circumstances take place resulting in increased demand, companies cannot increase their production, which leads to drug shortages.

2.2.5.2. Behaviors and practices of Healthcare providers and patients

Similar to practices of distributors who stockpile medicines, patients tend to build up a safety stock if there are rumors for an impending shortage (Bogaert et al, 2015; Awad et al, 2016). Such practices induce further shortfalls and create false demand. Besides, perceptions of patients about drug analogues and alternatives play an influential role in amplifying the problem (Abdelrahman et al., 2016). This means that patients will refuse to take any other medicines if they did not find the medication they are used to.

On the other hand, the lack of physician awareness about drug alternatives and the lack of treatment guidelines may worsen the situation (Awad et al., 2016). Another study conducted in Egypt showed that complaints from pharmacists about physicians' refusals for prescribing drug alternatives had been raised (Abdelrahman et al., 2016). In other words, because the physician may not be aware of other medicines with similar effects to that in shortage, they insist on this unavailable drug, and thus exacerbate the problem. Abdelrahman et al. (2016) also argued that some pharmacists did not suggest analogues to many patients. Thus, all these factors lead to defects in the whole process of prescribing and consuming medicines which increase drug shortages.

Generally, patients' stockpiling of medicines may lead to a false increase in demand leading to drug shortages. Besides, few studies which are mainly conducted in developing countries pointed out to patient perception and physician knowledge about analogues (medicines with the same active ingredient) and alternatives (medicines with the same pharmacological effect) as factors to amplify the drug shortage problem.

2.2.6. Natural disasters

Natural disasters and unforeseeable events include hurricanes, fires, tornados, floods, or any other unexpected condition. Very few shortages are linked to natural

disasters, as reported by (Woodcock & Wosinska, 2013). This was evident by ASHP (2019) that announced that only 3% of the drug shortage in the US was due to natural disasters. An example of a recent natural disaster leading to shortages of many critical drug products is Hurricane Maria which hit Puerto Rico in 2017. Puerto Rico is a hub of pharmaceutical manufacturing so the hurricane negatively affected many production facilities which are pivotal sources of many drug products which lead to a global drug shortage (FDA, 2017). Moreover, natural disasters may hinder the importation of raw materials or finished drug products due to interrupted transportation leading to supply interruptions (Awad et al., 2016). Consequently, natural disasters may generate drug shortages due to destruction of manufacturing facilities and impediment to importation and transportation which lead to disruption of supply and halting of production.

In conclusion, the literature review showed that numerous intertwined aspects could potentially lead to drug shortages. First, the regulatory framework may adversely influence the manufacturing process and distribution because of the legislation itself or due to bureaucracy and delays. Second, economic aspects may create drug shortages because they influence business decisions to cease production of a particular drug due to low profitability and small market size. Besides, maintaining low inventory levels to reduce expenses increases the risk of drug shortage. Third, the manufacturing of drug products encounters many challenges, such as quality issues, limited production capacity, raw materials scarcity, and logistics problems resulting in production delays, disruptions, or even stoppage. Fourth, issues related to distribution such as parallel trade, drug stockpiling, and grey-market can worsen the drug shortages. Additionally, poor supply chain management and improper procurement and tendering systems may negatively influence the availability of medicines. Fifth, increased demand due to shortage of other similar products, expanded

use of a drug, and disease outbreaks may initiate a drug shortage. On the other hand, some patients and physicians can create false demand or worsen an existing shortage due to medicine stockpiling and unawareness of drug analogues and alternatives. Sixth, although natural disasters participate in very few shortages, their influence may be severe because they substantially affect the manufacturing process, transportation and distribution.

After highlighting the root causes of drug shortages discussed in the literature, we will now turn to the actions taken by governments to tackle and mitigate this problem.

2.3. Countries' experiences in mitigating drug shortages

Drug shortage is a complex and multi-faceted problem that has numerous causes and multiple stakeholders. Mitigation and prevention of such a problem requires cooperation between, and involvement of, all entities related to the supply chain as well as regulators.

2.3.1. United States

FDA acknowledged its attempt to tackle the problem of drug shortage. However, despite the many efforts exerted by FDA to mitigate drug shortage, there are some causes of drug shortage which cannot be controlled by the FDA such as the type of products companies choose to produce, and the production volume for each product (FDA, 2018).

Modification of Regulations and formulation of a task force on drug shortage

In response to the presidential Executive Order number 13588/20111 in which drug shortage was recognized as a serious problem and a growing threat to public health, the Food and Drug Administration Safety and Innovation Act (FDASIA) was passed in 2012 which has many articles to mitigate drug shortages (Dill & Ahn, 2014).

A task force was established according to FDASIA to come up with a strategic plan to mitigate drug shortage. This plan was developed in 2013 by the FDA drug shortage task

force to be the guidance for dealing with drug shortage. Moreover, a drug shortage manual of policies and procedures was developed, and this manual is regularly updated. The last update was in April 2018.

Notification and communication of drug shortage

In addition, the act mandates all manufacturers to notify the FDA when the product has been discontinued whether permanently or temporarily, at least six months prior to discontinuation or as soon as possible. This act requires the FDA to send a noncompliance letter to manufacturers which fail to notify the FDA. In addition, information about drug shortages is regularly updated and made available in a searchable online format which is accessible to everyone. In March 2015, the FDA launched a new mobile App for drug shortage that allows public access to information about current drug shortages, resolved shortages and discontinuation of medicines (FDA, 2015).

The FDA has announced in 2017 the development of CDER Direct NextGen Collaboration Portal for the industry, which is an online tool to minimize data entry and facilitate the notification process. Moreover, the FDA works closely with manufacturers to determine the shortfalls and to help them to restore the production. Furthermore, it encourages other manufacturers to increase their production to fill the gap. The FDA succeeded in reducing reported drug shortages from 251 in 2011 to 35 in 2017.

2.3.2. The European Union

The competent authority for granting marketing authorizations for human and veterinary medicines in the European Union is the European Medicine Agency (EMA). Most drug shortages are handled by the national authorities at each member state (Dill & Ahn, 2014). On the other hand, the EMA is only involved in drug shortages that affect or are likely to affect more than one country in the European Union (EU). It regularly

publishes information about drug shortages and provides recommendations for healthcare providers and patients to deal with such shortages (EMA, n.d).

Notification and communication of drug shortage

The EMA requires mandatory pre-notification for any disruption of supply whether it is permanent or temporary and, unlike the FDA, it imposes financial penalties for non-compliance. Similar to the FDA, the EMA works closely with the manufacturers and other stakeholders to identify the root causes of shortages and tackle them, and to take actions to allow alternative medicines.

Adopting exceptional measures

The EMA also takes some exceptional measures to prevent drug shortages such as "expedited variations, waived inspections, and rational risk-benefit decision making more frequently with consultation". The Heads of Medicines Agencies HMA/EMA task force on availability of authorized medicines was established to provide support and coordination to ensure availability of medicines.

Therefore, the EMA takes different measures to tackle drug shortage such as establishing a task force and providing access to all information related to drug shortage, cooperating with different stakeholders, establishing exceptional regulations to deal with shortages, and making it mandatory to pre-notify about production interruption. Such collective efforts can positively influence drug shortage.

2.3.3. Canada

In 2012, Health Canada created a Multi-Stakeholder Steering Committee on drug shortages (MSSC). This committee is comprised of representatives from health care and industry. It is endorsed by the ministry of health in different territories and provinces, and

its main responsibilities are improving the communication of drug shortage to the public and developing strategies to mitigate this problem.

The MSSC developed a number of tools to deal with this problem. These tools comprise the development of a protocol for the notification and communication of drug shortages, creating a multi-stakeholders toolkit, articulating a guidance document to mitigate drug shortages through contracting and procurement.

Notification and communication of drug shortage

The notification and communication of drug shortages started in 2012. At the beginning, the notification of drug shortage by the industry was voluntary (Donelle et al, 2018). The innovative and generic drug industries were posting the anticipated shortage on a website which was managed by the professional association of research pharmaceutical industries which is now called Innovative Medicines Canada. This reporting mechanism was inadequate; most of the shortages were listed after the shortage had begun, or were not listed at all, and the causes behind these shortages were vague. Due to these shortcomings, drug shortage reporting became mandatory in March 2017. In addition, a new third-party reporting website Drug Shortage Canada was launched which is managed by Bell Canada (Health Canada, 2017). In response to the introduction of a mandatory drug shortage reporting system, the MSSC developed a protocol for the notification and communication of drug shortages. A tiered process of notification and communication of information on drug shortage or discontinuation was determined by this protocol (MSSC, 2017). According to this protocol, drug manufacturers are required to report on anticipated drug shortage or discontinuation no less than six months in advance, or otherwise within five days of becoming aware of the anticipated or actual drug shortage.

Developing a strategy to coordinate efforts to mitigate drug shortage

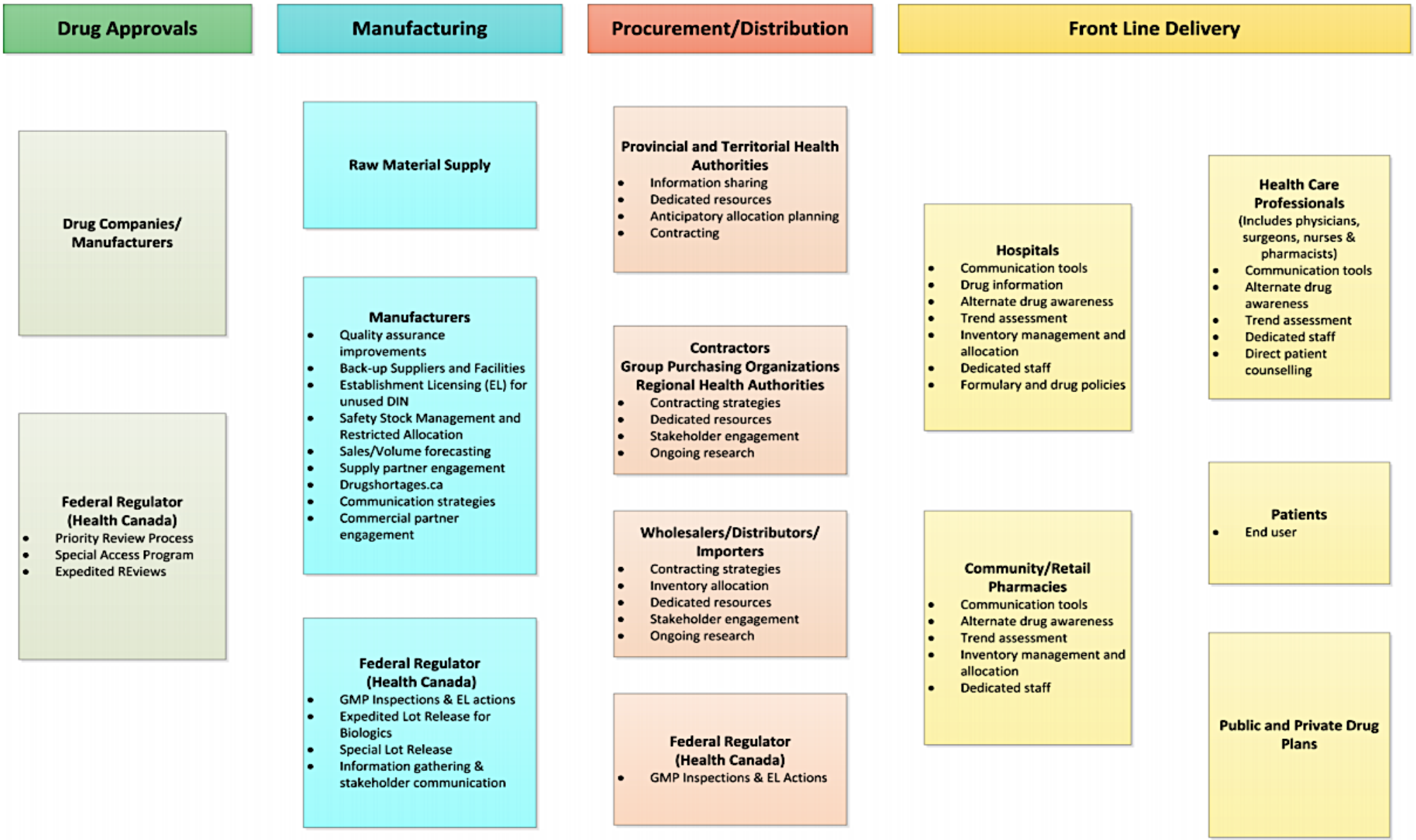
The second tool that has been developed by MSSC is the multi-stakeholder toolkit. It was developed in 2013 and updated in 2017 after the introduction of the mandatory reporting system (Health Canada, 2017). The main aim of this toolkit is to support and coordinate the efforts of different stakeholders to identify, mitigate and prevent drug shortage. The multi-stakeholder toolkit describes the drug supply chain in Canada. Moreover, it sets out the strategies, roles, and responsibilities of each party to address drug shortage at each stage of the supply chain (MSSC, 2017) as illustrated in Figure 2.

A guidance document to mitigate drug shortages through contracting and procurement

The final method which MSSC has adopted to mitigate drug shortage is developing guidance for contracting and procurement. This was in direct response to the fact that, in 2012, sole source contracting was highlighted as the most significant reason for drug shortage (Health Canada, 2017). In addition, it provides recommendations for drug manufacturers to overcome manufacturing-related drug shortage.

To conclude, Health Canada has made many attempts to mitigate drug shortage, and it mainly depends on providing guidelines and guidance documents to improve the process at all stages of the drug supply chain, and to enhance coordination between different stakeholders to minimize drug shortage. Moreover, it puts in place strategies for proper notification and communication of drug shortage information to allow for early actions to be taken.

Figure 2 Overview of drug shortage tools and strategies in Canada



Source: (MSSC, 2017, p.13).

2.3.4. Australia

Notification and communication of drug shortage

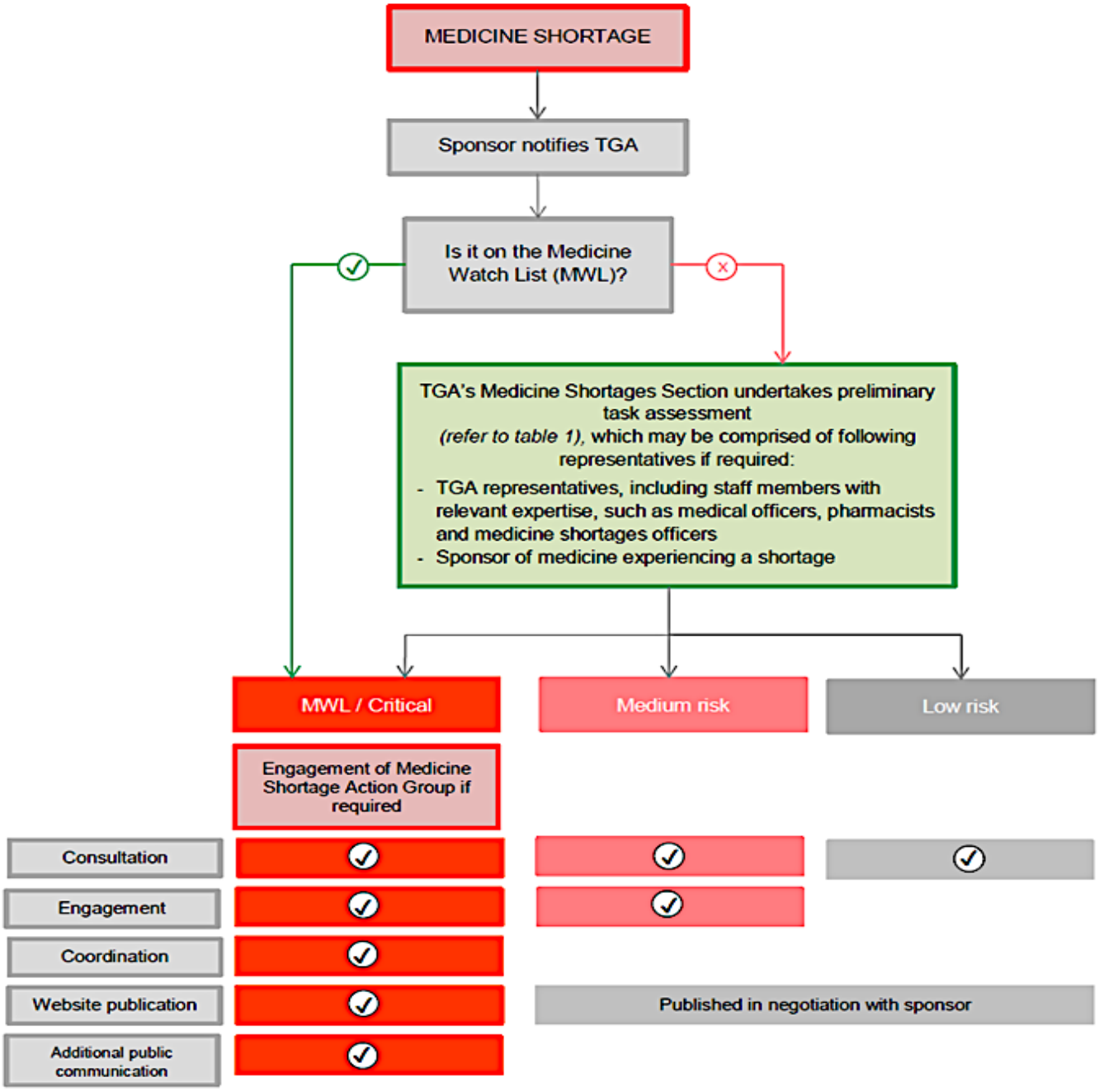
The Therapeutic Goods Administration (TGA) is the regulatory authority for medications which is responsible for ensuring drug availability in Australia. In an attempt to mitigate drug shortage, the National Medicines Shortage Information Initiative (MSII) and a website were launched for voluntary notifications of drug shortage (TGA, 2018). Unfortunately, this initiative did not achieve the desired results; neither healthcare professionals nor other stakeholders saw this website as a credible source of information. This insufficiency was a result of the incomplete information provided on the website. Furthermore, the website listed shortage of food and herbal extracts as well which made it more difficult and slower to search, and it only listed the anticipated shortage not the current one (Tan, Moles, & Chaar, 2016).

In response to concerns raised by different stakeholders about the aforementioned notification system, a new protocol for management and communication of medicine shortages was developed in 2018. This protocol was jointly articulated by TGA and representatives from professional associations of pharmacists and physicians, and from the industry as well (TGA, 2018). This protocol aims at improving the management and communication of drug shortage by making the reporting of shortages mandatory. The protocol determines the role of different players to mitigate drug shortage.

Furthermore, TGA categorizes the drug subjected to shortage according to the impact it has on patient into four levels: low, medium, high, and extreme. This categorization is determined by the size of the patient population affected by the shortage, and on the availability of a similar or alternative drug. In addition, TGA developed a Watch List which is derived from emergency and life-saving drug lists and from the essential drug

list. This list was developed to speed up the decision-making process with respect to those drugs that are directly considered as having an extreme impact on patients. According to this categorization, TGA determines the proper response to drug shortage as illustrated in Figure 3.

Figure 3 Response to a medicine shortage in Australia



Source: (TGA, 2018)

In case of non-compliance to the notification system, (TGA) publishes the names of license holders who have been non-compliant on the MSII website. In addition, civil penalties in the form of fines are imposed if deliberate repeatable non-compliance was demonstrated.

Adopting Exceptional measures

In addition, TGA allows importation of medications which are not registered for a specified period of time as long as the registered products are in shortage and have no other substitutes (TGA, 2019).

To sum up, the TGA works in two key directions. Foremost is improving the notification and communication of drug shortage information according to the impact of drug shortage on patients. The second is to approve the importation of pharmaceutical products without prior registration in case of unavailability of registered products.

2.3.5. Brazil

Notification and communication of drug shortage

The National Health Surveillance Agency (ANVISA) is the drug regulatory authority concerned in Brazil. ANVISA issued the resolution RDC NO. 18 in April 2014 to regulate reporting of the withdrawals from the market. It states that the withdraw should be reported 180 days in advance and the supply should be continued during this period, and it imposes penalties in case of non-compliance (ISAGS, 2017).

Coupled with the mandatory notification system, ANVISA communicate information about drug shortages though its online website to help healthcare providers to identify the problem and so facilitate the identification of intervention strategies. Furthermore, it enhance both public and private pharmaceutical companies to develop their plans to meet market need (Rosa et al., 2016).

From the above-mentioned best practices adopted by governments, it can be concluded that many policies and measures have been developed and adopted to mitigate and prevent drug shortage as follows:

- A task force or a committee which comprises of different stakeholders is formulated.
- A strategic plan to mitigate drug shortage can be developed to determine the role that should be played by each stakeholder, and to coordinate efforts.
- Notification of anticipated or current drug shortage to competent authorities is key to alleviate the severity of the problem.
- Communication of drug shortage information allows early actions to be taken and enables healthcare providers to make timely and well-informed decisions.
- Exceptional measures can be taken such as expedited procedures for registration and inspection.
- Modifications of laws to ensure the implementation of the aforementioned strategies and procedures, and to introduce penalties for non-compliance.

In comparison with numerous studies about drug shortage conducted in developed countries, there are only few studies performed in developing countries. Therefore, more studies are required in developing countries, specially Egypt to account for the different political, economic and legislative context, all of which may lead to more appropriate and specific outcomes. Since the 2011 revolution, Egypt has faced numerous events that have challenged the country's stability and security and economic development. Because of political and economic instability, many sectors have been adversely affected in Egypt including the pharmaceutical industry. Additionally, many economic changes have occurred such as the scarcity of hard currency in 2015, the liberalization of the exchange

rate, the devaluation of the Egyptian Pound, the reduction of subsidy on electricity and fuel. These economic changes impacted the ability of many businesses to continue operating in Egypt including pharmaceutical companies. Furthermore, the legal framework of pharmaceutical sector in Egypt differs from other countries in terms of regulations for drug registration, pricing, and importation. Thus, the special political, economic, and legislative context of Egypt encouraged conducting this study that may lead to a different analysis of the drug shortage problem and allow for a better understanding of the problem according to the Egyptian context.

Chapter Three: Conceptual Framework and Research Methodology

3.1. Conceptual Framework

Operational definitions

Throughout the study the following terms are used as follows:

Innovative /brand-name/ branded drug

The product has chemical structure that has never been approved before. This new drug may have similar actions to earlier therapies, and it may not offer unique clinical advantages over existing medicines (CDER, 2015).

Generic drug

The medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics (FDA, 2018). Generic medicines, usually, have lower prices than brand-name medicines because they cost less as they do not need to repeat the clinical trials which were already performed by the innovator.

Drug analogue/similar drug product

A drug product that has the same active ingredient but made by different manufacturer.

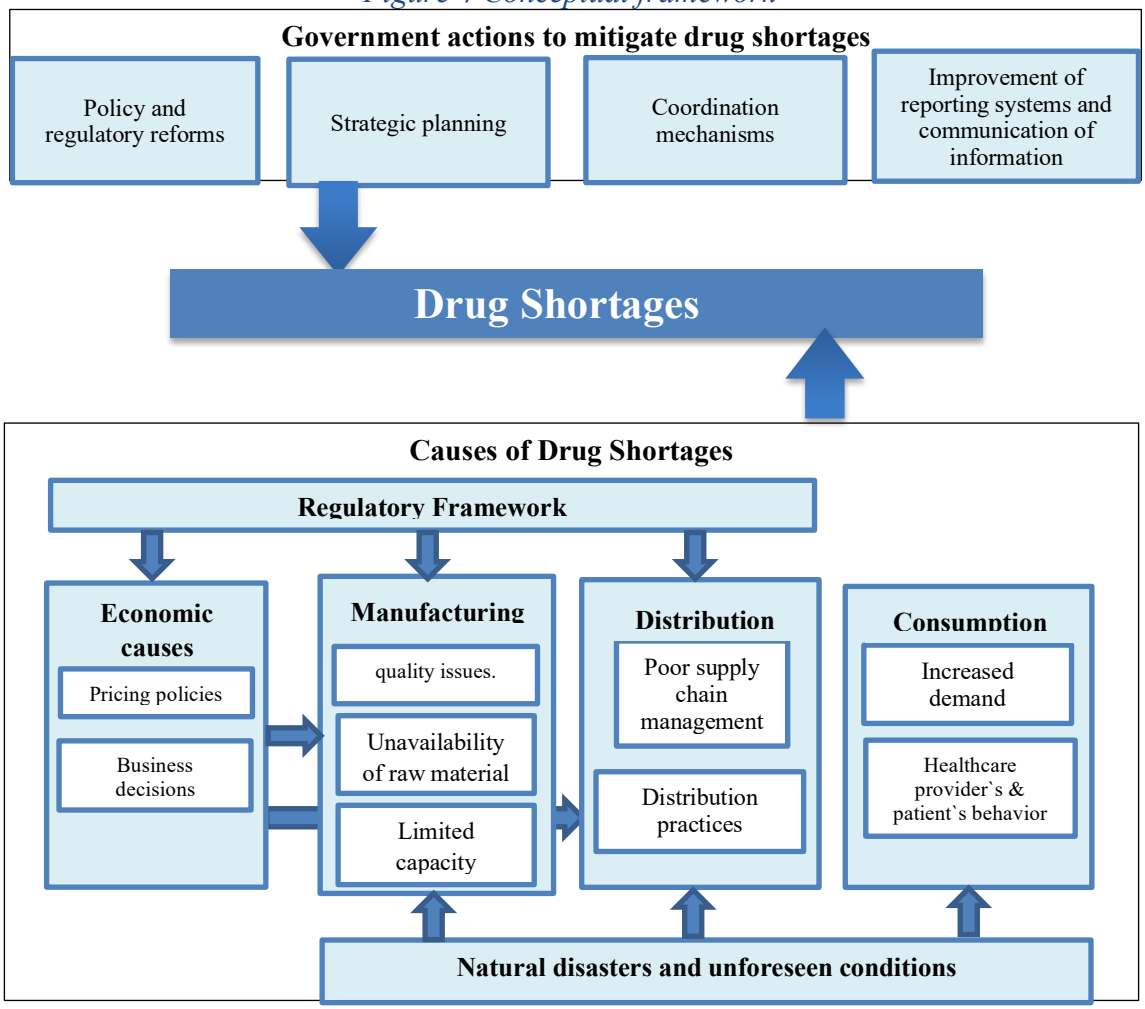
Drug alternative

A drug product that has different active ingredient but from the same pharmacological class as the original prescribed drug.

Drug shortage is an old problem that does not have a unified definition, which is evident in the various definitions provided by many scholars and organizations (Awad et al, 2016; Mayers et al., 2012; ASHP; FDA). Besides, drug shortage is a problem with a complex origin, so identifying the causes of the problem is essential in solving it. A review of the literature has indicated that drug shortages are mainly due to issues related to drug manufacturing, distribution, or consumption. Additionally, economic factors, regulations and policies, and natural disasters can generate drug shortages.

This study is conducted with an overall aim of determining root causes of drug shortage in Egypt and exploring how the government deals with the problem which allows for identification of gaps and proposal of more effective solutions to mitigate the problem.

Figure 4 Conceptual framework



Source: developed by the researcher.

All conceptualizations are based on studies conducted in various countries and reports from drug regulatory authorities and international organizations: ASHP (2009), Kaakeh et al. (2011), Markowski (2012), Mayers et al. (2012), Woodcock & Wosinska (2013), Birgli (2013), Dill & Ahn (2014), Bogaert et al. (2015), Awad et al. (2016), Abdelrahman et al. (2016), Heiskanen et al. (2017), Alruthia et al. (2018), Fox et al. (2018), FDA, EMA, Health Canada, and TGA.

The above figure is a visual representation of the conceptual framework guiding this study. It includes the causes of drug shortage problem and how they relate to each other. It also comprises actions taken by governments to address the problem.

The causes of drug shortages include manufacturing issues which are mainly related to quality issues, raw material issues, limited production capacity (Woodcock & Wosinska, 2013; Dill & Ahn, 2014). Not only do the problems related to the manufacturing of raw material and finished products cause drug shortages, but also issues related to distribution and supply chain management can create shortages.

Numerous studies showed that poor supply chain management and Inefficient procurement and tendering systems contribute to drug shortages (Alruthia et al., 2018; WHO, 2015; Woodcock & Wosinska, 2013; Awad et al., 2016). In addition, distribution-related issues such as parallel trade and gray-market increase the shortages of medicines in low-income countries (Birgli, 2013; Bogaert et al., 2015; ASHP, 2009; Alruthia et al., 2018).

Coupled with issues related to distribution, consumption's issues may result in drug shortages. Increased consumption due to expanded use of a drug, shortages of similar drug products, or outbreaks of disease are likely to lead to drug shortages (Fox et al., 2009; Jensen et al., 2002). On the other hand, false increased demand which is generated from

medicine stockpiling either by patients or distributors may result in stock-outs and shortfalls (Bogaert et al., 2015; Awad et al., 2016). Another issue that was discussed mainly by studies conducted in developing countries is the perceptions of physicians and patients about drug analogues and alternatives, which have been identified as a cause of amplifying the drug shortage problem (Awad et al., 2016; Abdelrahman et al., 2016).

It was also reported in literature that regulatory framework may adversely influence the manufacturing process, distribution, and business decision which consequently affect the availability of the drug. Some studies reported that tighten regulations increase the likelihood of non-compliance leading to production interruptions and drug shortages (Dill & Ahn, 2014; Heiskanen et al., 2017; ASHP). Besides, other regulations such as drug pricing policies may lead to low profitability and production ceasing. Finally, some scholars argued that legislation supporting parallel distribution could generate drug shortages (Birgli, 2013; Bogaert et al., 2015). It can be concluded that the regulatory framework is intertwined with drug manufacturing, distribution, and economic aspects, which can affect the drug availability.

Furthermore, previous studies have emphasized the economic aspects as an essential cause of the unavailability of medicines. Unfair pricing mechanisms and inadequate profits lead to ceasing the production of many products and shifting to more profitable products (Alruthia et al., 2016; Yang, et al., 2016; Awad et al., 2016; Markowski, 2012). In addition, economic aspects can influence the supply chain management since some pharmaceutical companies decide to maintain low inventory levels which increases the vulnerability to shortages (Bogaert et al., 2015; Woodcock & Wosinska, 2013). It is also reported that manufacturers may reduce investments in quality management which leads to further quality issues and production interruptions (Dill & Ahn, 2014; Markowski,

2012). In short, economic aspects can adversely influence manufacturing processes, quality issues, business decisions and inventory management which lead to drug shortage.

Natural disasters and unforeseeable events were reported as a cause of the shortage which affect the drug manufacturing and transportation leading to supply shortfalls (FDA, 2017; Awad, 2016). On the same hand, they may increase the demand for medicines and cause stock-outs (Lyengar et al., 2016).

In response to the aforementioned causes of drug shortages and their expected dire consequences on health, many governments have taken many actions to address the problem, as explained in literature and official reports (FDA; EMA; TGA; Health Canada; Dill & Ahn, 2014). These actions include: formulation of a task force or a steering committee (Dill & Ahn, 2014; EMA, n.a; Health Canada, 2012), developing a strategic plans and manuals to determine the role and responsibility of each stakeholder, imposing a mandatory notification system of anticipated or current drug shortage to competent authorities (FDA; EMA; Health Canada, 2017; Dill & Ahn, 2014; TGA, 2018; Donelle et al, 2018), enhancing communication of drug shortage information, and finally adopting exceptional measures to expedite procedures for registration and inspection (TGA, 2019).

3.2. Research Methodology

3.2.1. Qualitative research design

This study adopts a qualitative exploratory research design to examine the causes of drug shortages in Egypt and to identify current actions to mitigate and tackle the problem. A qualitative approach is beneficial when the study aims at delving deeply into complex processes, and when the relevant variables of the research have yet to be identified (Marshall & Rossman, 2014). This is highly applicable in this study since the drug shortage is a complex problem that involves many stakeholders. Besides, there is a very little

research on this topic in Egypt. Therefore, a qualitative approach provides the researcher with a space to explore and describe the problem.

3.2.2 Overall research strategy

The study depends on in-depth interviews as a primary data collection method with several respondents who have been part of the problem. In-depth interviews take place in one-on-one meetings which provide a room for easy questioning and allow the researcher to delve deeper into the answers. In addition, it minimizes the risk of misunderstanding of the question by participants because the interviewer is present in the process (Babbie, 2013). Semi-structured interviews are conducted to collect focused and qualitative data to achieve the study objective and answer the research questions that are qualitative in nature. This method provides a balance between the flexibility of unstructured interviews and the focus of structured interviews. For triangulation purposes, interviews are conducted with diverse stakeholders to correlate between different points of view, second, verifying the obtained primary data by reviewing secondary data, third, being working in the pharmaceutical field facilitates personal interaction between the researcher and participants.

3.2.3. Sampling

A non-probability purposive sampling technique is used to identify the key interviewees in this study. Purposive sampling helps in reaching a specialized population by using different methods to find all possible cases that fit the criteria of the study (Neuman, 2000). This is specifically useful when conducting in-depth investigations and exploratory research, which is the case in this study. The selection was done in a way that

guarantees the involvement of different stakeholders. Accordingly, 20 one-on-one interviewees were conducted, as illustrated in Table 1.

The interviewees were grouped according to their professional roles. First, seven participants are from drug regulatory bodies, they are at managerial positions in various organizations and departments at MoHP. Second, five interviewees are from pharmaceutical companies, which are among the top 10 in the pharmaceutical market. Both local manufacturers and Multinational Corporates (MNCs) are represented to allow a better understanding of the problem from various angles because the management system and the encountered challenges may be different. Third, four participants from pharmaceutical industry associations and civil society were recruited, two of them are from the Egyptian Pharmacists Syndicate to explain the problem in terms of distribution and dispensing, and the two others are from the Federation of Egyptian Chambers of Commerce, and from the Chamber of Pharmaceutical industry to provide a holistic view of the problem because they are sharing experiences with many pharmaceutical companies. Fourth, to delve deeply into understanding the problem from the distribution side, two interviews were conducted with two of the top distributors in the market. Finally, two interviews were conducted with pharmacists at community pharmacies to reflect dispensing problems and patients' perceptions.

Thus, this diversified sampling helps in understanding the problem from different perspectives to recognize the root causes of drug shortages and actions taken to address the problem.

Table 1 Interviewee's Profiles

	Regulatory bodies	
	Position	**Organization**
1	Government official 1	Ministry of Health and Population (MoHP)
2	Government official 2	
3	Government official 3	
4	Government official 4	
5	Government official 5	
6	Government official 6	
7	Government official 7	
Pharmaceutical companies		
	Position	Organization
8	CEO	Local pharmaceutical companies (among the top 10)
9	Senior leadership position	
10	The head of the supply chain department	
11	The head of Business Development Unit	Multinational pharmaceutical company
12	The head of Registration Department	
Pharmaceutical industry associations and civil society		
	Position	Organization
13	Top leadership position	The drug division at the Federation of Egyptian Chambers of Commerce FEDCOC
14	Member	Chamber of the Pharmaceutical Industry
15	A former chairman of the pharmaceutical manufacturing committee	Egyptian pharmacists syndicate
16	Member	Egyptian pharmacists syndicate
Drug Distributors and Wholesalers		
	Position	Organization
17	General manager	Distributor and importer
18	Branch deputy manager	
Pharmacists		
	Position	Organization
19	Pharmacy owner	Community pharmacies
20	Pharmacist	

Source: developed by the researcher

3.2.4. Data collection

Given the limited evidence in the literature on drug shortage in Egypt, this study heavily depends on primary data. However, relevant secondary data is reviewed. To achieve primary data collection, semi-structured in-depth interviews with each participant were conducted. The interviews were conducted in Arabic, and instant notes were taken

in a writing form during interviews. The duration of interviews ranged from 30 to 60 minutes each. The secondary data is gathered from published governmental and non-governmental data, reports and journal articles.

3.2.5. Data analysis

The interviews were translated into English by the researcher. An initial manual categorizing system was generated in alignment with the conceptual framework. Each interview transcript was divided into several parts and clustered according to the initial themes. During the process, subthemes were added, and the initial categorizing system was modified. The final thematic index was created, and according to this index, all data were coded.

3.3. Ethical considerations

The researcher obtained the approval of the International Review Board (IRB) at the American University of Cairo (AUC) on the 15th March 2019 before the data collection process. All participants were mentioned by their jobs to protect the confidentiality of their identity, and to make sure to do the participants no harm. Informed consent was obtained from interviewees either written or orally because some participants were reluctant to sign the document. Besides, the researcher thoroughly explained the scope of the study and research purpose before conducting the study. The interviewees were informed that participation is voluntary and that the researcher will not have any benefits from the study (Babbie, 2013).

3.4. Limitations and delimitation of the study

Although most participants were easily accessed since the researcher is in the same field, some participants were sensitive to freely speak because the researcher is a

government official. Additionally, physicians and patients as stakeholders were not involved in the study, because the main objective of the study is to investigate the causes of drug shortage so the researcher prioritized interviewing stakeholders who may often contribute to the causes of the problem, rather than interviewing affected stakeholders. Furthermore, the role of public sector companies in the pharmaceutical sector in Egypt is not covered in this study because these companies have specific settings that do not apply to other companies, so the researcher gave priority to interviewing participants from companies representing the majority of the market. Further work on pharmaceutical companies in the public sector is recommended to determine their role and to identify opportunities to achieve higher efficiency and better competitive positioning in the market. Another limitation from a logistical point of view were the interview settings. Some interviews which were conducted at the interviewees' workplaces included unavoidable interruptions, which may have affected the depth of shared information. Besides, an unintended bias cannot be ruled out because the researcher works in the same field.

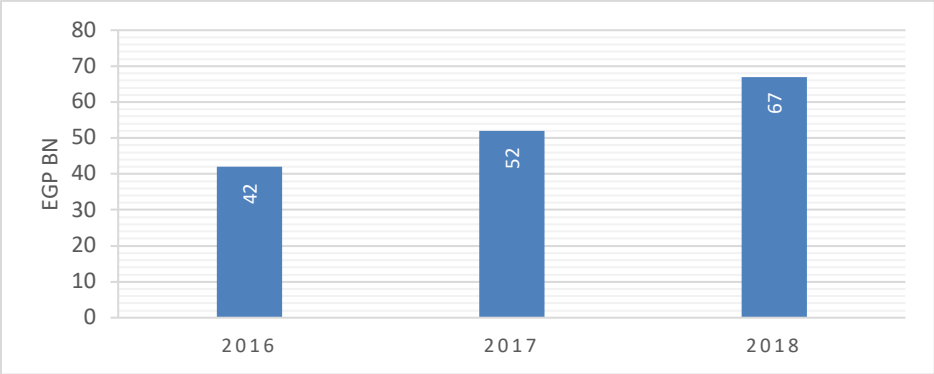
The delimitation of this study is that it is concerned with identifying the common and general causes of drug shortage in Egypt so understanding drug shortage in special settings such as government hospitals and healthcare units need deeper study and examination that is not covered by this study.

Chapter Four: The pharmaceutical industry and regulatory framework in Egypt

4.1. The pharmaceutical industry and market in Egypt

The pharmaceutical industry is considered as one of the nation's oldest strategic industries in Egypt. It started in the 1930s and continues to expand over the years. Despite the turbulent economic environment in Egypt over the last few years, the pharmaceutical market has grown. In 2016, It had a value of around EGP 42 billion, which has significantly risen to EGP 52 billion in 2017. By 2018 the pharmaceutical market reached its highest value of around EGP 67 billion (Information Medical Statistics IMS, 2019), as illustrated in Figure 5. This considerable increase in the value of sales may be due mainly to the increase in prices after the devaluation and to the high population growth. According to the Central Agency for Public Mobilization and Statistics (CAPMAS), the population dramatically increased from 91 million in mid-2016 (CAPMAS, 2017) to 98 million in January 2019 (CAPMAS, 2019).

Figure 5 Pharmaceutical sales in Egypt (EGP bn)



Source: developed by the researcher according to IMS data

In this section, the key characteristics of the Egyptian pharmaceutical industry and market are illustrated including the historical context of this industry. In addition, the structure of the market and sales distribution are determined to understand how it may

influence drug shortages. Moreover, it illustrates the extent to which the Egyptian pharmaceutical industry relies on imports. At the end of this section, the most significant recent economic changes and reforms are explained. This overview helps in giving the study findings more validity and allows a better understanding of the causes behind the drug shortage in Egypt which will, in turn, help in proposing better solutions.

4.1.1. Historical overview

Understanding the current situation requires knowledge about the history and the development of the pharmaceutical industry in Egypt. The pharmaceutical industry dates back to the late 1930s when the first Egyptian pharmaceutical company, Misr Company for Pharmaceutical Industries, was established (Holdipharma, n.d.). Misr Company was founded in1939 by Misr Bank. The bank was founded by the economist and financial expert Talaat Harb Pasha to reflect the Egyptian identity during the British occupation. After the foundation of Misr Company for Pharmaceutical Industries, many other private pharmaceutical companies joined the market such as Memphis, Al Kahira, CID and Al Nasr. After the 1952 revolution, the nationalization of all private pharmaceutical companies took place. In addition, in 1965, during the Gamal Abd Al Nasser era, the Egyptian Pharmaceutical Trading Company EGYDRUG was established as a national public company (Holdipharma, n.d.). At that point of time, EGYDRUG was responsible for all wholesaling, distribution and importation of pharmaceuticals all over the country (Rakha & Smith, 1985).

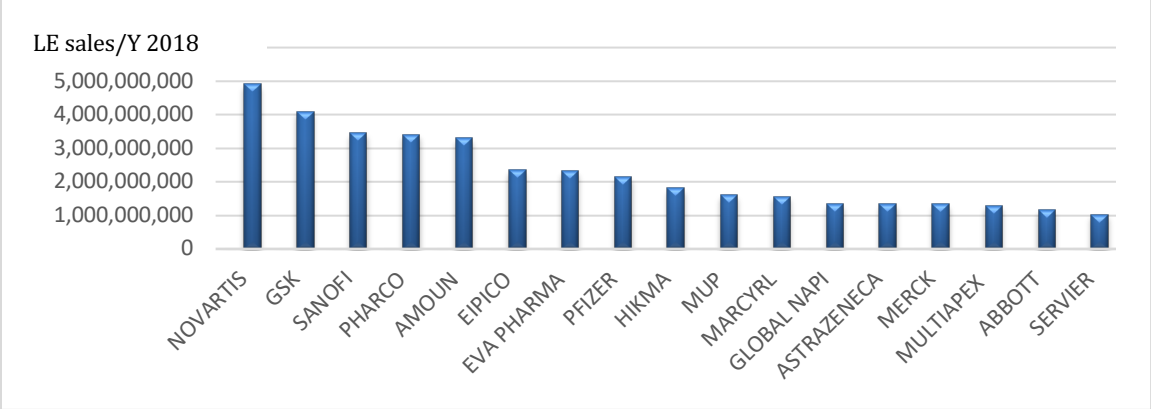
On the other hand, during the Sadat era, an open-door economic policy to attract foreign investments was adopted and paved the way for increased private investments (Selim, 2015). Moreover, the importation of foreign drugs by private sector agents was permitted. Since then, the pharmaceutical industry has grown in Egypt. Consequently,

Egypt is considered the largest producer and consumer of pharmaceuticals in Africa and the Middle East. Currently, the pharmaceutical market provides a competitive environment due to a large number of companies of different types that operate in Egypt, e.g. local, multinational companies, and importers.

4.1.2. Ownership structure

The domestic pharmaceutical industry in Egypt is strong. At present, there are around 160 licensed pharmaceutical factories operating in Egypt. They fall into three main categories; public sector companies, private local companies, and Multinational Corporates (MNCs). According to Information Medical Statistics (IMS)[1], almost half of the market is controlled by 20 companies, half of them are MNCs and the rest are local private companies, as shown in Figure 6.

Figure 6 Top 20 pharmaceutical companies in 2018 sales/value

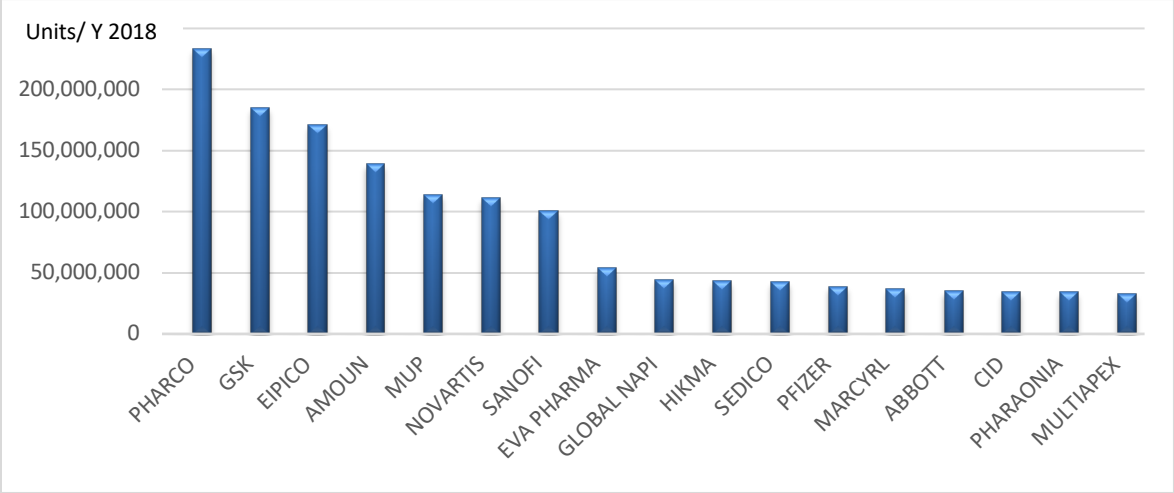


Source: developed by the researcher according to IMS data

On the other hand, by examining the market share in terms of volume, a different company ranking has been obtained, as illustrated in Figure 7.

[1] IMS reflects only the private market statistics

Figure 7 Top 2o pharmaceutical companies in 2018 sales/volume



Source: developed by the researcher according to IMS data

It can be seen in Fig. 7 that when it comes to the number of units sold, which reflect the actual consumption and need, the local manufacturers have higher values which shows their dominance in the market. Because of the higher prices of the branded products owned by MNCs, they have higher sales value. It is worth noting that there are some classes of drugs such as some types of chemotherapy and biologics are totally brought by MNCs and other importers, and they are highly expensive.

In addition to the 160 pharmaceutical factories, there are 1110 registered companies in the toll manufacturing register. These companies do not own factories, but they are allowed to manufacture their products at a third-party factory under toll manufacturing scheme. According to IMS, the market share of these companies is very low compared to the share of MNCs and pharmaceutical manufacturers (2019).

To sum up, the pharmaceutical market seems to allow competition since it includes large numbers and different types of companies; private, public, multinational companies, and toll-companies. However, this diversity in the market does not prevent the emergence of drug shortages.

4.1.3. Pharmaceutical sales distribution

The Egyptian pharmaceutical market includes the private market and public market. The sales of the private segment are mainly for private pharmacies and hospitals (AmCham Egypt, 2012). On the other hand, the public sector sales are mainly requested by the government – Ministry of Health and Population and Ministry of Higher Education- to supply health units and hospitals. The government purchases drugs by reverse auctions, so it has discounts and pays less for the same drug than that paid by the private market. The private sector represents the majority of the total pharmaceutical market because pharmaceutical sales are based on out-of-pocket expenditures (AmCham Egypt, 2012). This is mainly due to the absence of the implementation of a comprehensive health insurance system. According to CAPMAS, only 52.8 million Egyptians are covered by health insurance, and this represents around 50% of the total population (CAPMAS, 2017). Despite the official promulgation of the universal health insurance law number 2 for year 2018, the actual implementation of the law to achieve a complete coverage will take fifteen years (Prime Minister Decree No. 909 for the bylaw of comprehensive health insurance law, 2018). This means that out-of-pocket payments will be continued until full enforcement of the law. These payments may absorb a large fraction of household resources, especially with the increase in prices, so the burdens on citizens to pay for their treatment will continue.

Pharmaceutical sales are mainly divided into two categories; prescription drugs and over-the-counter OTC drugs. Prescription drugs account for most sales of Egypt's pharmaceutical market with a percentage of 80% of the total sales in 2018. On the other hand, OTC drugs represent 20% of the total market (IMS, 2019). Taking into consideration that due to the laxness of pharmacies in Egypt and the absence of strict penalties applied

by MoHP, pharmacies sell prescription drugs without submission of the prescription which resulted in blurred boundaries between prescription and OTC drugs (N Gage Consulting, 2017).

We can conclude that the sales of private pharmacies and hospitals are the main indicator of the pharmaceutical market because they constitute a larger market size compared to government hospitals and healthcare units, as reported by (AmCham Egypt, 2012). Consequently, the prescriptions written by physicians determine the sales of each company and are the main driving force behind the market growth.

4.1.4. Foreign trade

Although the domestic pharmaceutical industry in Egypt is strong, it heavily depends on the importation of most of its production inputs. Local manufacturers import nearly 90 percent of raw materials; both active and inactive ingredients (N Gage Consulting, 2017; Lofgren & Williams, 2013). Lack of capabilities and technologies necessary for the production of Active Pharmaceutical Ingredients (API) may be the reason behind the overdependence on importation. In addition, not only do manufacturers import raw materials, but they also import most of the packaging materials, equipment, and appliances. On the other hand, most of pharmaceutical exports in Egypt go to other developing countries in the Middle East and Africa (AmCham Egypt, 2012).

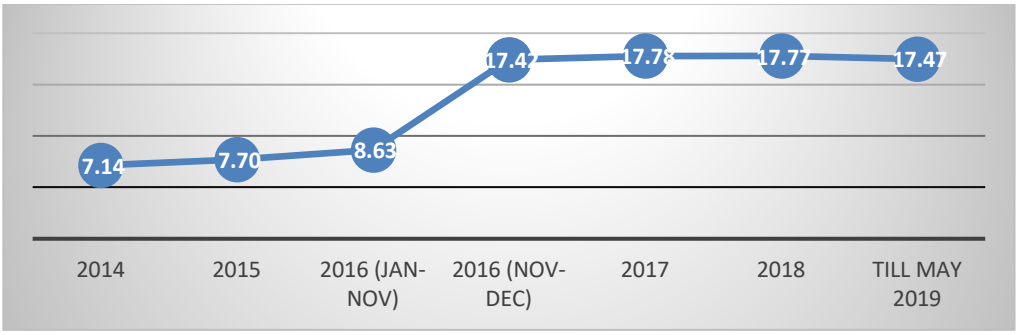
Accordingly, relying on importation affects the independence and sustainability of Egypt`s domestic pharmaceutical industry because it directly influenced by the economic and political relations with other countries, availability of hard currency, and the exchange rate of the Egyptian Pound. In fact, over the last decade, Egypt experienced many economic changes that affected drug availability.

4.1.5. Economic environment

During the last few years, and after the January 25th revolution, Egypt has witnessed political turbulence and economic instability that negatively impacted different sectors in the country. This resulted in a declining investment trend. In 2015, Egypt faced difficulties due to the shortage of foreign currency which made it more difficult for manufacturers to import raw materials needed for domestic production (El Agroudy, Shafiq & Mokhtar, 2015). As a result, the black market emerged, and it was selling and buying foreign currency outside the range determined by the Central Bank of Egypt (CBE). In March 2016, the government decided on a partial devaluation of the Egyptian Pound EGP to decrease its value against the United States Dollar USD from 7.73 EGP to 8.85 EGP. However, the problem continued, and the situation became worse. In an attempt to stabilize the economy, CBE floated the Egyptian Pound in November 2016 (Business Insider, 2016). After the floatation, the EGP to USD exchange rate was 17.42 compared to 8.63 before floatation (CBE, 2019) (Figure 8). The goal behind this decision was to meet one of the key requirements of the International Monetary Fund IMF to secure a twelve billion USD loan, and to end the black market, and to encourage external competitiveness through weaker currency (Abisourour, 2018).

Egyptian Pound floatation influenced the prices of all commodities because manufacturers set the price of their products according to the value of the dollar. However, the situation in drug prices was different because medicines are subjected to a compulsory pricing system, so pharmaceutical companies could not automatically increase drug prices. Accordingly, many companies could not cope with these economic changes and high importation costs without increasing drug prices.

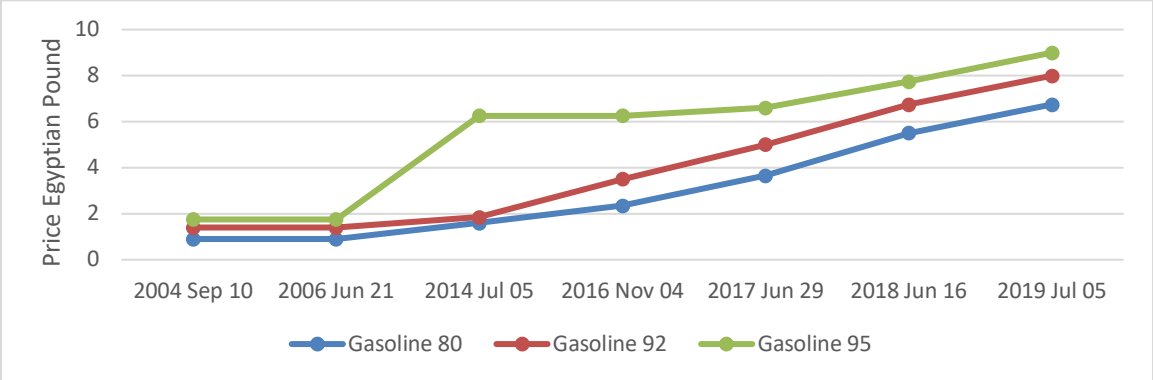
Figure 8 EGP to USD exchange rates since 2014



Source: developed by the researcher according to published CBE data

In addition, the government took other measures toward economic reform. For example, it adopted a five-year strategy to restructure the energy subsidy program. Energy subsidy reform strategy began in 2014 and aimed at stopping energy subsidy by 2019. Electricity prices have been increased two times since 2016. The first increase was in August 2016 by 25-40 % depending on the usage rate. In July 2017, another increase in electricity prices took place, by 5-42% for domestic use and by 29-46% for commercial use (Abisourour, 2018). Furthermore, fuel prices have been increased four times since the floatation (Figure 9).

Figure 9 Historical gasoline prices in Egypt



Source: developed by the researcher, data retrieved from https://www.thefuelprice.com/Feg?lang=en

Consequently, many industries faced difficulty in passing through these price increases, especially the pharmaceutical industry because the government sets the medicine prices. Beyond the economic environment, the regulatory framework may influence the ability of the pharmaceutical companies to run their business in Egypt and to sustain drug availability, so the following section sheds light on the regulatory authorities and the major pharmaceutical regulations.

4.2. Regulatory framework in Egypt

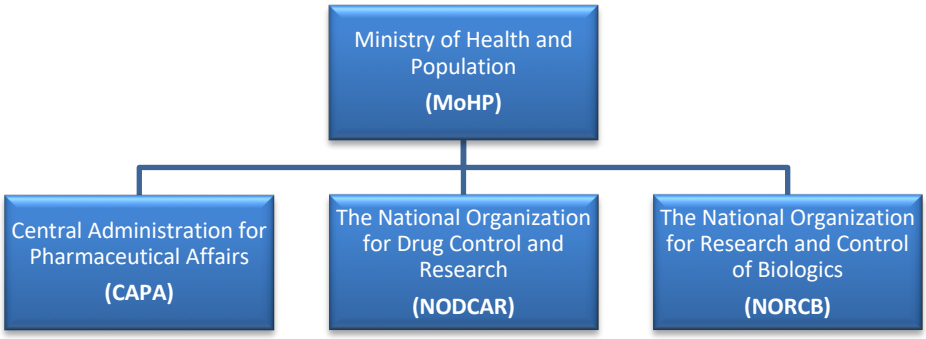
Despite the fact that such legislation aims to ensure safe, effective and affordable drugs, it may become, at certain points, a constraint to the operation of pharmaceutical companies in the country. In this section, the main regulatory bodies in the pharmaceutical sector are illustrated. In addition, the basic ministerial decrees regulating drug registration and pricing in Egypt are explained. This section allows for a better understanding of the regulatory environment that may affect drug availability, and to determine the gaps which need to be addressed to mitigate drug shortage in Egypt.

Achieving goals of accessibility, affordability, and quality of medicines requires effective and enforceable legislation and regulations for the pharmaceutical sector. Since the establishment of the first pharmaceutical company in Egypt in 1939, much legislation has been passed to regulate and control the pharmaceutical sector. In 1941, the first act number 5 for practicing pharmacy was issued (Kandil, 1989). This was followed by law number 127 in 1955 which is still valid until today. In accordance to this law, many ministerial decrees and regulations were issued to control and monitor the pharmaceutical market.

4.2.1. Regulatory authorities

The Ministry of Health and Population (MoHP) is the responsible body for regulating issues related to pharmaceuticals. Three bodies stem from MoHP: Central Administration for Pharmaceutical Affairs (CAPA); The National Organization for Drug Control and Research (NODCAR); and The National Organization for Research and Control of Biologics (NORCB) (EDA, n.d.), as show in Figure 10. These three entities work cooperatively to ensure availability and affordability of safe, effective, and high-quality medicines.

Figure 10 Drug regulatory authorities in Egypt



Source: developed by the researcher, data retrieved from http://www.eda.mohp.gov.eg/Articles.aspx?id=4

CAPA is a governmental agency responsible for regulating prescription and non-prescription human drugs, biologics, veterinary drugs, medical devices, food supplements, cosmetics and pesticides (EDA, n.d.). It is responsible for granting a registration license for the aforementioned products. In addition, it oversees the manufacturing and distribution of these products, and ensures manufacturers' compliance with the Good Manufacturing Practices (GMP). Moreover, it provides licenses for different pharmaceutical facilities, with the exception of pharmaceutical factories. Recently, pharmaceutical factories obtain their licenses from the Industrial Development Authority (IDA), and this license is issued in cooperation with CAPA. Furthermore, CAPA is responsible for setting drug prices. It also provides approvals for importation and exportation of raw materials and finished products.

Beside these functions, CAPA created the Drug Shortage Department (DSD) to deal with drug shortage issues (Abdelrahman et al., 2016 & EDA). Thus, CAPA is the main governmental body responsible for identifying drug shortages and resolving these through communication with pharmaceutical companies, wholesalers and Health Affairs Directorates in all governorates across the country.

The second organization contributing to ensure the quality, safety and effectiveness of the drug is NODCAR. It works as a national quality control authority through performing physical, chemical, biological, and microbiological tests for raw materials and finished products (NODCAR, n.d.). Samples of registered human pharmaceuticals, veterinary medicines, medical devices, pesticides, food supplements and cosmetics or products still under registration are analyzed in NODCAR labs to evaluate their compliance with standards. Obtaining a compliance certificate from NODCAR is essential for pharmaceutical products to be registerd, marketed and imported.

Similarly, NORCB is a public quality control authority, but it has the responsibility for ensuring safety, quality and efficacy of imported and domestic biological products and vaccines (NORCB, n.d.). It assesses the compliance of the biological products with the national and international standards. In the same manner as NODCAR, a compliance certificate from NORCB is necessary for registration and batch release of biological products.

It is noteworthy that the law number 151 for year 2019 has been ratified on 25th of August 2019 for the establishment of an independent unified authority under the name of Egyptian Drug Authority. This authority will include the three organizations mentioned above, and it will handle all matters related to drugs. It will be independent body reporting directly to the Prime Minister.

Briefly, it can be said that there are three separate entities that regulating and evaluating drug products in Egypt. This shows that insufficient cooperation or coordination

between these three organization may negatively affect the availability of medicines. Not only is the structure of the regulatory authorities crucial for controlling the pharmaceutical market and ensuring drug availability, but also the laws and regulations implemented by these authorities are important.

4.2.2 Pharmaceutical legislations

The drug legislation, in general, includes many provisions to regulate the manufacture, trade, and use of medicines. Regulations are important for both domestic and imported products, and they are also essential for new and existing products (Agarwal & Karwa, 2018). The aim of this legislation is to ensure that all medicines meet the criteria of safety, efficacy, and quality at every step (WHO, 2012). In Egypt, law number 127 provides the basis for pharmaceutical regulations. In accordance with this law, many ministerial decrees have been issued to regulate importing, manufacturing, distributing, marketing, drug testing, exporting, registering, and pricing of medicines.

This section considers further the medicine registration system and the pricing mechanism in Egypt because they are the major elements that affect the availability and affordability of medicines.

4.2.2.1 Drug registration

In Egypt, different Ministerial Decrees were issued and amended over the years to regulate medicine registration. The current ministerial decree regulating human drug registration is the Ministerial Decree No. 425/2015, and for biological products it is the Ministerial Decree No. 297/2009 (EDA, n.d.). The medicine registration process in Egypt depends excessively on various scientific and technical committees to assess the registration dossier. This overdependence results in long waiting lists of products awaiting review by these committees. According to the aforementioned ministerial decrees, only a

limited number of products of the same active ingredient are allowed to be registered. The registration process is based on the "box of similar products" system, in which pharmaceutical dosage forms (e.g. tablet, gel, spray, cream, capsule….) are grouped into a number of boxes, as illustrated in Appendix 1. In each box, only twelve pharmaceutical products of the same active ingredient can be registered. According to this system, the innovator product is guaranteed a place in the box, and the other eleven are for generic products (MoHP, 2015).

Although Ministerial Decree No. 425 is aimed at raising the quality of medicines and accelerating the registration procedures, there remain lengthy waiting lists of products to be presented to the committees. Besides, the "box" policy itself has some drawbacks that may influence the availability of pharmaceutical products in the market. One of these weaknesses is that the system depends on a first-come, first-served basis, so some companies can apply for medicine registration without having the real intention to produce the product, at the same time depriving other serious companies from submission because the box becomes full (Saed, 2016). It is worth noting that the "box" system is specific to Egypt as most countries do not restrict the number of products to be registered, and they depend mainly on the competition.

In an attempt to overcome the pitfalls and limitations of Ministerial Decree No. 425 and 297, MoHP issued decree number 820/2016 and decree number 645/2018. Decree No. 820 aims to accelerate the registration procedures for products that have approval from FDA or EMA, and products that are submitted according to the Common Technical Dossier (CTD) format[2]. On the other hand, Ministerial Decree No. 645 provides an exception for

[2] CTD is a standard format for sending drug data including administrative, quality, safety, and efficacy data from applicant to authority to be registered and marketed (ICH, n.d.).

some categories of drugs to be registered without adhering to the cap of similar products per box. One of these categories is the human medicines that do not have similar products in the market and were reported to be in shortage during a year before. CAPA is the responsible body for determining and publishing a list of these products every three months (CAPA, 2019).

The issuance of Ministerial Decree 645/2018 provoked a lot of arguments (Yousef, 2018; Sabry, 2018; Al Bawaba News, 2018). Those who are in favor of the decree contended that this decree will significantly facilitate resolution of drug shortages and will encourage further investment in the pharmaceutical industry. In contrast, the owner of community pharmacies and the Egyptian Pharmacists Syndicate opposed this decree because it will lead to proliferation in the number of medicines within a short period resulting in small pharmacies being unable to afford all these products. In short, we can say that not all parties agreed upon the aforementioned ministerial decree, and its positive or negative impacts did not fully manifest until now given it has only recently been implemented since a few months.

Even though the total number of registered medications in MOHP is around 14000 products, only around 8000 medicines are marketed (Babar, 2015). The “box” system may limit the generic competition, and at the same time, it cannot guarantee that all registered products will be marketed due to applied pricing policies. Accordingly, the system falls short of ensuring the availability of an adequate number of products for each active ingredient.

It is clear from the above that the “box” system is the main policy used to register medicines in Egypt, except in some cases which are regulated by Ministerial Decree No. 645/2018. It must also be noted that the registration decisions are mainly made by the

assisstance of external committees, which create long waiting lists of products to be presented to these committees and to obtain approvals.

4.2.2.2. Drug pricing

Drug pricing is a controversial topic in the pharmaceutical sector. According to law number 163 for year 1950 pharmaceutical products are compulsorily priced. The Minister of Health is responsible for creating a committee to determine the price of medicine which thereafter should be approved by the Minister of Health (law no. 113, 1963, article 10). Compulsory pricing has the advantage of ensuring the affordability of medicines but at the same time, it has disadvantages. The challenges of implementing a strict pricing policy for pharmaceuticals include delays in the access to innovative medicines in Egypt, the unsustainability of production, and the shortage of medicines (Ragab, et al., 2015).

Several ministerial decrees were issued to regulate drug pricing starting from Ministerial Decree no. 314/ 1991, which introduced the cost-plus pricing, where prices are regulated according to their manufacturing cost plus a predetermined profit margin. Thereafter, a new pricing approach was adopted by Ministerial Decree no. 373/2009, which included two different pricing systems; one for branded drugs and the other for generic ones. Branded drugs were priced at 10% less than the cheapest retail price found in 36 reference countries. On the other hand, generic drugs were priced based on a fixed percentage markdown versus the branded drug.

In 2012, Ministerial Decree no. 499 was issued to replace decree no. 373/2009. Decree no. 499/2012 is still in force and it combines the External Reference Pricing (ERP) and mark-up regulations, as it determines the profit margins for pharmacists and distributors. The branded medicine is priced according to the lowest selling price where it is marketed. The same list of 36 reference countries used in the preceding decree is used in

this decree for guiding purposes. For generic drugs, the first five generic products submitted for pricing are priced at 65% of the price of the branded drug, and the remaining generic products in the "box" are priced at 60% of the price of the branded drug.

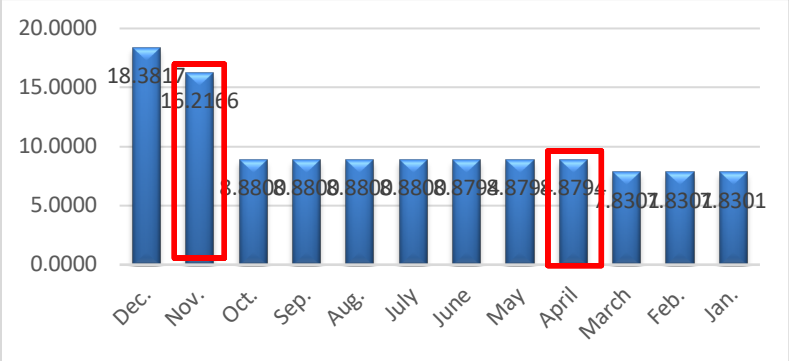
Despite the clear pricing legislation, companies blame the non-transparent, conservative and rigid manner by which it is implemented (Babar, 2015). In some cases, should application of decree 499/2012 cause the medicine to be highly-priced, the pricing committee sets lower prices which are not based on defined clear criteria, and then start negotiations with companies (as cited in Barbar, 2015). There is always a wide space for negotiations about prices between the pricing committee and pharmaceutical companies. Companies usually have to accept prices decided by the committee, otherwise, their registration file would be suspended.

In addition, article no. 12 of decree 499/2012 states that prices should be reviewed and adjusted in the following cases: "1) If there is an average increase or decrease of 15% in the currency exchange rates within one year as announced by the Central Bank of Egypt; 2) If a company request a price revision for its products, not exceeding 5% of its products per year" ((MoHP, 2012). However, price increases are not usually accepted by the government (Babar, 2015).

As noted before, Egypt has experienced economic changes including EGP devaluation, which resulted in higher production costs. As a consequence, many pharmaceutical companies lobbied for price increases to cope with these changes, because the drug prices did not change since the 1990s when the USD was equivalent to 2.7- 3.4 EGP (Gaballa & Knecht, 2016). Pharmaceutical companies succeeded when the Prime Minister issued decree no. 32/2016 on May 2016 to increase the price of drugs which are less than 30 EGP by 20% with a maximum increase of six pounds per pack.

The situation partially stabilized until the decision of CBE in November 2016 to fully float the Egyptian Pound which halved the value of EGP (Holodny, 2016), the exchange rates of USD to EGP during 2016 showed a slight devaluation in April and a more pronounced devaluation in November as illustrated in Figure 11.

Figure 11 Exchange rates of USD to EGP (2016)



Source: developed by the researcher, the data retrieved from CBE website (CBE, 2016).

Given the overdependence on imported raw materials and higher operating costs, an increase in drug shortage was experienced at that time. This shortage was a result of interruptions in production or even the termination of manufacturing of some medicines due to higher manufacturing costs. In an attempt to overcome this shortage, the MoHP issued Ministerial Decree 26/2017 to increase prices of 3010 medicines by 30-50%. The number of products that could be submitted for the price increase and the percentages of the increase were regulated as shown in Table 2.

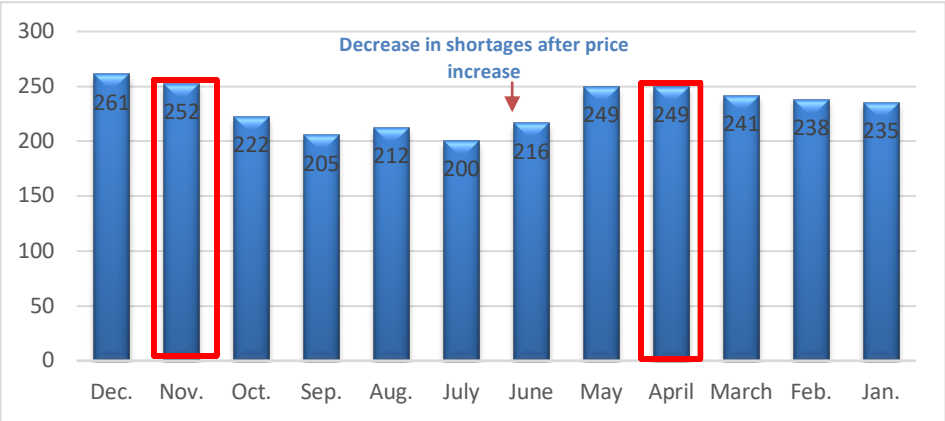
Table 2 Criteria for price increase as stated in Ministerial Decree 26/2017

	Percentage of drugs per company that can be submitted for price increase	Current price	Percentage of increase
Local medicines	15 %	1-50	50 %
		50- 100	40 %
		>100	30 %
Imported medicines	20 %	1-50	50 %
		50- 100	40 %
		>100	30 %

Source: developed by the researcher.

By reviewing the number of drug shortages during 2016 as published in Drug Shortage Bulletins (CAPA, 2016), a profound increase in the number of pharmaceuticals in shortage can be noticed in April and November correlating closely with the devaluation in EGP. Notably also there is an adequate decrease in the number of shortages after drug price increases in May as shown in Figure 11.

Figure 12 Drug Shortages 2016



Source: developed by the researcher, the data retrieved from Drug Shortage Bulletin (CAPA, 2016).

In general, this indicates that the drug shortage is very sensitive to drug pricing. This comes in accord with Markowski`s argument that the ultimate cause of drug shortage is low profits because low profits also lead to quality problems. Quality control is considered another important factor of drug shortage because producers will accordingly try to increase their profits by decreasing costs and therefore quality (Markowski, 2012).

To sum up, drug pricing policies in Egypt have been changed over the years. Pricing shifted from cost-plus and mark up regulations to ERP and mark up regulations. However, the concept of compulsory pricing, which may be unfair in many cases, remains. The drug pricing legislation is still seen as disconnected from the reality of the pharmaceutical market, and there is a gap between policies and implementation.

Chapter Five: Data Analysis and Findings

This chapter presents the data collected from interviews with the key stakeholders in the pharmaceutical field according to the research methodology described earlier in chapter three. The interviews provided a detailed description of the drug shortage problem to allow a better understanding of the problem in the Egyptian context. In accordance with the conceptual framework, the primary data was organized under three key themes: drug shortage definition, causes of drug shortages, and the current actions taken by the government to address the problem. The first section describes the definition of the drug shortage and determines when the government considers a shortage. The second section provides a thorough analysis of the causes of drug shortages in Egypt which is divided into seven subthemes: causes related to the regulatory framework and drug pricing policies, economic causes including the devaluation and low profit margin, causes related to the manufacturing process, causes related to the distribution and supply problems, causes related to the consumption, natural disasters and unforeseeable events, and causes exaggerate the drug shortage problem. The final theme illustrates the current actions taken by the government to address the problem. The three main sections are an integral part leading to an answer to research questions, and they allow for determining gaps and proposing more effective solutions to address the drug shortage problem.

5.1. Drug shortage definition

Our field study results illustrate that it is difficult to agree on one common and consistent definition of drug shortage due to the complexity of the problem. From the government's perspective, it was found that there is no published clear definition of drug shortage, but instead a government official during a personal interview explained that drug shortage is supposed to be the unavailability of both a drug as well as its similar and

alternative products in the market (government official 1, June 2019). However, he described that the concept of drug shortage is yet more complex in Egypt as patients insist on purchasing the trade name version of a medicine and do not accept pharmacist's recommendation for a similar product. Patients consider this situation as a drug shortage and complain about this shortfall. Consequently, MoHP in Egypt deals with the unavailability of a drug produced by a particular company as a drug shortage even if it has similar products, which is consistent with previous definitions provided by other regulatory authorities including TGA, Health Canada, and AIFA.

In addition, the official illustrated during the interview that there is a monthly bulletin of drug shortages, in which drugs are classified into three categories: 1) drugs that have similar products, 2) drugs that do not have similar products but have alternative ones, 3) drugs that have neither similar nor alternative products. The inclusion of drugs in the bulletin is based on a real shortage and patients' complaints but, recently, some products may be added according to an expected shortage.

When other interviewees were asked about the government's definition of a drug shortage, the majority commented that MoHP considers drug shortage when there is a failure to meet patient needs, and the government's actions based on patient complaints. The head of the Business Development Unit at an MNC said that:

> "*If the government received many complaints about a shortage of a particular drug, and this shortage was voiced out, the government would consider it a shortage".* (The head of the Business Development Unit at an MNC, June 2019)

This indicates that most stakeholders may believe that the government response depends on the negative consequences of the drug shortage, and on how it could provoke public anger.

On the other hand, representatives from pharmaceutical companies consider a drug shortage if there is any deviation from the company's production or importation plan and if the inventory level at distributors covers less than the average monthly consumption. This confirms the previous findings in the literature that companies perceive drug shortage as any supply interruption due to production or importation problems (Awad et al., 2016; EFPIA,2013). Moreover, because companies monitor the inventory level, they can anticipate a shortage of at least one month in advance.

In contrast, pharmacists at community pharmacies and representatives of the Egyptian Pharmacists Syndicate and the drug division at the Federation of Egyptian Chambers of Commerce (FEDCOC) contended that drug shortage occurs when a drug as a trade name and all its similar products are not available at the pharmacy level for a period of time (June, 2019). Thus, patients will not have access to this medicine.

In summary, there are a variety of opinions regarding the definition of drug shortage which matches well with the WHO argument that there is no common definition (WHO, 2016). Although the relevant authority does not have an obvious published definition of drug shortages, it seems that it deals primarily with patients' complaints about the unavailability of drugs and attempts to address the shortage. Recently, the government adopted a new approach to anticipate a shortage of specific classes of drugs. Nevertheless, this approach is not known to many other stakeholders which may indicate a lack of communication between different stakeholders and an undeclared government direction. On the other hand, manufacturers and importers see drug shortage from the perspective of interruptions in supply due to any failure or problem, which agrees with Awad et al, 2016, and EFPIA, 2013. On the contrary, community pharmacies and civil society perceive drug shortage as the unavailability of drugs in pharmacies for certain period. Generally, each

stakeholder describes drug shortage according to his/her role in the field. However, finding a clear definition of drug shortages is important to determine the direction of MoHP and help to inform situations that require direct government intervention.

5.2. Causes of drug shortages

Consistent with previous findings in research literature, this field study found that causes of drug shortage are complex and wide-reaching. Causes of drug shortage are categorized according to the main themes in the conceptual framework: causes related to the regulatory framework, causes related to the manufacturing process, causes related to distribution and supply problems, causes related to consumption, economic causes, and natural disasters.

5.2.1. Causes related to the regulatory framework

As illustrated earlier, three governmental bodies are regulating and monitoring the pharmaceutical industry and market in Egypt (EDA, n.a.). Although these entities aim at ensuring access to effective, safe and affordable medicines, they seem to contribute to the problem due to bureaucracy and delays. In addition, some legislation may participate in generating drug shortages such as drug variation regulation, importation regulations, and pricing policies.

5.2.5.2. Excessive bureaucracy and delays

From the field study it appears that there is a consensus that the procedures within the regulatory authorities are excessively routine and rigid, which leads to many delays. A top leadership team at a local manufacturer enterprise said that:

> "*Many officials at the MoHP in important positions just follow rigid rules and regulations without having a clear understanding of different situations*". (A top leadership at a local company, June 2019)

The interviewee emphasizes that procedures within MoHP are very complicated, and what makes the situation more problematic is that seniors and managers who have such rigidity will infuse the same mindset to their subordinates.

Some interviewees from the government argued that the reason behind the inflexibilities is the malpractice of some companies and the absence of sanctions as a deterrent, which reflects arguments made by Alruthia, et al. (2018). Similarly, many industry representatives commented that the lack of trust between MoHP and companies results in the adoption of drastic measures and regulations by the government.

Besides, bureaucratic and complicated procedures may be due to a lack of proper automation, which results in inappropriate linkage between departments and duplication of procedures, thus wasting time and effort of both officials and companies. A government official illustrated that there are efforts for automation, but they are still insufficient to give the desired results (a government official 2, June 2019). In addition, there exist long waiting lists of drug applications which are subjected to review by several committees before a proper decision is made, all of which results in more delays.

> "*Most cases of drug shortages require quick crucial decisions from committees, and this is not always achieved due to delays in submission to these committees*", (A government official 1, June 2019).

This reflects that resolving a drug shortage may not be as fast as it should be, and this also highlights the lack of awareness of other departments of the seriousness of the situation.

Overdependence on external committees arises from a lack of autonomy in MoHP, given the staff is often afraid and does not have the power to make decisions. Accordingly, and as reported by Saed (2016), long queues and lengthy processes may result in depriving the market of some products. For example, the CEO of a top local company said that

> "*Eye drops are a type of products for which the box of similar products was opened to allow more companies to apply for registration while we have a lot of eye drop*

> *products under registration, and our eye drop production line is not running at full capacity*" (CEO of a local company, June 2016)

This may show poor decision-making because reviewing the status of the products under registration and accelerating their procedures should be a priority instead of opening the "box" and increasing the burden upon the departments and creating new queues.

Delays in batch release and analysis at the national labs

In addition to delays in administrative procedures, delays in the analysis in the national lab is another issue leading to drug shortage. The majority of interviewees considered delays in sample analysis at NODCAR and NORCB as a cause of drug shortage. A government official highlighted that delays in batch release are simply due to the slowness of sample analysis in the national labs, as batches from which samples are drawn cannot be released until a certificate of conformity has been obtained (A government official 1, June 2019). Another government official attributed these delays to a large number of samples drawn for analysis which exceed the capacity of the national labs (A government official 7, June 2019). She also said that the slow speed at which companies respond to inquiries may elongate the process.

Moreover, drug variation guidelines require companies to reanalyze products in the national labs for most of the introduced changes, and they do not consider analysis carried out in-house by the company.

> "*From twenty to thirty of our products are in NODCAR to be analyzed, and we are not allowed to release batches until obtaining the analysis results, which takes over three months*", (CEO of a local company, June 2019).

This means that the market will be deprived of these twenty or thirty products for three months, especially if the company has not sufficient stock of their products. Notably, the situation may be very critical if these products do not have other alternatives in the market, which may lead to clinical complications and health hazards.

An interviewee from a local company also commented that medicine analysis should be corporate responsibility, and NODCAR/NORCB may only analyze random samples from the market, and in the event of any deviation, deterrent actions should be taken against the company. Similarly, the head of the registration department at an MNC suggested during the interview that MoHP may accredit some in-house labs or a quality control personnel within the manufacturers and make them responsible for batch release (June, 2019). However, handing over the responsibility of analysis and batch release to companies may not be successful given a lack of trust in companies and the absence of deterrent penalties.

It can be concluded that excessive bureaucracy, complicated procedures, and long processes are due to overdependence on external committees, excessive requirements, lack of effective automation, improper communication between departments, and lack of trust between the government and companies. These causes lead to delays and increase the probability of a drug shortage or worsen an existing one. Moreover, the excessive number of withdrawn samples and delays at the national labs result in delays in batch release depriving the market of medicines which may be critical to patients. Therefore, imposing effective sanctions may be an essential element to deter companies from violations and encourage regulators to trust companies and allow some flexibility in regulations. In addition, a more efficient automation system should be implemented to allow effective communication and facilitate procedures. Any method to decrease dependence on external committees may help to speed up the procedures. Finally, rationalizing the number of samples is a key element to relieve pressure on the national labs and to avoid delays.

5.2.5.2. Regulations and legislation

Our findings lend support to the previous results of Heiskane et al. (2017) that regulations may lead to drug shortages. Generally speaking, it was found that policy is, usually, formulated entirely by the government without involving other stakeholders. Thus, the implementation of these policies may be difficult and may have negative consequences because of the lack of input from key stakeholders. Furthermore, participants from the industry emphasized that many ministerial decrees and regulations are declared without prior notice, and the grace periods and due dates for their execution are not reasonable, which may affect the sustainability of production. The main regulations found to affect the availability of drugs in the market are drug variation regulations, importation regulations, and pricing policy. In addition, the absence of regulation on how to deal with drug shortage was reported as a reason to worsen an existing or an anticipated drug shortage.

The absence of regulations to address drug shortages

Unlike other regulatory bodies such as FDA, EMA, TGA, and Health Canada, MoHP does not have definite guidelines to mitigate drug shortage. A government official illustrated that drug shortages require an overall and a clear vision to deal with it and to use all available flexibilities to address the problem, which is not always achieved (A government official, June, 2019). Thus, the absence of precise obligatory regulations on how to deal with drug shortage means that actions depend on how different stakeholders will respond to the problem.

> "*Lack of awareness of some officials in MoHP about how to deal with the drug shortage worsen the problem"* (The head of supply chain unit at a local company, June 2019).

The head of the supply chain unit at a local company accentuates that some officials at the regulatory bodies are not aware of their exact role and responsibility to address drug

shortages, and this may lead to fragmented efforts without achieving the goal of ensuring the availability of medicines.

Indeed, not only are some officials unaware of the criticality of the situation but also many companies may be irresponsive and reluctant to cooperate with the MoHP as expressed by a government official, as well as some industry representatives during the field study. Therefore, clear regulations should be developed and implemented to address drug shortages. These regulations should include the roles and responsibilities of each party to address drug shortage at each stage.

Drug variation regulations

A drug variation is a change to any terms of the drug registration license. Drug variations have many types, such as a change in API and raw material supplier, change in drug composition, or change in manufacturing site. Based on the type of variation, particular studies must be performed and submitted to the relevant regulatory authority to obtain approval for this change. Thus, and as illustrated by a government official, drug shortage may arise from drug variations because conducting studies, analysis in national labs and receiving CAPA approval may take over three months, and companies cannot release batches during this time. Moreover, the head of business development unit at an MNC contended that in the event of even very minor variations, the company must have CAPA approval before implementation and resuming production.

> "I *spent one month to change the company logo on packs. CAPA should have some flexibility for minor changes and it should adopt the concept of do and tell/ tell and do*", (the head of business development unit at an MNC, June 2019).

According to the European regulations, there are different types of variations, some of them which are minor and do not require approval from regulatory authority "do and tell". In contrast, other variations, which are major and affect the quality, safety or efficiency of the

product, must obtain approval before implementation "tell and do" (EMA, 2016). Although some developed countries adopt more flexible regulations, the Egyptian MoHP do not accept these flexibilities. In this regard a representative of an MNC said:

> "*At time of shortage, drug importers may have the flexibility to import quantities of medicines with different carton packs which were originally manufactured for another country, but MoHP does not have the same flexibility; the importation of these packs require MoHP approval which takes time since requests should be submitted to different committees*" (Representative of an MNC, June 2019).

The statement of the representative of an MNC proves that, despite the fact that this change may be a minor one, CAPA insists on deciding on this change before implementation, which is achieved by different committees.

During a personal interview with a government official, he argued that the idea of only notifying the regulatory authority with certain types of drug variation cannot be currently applied because of inappropriate linkage between different departments (A government official 2). Thus, obtaining approval from the Registration Department is the only evidence that the company has notified the authority of drug variation.

Besides, both interviewees from local companies and importers said that there is no grace period to implement the new variation requested by the company. That is to say, if the company, for example, obtained approval to change the outer pack design, it cannot produce with the old outer pack once it receives CAPA approval. Therefore, production must be ceased until the preparation of new packs which may take time.

As noted before, the introduction of some types of variations may disrupt production, but what makes the situation more complicated are the regulations and procedures adopted by MoHP. The negative aspects of these regulations can be summarized in two main points: rigid variation guidelines, and absence of grace periods. Therefore, the government may revise these regulations to take into consideration the

possibility of implementation of the notification system for some types of drug variations, and the implementation of grace periods to execute the new change requested by the company.

Importation regulations within MoHP

Almost two-thirds of the participants said that the lack of importation regulations might be a significant cause of drug shortage. Similarly, a government official illustrated that there are no adopted regulations for the importation of APIs (A government official 5, June 2019). That is to say that there are no definite criteria for foreign API suppliers, except that the supplier must have a GMP compliance certificate from the health authority in the country of origin, which is based on the decision of the Technical Committee for Drug Monitoring. There is no clear list of requirements, so the evaluation of documents is mainly based on different personal judgments, which lead to inconsistent decisions, as highlighted during interviews with companies' representatives and confirmed by a government official.

The Importation Department prohibits importation from certain suppliers based mainly on FDA or EMA alerts and warnings. The problem arises from the sudden prohibition of APIs importation without giving a transitional period for companies to contract with another supplier. This leads to a halt in production and drug shortage, especially if there is a sole supplier for all local companies.

In addition, an MNC representative highlighted that the company must receive CAPA approval every year on both the importation plan and on any modifications to this plan. Besides, a respondent from a distributing agency illustrated that CAPA may reduce the amounts submitted in the importation plan without any justification. Thus, the time required to obtain approval on the new plan or the amended plan might hinder the importation of products at that time leading to a shortage.

The importance of obtaining an importation approval from CAPA is debatable. Some interviewees argued that cancellation of this step is the solution because obtaining an importation approval for a product for which there already exists marketing approval is considered as a duplication of procedures. On the other hand, an interviewee from a regulatory body contended that approval of importation is necessary to ensure the compliance of companies with the terms of the drug registration license.

To sum up, the lack of importation regulations results in inconsistent decisions, that may elongate the procedures or wrongly prohibit importation from certain suppliers causing production disruptions and drug shortage. Thus, development of clear guidelines for importation is critical to avoid personal judgments and sudden prevention of importation. Moreover, CAPA may approve a list for particular suppliers based on their compliance with GMP, from which companies can directly import without the need to resubmit the same documents each time.

Drug Pricing policy

As determined by all stakeholders during the field study, including government officials, the most remarkable and critical cause of drug shortage in Egypt is the pricing policy, which is also confirmed by a study conducted by Ragab et al. (2015). It was interesting to find out that the problem lies not in the legislation around pricing, but rather primarily in its implementation. As reported by Barbar (2015), the evidence this study found points to improper implementation of Ministerial Decree no. 499/2012, which regulates drug pricing. In other words, the pricing committee does not implement the criteria for determination of price and depends on negotiations with companies, as said by an interviewee from the industry. The improper negotiation of prices means some companies accept a low price suggested by the committee just because they want to obtain

the marketing approval. However, such low prices mean that profitable production is not possible, which may lead to a shortage. Thus, an MNC representative suggested that the Pricing Department should set a mechanism to ensure that production is profitable at suggested prices before these are agreed, he said:

> "*Some small companies may accept low prices suggested by the pricing committee just to obtain the registration license, taking into consideration that when any company agrees on the price, other companies cannot be assigned higher prices for their similar products. However, and on the ground, all these companies cannot produce the medicine at this low price*" (An MNC representative, June 2019).

The interviewee's statement emphasizes the importance of developing a mechanism to avoid the negative impact of the acceptance of the price from some companies without real study. This mechanism would need to be complex to take into account key factors such as company size, past experience, and production commitment.

Coupled with the lack of robust criteria for price determination, the Pricing Department also does not regularly review cases where the price has been set at unprofitable levels, especially with the current economic changes and the devaluation. These findings corroborate with the previous results of Gaballa & Knecht (2016). Senior leadership at a local manufacturer commented:

> *"It is the role of the country to subsidize medicines, not the role of the companies, we cannot run our business in loss*", (June 2019).

This significantly infers the fact that pharmaceutical companies, like any other private sector, mainly seek for profits, and if they make low profits, they will cease the production and close down. On the other hand, it is the responsibility of the government to ensure access to high-quality health care services including access to medicines. Although the government may not be able to subsidize all medicines for the whole population, it should find other solutions to create an enabling environment for such crucial industry, and it may accelerate the implementation of the comprehensive health insurance system.

An interview with a government official revealed that due to a backlog of new products to be priced, there is no capacity to review those products that have already been priced and marketed (A government official 4, June 2019). He also added that many companies are requesting an increase in price, but the Pricing Department gives priority only to medicines listed in the Drug Shortage Bulletin. The decision of a price increase depends on many factors such as the market share of the product and the presence of similar products. On the other hand, MNC representatives believe that government should ensure the availability of many similar products, not only one or two, so the Pricing Department should review all prices to avoid stoppage in production due to low profits.

> *"CAPA refused to increase the price of our branded product because the similar generic products are available in the market, so we decided to be out of the market. After that, all local companies stopped production and there was a complete shortage*", (An MNC representative, June 2019).

The statement of the industry representative highlights two main aspects, first the importance of having branded products in the market because even if they have higher prices, they have their customers. Second, the government should ensure the availability of many similar products for different companies which can sustain production.

Although the government may increase the prices of some products, this increase does not mitigate the devaluation of the Egyptian Pound as well as the increased costs.

> "The price of a contraceptive drug was L.E. 27 before devaluation which is equivalent to $ 3, and after the devaluation, the price increased to L.E. 45 which equates to $ 2.5" (Syndicate representative, June 2019).

This clearly accentuates that the prices have not been set according to costs. Given the significant drawbacks that may occur due to the disappearance of contraceptives from the market such as population explosion that goes against the government's policy agenda, and increase in household expenses, the Pricing Department should revise its decisions about drug pricing policies. Thus, the Pricing Department should take into account the

importance of medicines and costly financial implications and drawbacks that may arise due to drug shortages.

A government official commented that the companies would never be satisfied with the prices "*They always want more*" (A government official 4, June 2019). Thus, the argument about prices will continue, and no party will be satisfied until the formulation and implementation of a fair and clear pricing policy without any discrepancies.

Furthermore, because of the current mechanism of pricing, companies cannot plan forward and make a prior decision about whether to seek marketing approval for a certain drug or not because there is no possibility of price prediction. Furthermore, the head of the business development unit at an MNC illustrated that pricing policy might hinder medicine access to Egypt. He said:

> "*For a branded product, MNCs prefer to delay access to the Egyptian market due to low prices in Egypt that might affect the price of the product in other countries"* (June, 2019).

This means that drug pricing policy not only influences the availability of marketed products, but it also affects the access of new medicines to Egypt, which is consistent with Bogaert et al. (2015). The head of the business development unit at an MNC and a distributor mentioned another drawback of low prices, which is the illegal exportation of medicines by either distributors or pharmacies to neighboring countries leading to further shortages.

Finally, industry representatives ensured that they do not seek price liberalization, but they ask for a fair pricing mechanism and periodical review of the priced products to ensure that the prices are in line with the economic changes. Some industry representatives suggest making price deals with companies to produce a critical product at unprofitable levels, and in return, the government will increase the price of other OTC or non-essential

medicines. A government official commented that there are no clear procedures for such deals. Additionally, there is no legal or written obligation on the company to keep the production of the critical product at a low price, for which the prices of other products have been raised.

> "*Only the people who made these deals know about them, so if the staff changed, no one would be able to track these deals, and therefore there is no commitment" (A government official 4, June 2019).*

Other industry representatives see that the implementation of a comprehensive health insurance system will most probably improve the situation because the government will ensure the whole population has access to affordable medicines, specifically the lower economic segment.

> "If the health insurance system is implemented, the pricing committee will be encouraged to review and raise drug prices". (Senior leadership at a local company, June, 2019).

The senior leadership at a local company emphasizes the importance of implementation of a comprehensive health insurance system as it will replace out-of-pocket payments. At that time, the government can increase drug prices without fear of public anger.

In summary, the results showed that the Pricing Department is very cautious when deciding to raise drug prices or when pricing a new product. Regardless of the provisions of Ministerial Decree 499/2012, the pricing department aims at providing the lowest possible price to ensure affordable medicines to patients, especially given most of the payments are out-of-pocket. However, the currently adopted mechanism for pricing leads to price discrepancies and negatively affects business decisions and access to medicines. Furthermore, the fact that many companies have been adversely affected by currency devaluation and that the cost of their products outgrows previously set prices indicates that the problem may continue and new shortages will emerge because companies will not

continue production of an unprofitable product. Consequently, the Pricing Department should adopt other approaches for pricing to fit with the Egyptian context. These approaches should take into account the actual cost of the drug especially after the devaluation and do not depend on the least price for similar products in the market. In addition, the pricing department should be equipped with highly qualified personnel to suggest and implement new policies. Finally, reviewing drug prices should be a priority to prevent further shortages.

5.2.2. Economic causes

As discussed earlier, Egypt has experienced political and economic instabilities after the revolution in 2011 that adversely impacted many industries and sectors. In 2016, Egypt suffered from a shortage of hard currency followed by a partial devaluation of the Egyptian Pound in March, then a complete flotation in November 2016 (Business Insider, 2016; CBE, 2019). All these changes negatively affected the pharmaceutical companies resulting in production disruption and stoppage (Huseein, 2016), and which is corroborated by our field study results. The main challenges faced by companies as revealed through the field research are summarized in three major points: the scarcity of hard currency and lack of financial liquidity, the devaluation and low-profit margin, and market turbulence.

5.2.2.1 Scarcity of hard currency and lack of financial liquidity

The scarcity of hard currency was a great obstacle faced by the companies in 2016. There is a consensus that companies could not come up with the hard currency to import raw materials as well as finished products. During this period, the banks stopped extending credit. Only state-owned banks continue to extend lines of credit, so companies must wait their turn amongst other importers to obtain hard currency, as stated by industry representatives. Otherwise, companies could obtain hard currency from the black market,

at twice the value of the official exchange rate. In addition to the illegality of the black market, companies could not afford a higher exchange rate because it would lead to increased costs without the ability to raise the prices of medicines. A representative of a local company said that:

> *"We were struggling (Etzalena) to get hard currency before flotation of the Egyptian Pound*" (June 2019).

Given that almost all of the pharmaceutical industry in Egypt relies on imports (El Agroudy, Shafiq, Mokhtar, 2015 & N Gage Consulting, 2017), companies could not make new orders due to the unavailability of hard currency, as highlighted by industry representatives. Thus, the scarcity of hard currency caused a shortage of both imported drug products and raw materials used in drug production, leading to a widespread drug shortage.

Moreover, insufficient financial liquidity is considered another factor contributing to the drug shortage in Egypt since the companies order only limited quantities of raw materials, which do not meet the market need (A government official 1, June 2019). Additionally, top leadership at a local pharmaceutical company said that, before 2011, companies had the leverage to pay invoices over a long period which may exceed three months, but after the revolution, companies must pay bills in advance which results in a heavy burden on companies (A top leadership at a local pharmaceutical, June 2019). Furthermore, the lack of liquidity affects the companies' ability to deal with the sudden machinery breakdowns that may require replacement of some expensive parts leading to the production stoppage until the problem is fixed.

It is clear from the above that lack of financial liquidity and hard currency adversely impact companies' ability to purchase raw materials or finished products resulting in a drug shortage. To solve the problem of unavailability of hard currency, the government decided

to float the Egyptian Pound. The flotation solved the problem of hard currency, but it caused increases in production costs that cannot be tolerated by the pharmaceutical industry due to fixed prices.

5.2.2.2. The devaluation and Low-profit margin

Many medicines became a loss-maker due to high production costs after the devaluation. Top leadership at a local company commented that when drug production becomes a loss-maker, companies choose either to cut quantities or to stop production because they cannot run their business at a loss (June 2019). Besides, the government did not respond to companies' requests to increase prices either to avoid public anger or to prevent possible industrial action such as stopping production to force the issue. Interviewee from a local company illustrated that, not only did the cost of raw material increase, but also operating costs increased which includes fuel, electricity, and labor, and this also was evident by Abisourour (2018). The head of the business development unit at an MNC said:

> "*Raw materials accounted for 10% of the total cost of the product, but suddenly after the devaluation they accounted for 30%, and the cost of imported finished products doubled"* (June 2019).

The increase in costs that is highlighted by the MNC's representative indicates that pharmaceutical companies cannot continue their business at the low prices which were set by the government before the devaluation.

The Egyptian Pound has lost half its value after the devaluation, and because all pharmaceutical companies rely on imported inputs, their working capital fell by as much as half. In accordance, an interviewee from the Chamber of Pharmaceutical Industry commented:

> "*Small companies could not tolerate these economic downturns and increased production costs, so they ceased production of many products due to the losses they*

> *incurred, and because they have a limited number of products, they cannot compensate for these losses through the profits of other products*", (Representative of the Chamber of Pharmaceutical Industry, June 2019).

This reveals that companies cannot run their business at a loss. In addition to cutting poorly performing products, some companies took some measures to cut costs such as employee downsizing, benefits reduction and hiring freeze, which enabled companies to survive in the market for a while.

Pharmaceutical importers and local agents incurred a lot of losses because they bought on credit, so they imported quantities according to the old exchange rate and after the devaluation, they paid according to the new exchange rate. The resulting debts have been scheduled to be paid over four or five years, so companies still bear the consequences of the devaluation until now.

> "*We did not offset losses resulted from Egyptian Pound devaluation until now*" (CEO of a local pharmaceutical company, June 2019).

> *"One company incurred losses of US $ 150 million, while another company suffered losses of LE 1 billion*" (Representative of the Chamber of Pharmaceutical Industry, June 2019).

Both statements reflect the drastic consequences of devaluation on business in Egypt. Some companies survived but are still suffering to this day, while others incurred great losses and thus closed down. Thus, many companies decided to downsize or cease the production of many medicines that lead to shortages.

Because of widespread drug shortages and media pressure on the government, MoHP increased the prices of some drugs through two waves. The price increase slightly improved the situation and saved companies from bankruptcy.

> "*Drug price increase represented a rescuer for the pharmaceutical industry in Egypt*" (Top leadership at a local manufacturer, June 2019).

Although these waves of price increase partially alleviated the problem, there are many drug prices that should be reviewed because companies will not continue production of these unprofitable products, as highlighted by a government official during a personal interview (June 2019).

Accordingly, low profit margin or even unprofitable products is a crucial cause of drug shortage because companies do not have incentive to continue production of medicines which are non-profitable or loss-making (Markowski, 2012; Alruthia et al., 2016; Yang et al., 2016; Awad et al. 2016). This confirms our earlier findings from the literature and field study that fixed low prices affect companies' ability to produce medicines.

5.2.2.3. Pharmaceutical Market turbulences

Interviews with an industry representative and drug importer explained that during the period of economic instability in Egypt, market uncertainty and business risks have increased. Companies were not able to set their production plans because of market turbulence. Market shares have been changed due to the inability of some companies to continue production at the same rate. At the same time, companies' decisions to take advantage of the disappearance of some products from the market, or to ramp up the production to address a shortage is very risky. A senior leadership at a local company commented:

> "*When Benzathine Penicillin G suddenly ran out in 2018, companies could not take the decision to import APIs and start production, fearing that other companies might be already started the production, which might result in a surplus rather than a shortage and companies might end up with expired products*", (June 2019).

As explained by the local company representative, when the company starts the ramp-up process, it has no guarantee that it will be able to sell its product because the severity and length of the shortage cannot be predicted. Thus, there would be a surplus if the original

company with high market share resumed production, and other companies who ramp up production in response to a shortage may incur losses. It can be seen that despite the importance of Benzathine Penicillin G as the only treatment in some bacterial infections whose shortage can lead to death, companies are still business-oriented. This emphasizes the role of the government to encourage company to produce medicines which are in shortage. A manager of the registration department at an MNC commented on that:

> "*Upon a government request, our company imported a lot of quantities of a particular medicine since the local manufacturer ceased the production due to specific problems. After the local manufacturer resumed the production by the support of MoHP, the government returned to the local manufacturer, leaving us with our enormous imported quantities of this drug which will be expired soon*" (A manager of the registration department at an MNC, June 2019).

This behavior of some government officials may reduce the credibility of the government and may hinder further cooperation between companies and the government. Instead, the government should ensure that all the requested quantities are sold, and it should also incentivize companies which cooperate in addressing a drug shortage.

Coupled with changing production capabilities, changes in pricing which emerged after government intervention resulted in shifts in market shares. The CEO of a local company mentioned that:

> "*Our company has chosen products with high market share to increase their prices, and other companies do the same with their products. Thus, our products which had high market share became higher in prices than their similar products, so we did not achieve the same selling rate because some patients and doctors preferred low-price drug*" (June 2019).

This highlights that although the waves of price increase slightly compensated for losses, it also led to market turbulences and companies did not generate the expected profits.

In sum, economic aspects are a critical cause of drug shortage, and this fits with earlier findings by Markowski (2012) and Yang et al. (2016). Generally speaking, the main obstacles, which resulted from economic changes in Egypt, include the lack of hard

currency and liquidity. Additionally, production costs have soared after the devaluation, so many firms considered halting production as drugs become a loss-maker. Finally, pharmaceutical market instability and uncertainty increased the difficulty of making business decisions to address the drug shortage. All the above challenges lead to production disruptions and drug shortages. One recommendation suggested during the interview with the head of the supply chain unit in an MNC is that the government may implement a differential exchange rate where the most essential goods should be assigned a favorable exchange rate, and non-essential goods may have a higher rate, so the production costs and prices of a good such as medicines will not increase. Besides, the government should incentivize companies to ramp up production to address shortages and, at the same time, it should determine sanctions for companies that deliberately halt production without having reasonable justification.

5.2.3. Causes related to the manufacturing process

5.2.3.1. Quality and manufacturing issues and limited production capacity

All interviewees from the industry agreed that manufacturing issues are one of the substantial reasons behind the drug shortage. Manufacturing issues include halting production due to quality issues and non-compliance with regulatory standards or due to machinery breakdowns. Limited production capacity is considered another challenge for the pharmaceutical industry that leads to supply shortfalls. First, ceasing production or delays in batch release because of quality issues, which is decided either by the health authority or the company itself. An interviewee from the local company claimed that CAPA regularly monitors the manufacturer's compliance with GMP. In case of a violation, the company stops production at CAPA's request, and it can only resume production after introducing the required corrections. Upgrading and revamping a production facility to

fulfil GMP most probably leads to an interruption in production for a period that may cause a drug shortage in the market as explained during a personal interview with a government official 1 (June 2019). On the other hand, another government official expressed that drug deficiencies due to quality issues may not be as significant as in other countries since the health authority prevents production only in the rare case of major defects (A government official 3, July 2019).

Second, unexpected mechanical failure and machinery breakdowns result in abrupt production stoppages as mentioned by all representatives of industry and FEDCOC. These breakdowns may require a foreign expert to identify the problem and a replacement of expensive parts that are not readily available on site which takes over three months.

> *"Very small part of a machine can interrupt the supply of plenty of products which are produced on this production line*" (A local company representative, June 2019).

The problem may worsen if the company does not have sufficient liquidity so it will probably need more time to resume production. In this case, a company may choose to contract with other manufacturers to produce its own medicine but changing the manufacturing site is a variation that requires specific studies to be approved from MoHP and reanalysis at NODCAR or NORCB. Generally, insufficient upgrades for aging facilities and infrastructures increase the probability of sudden production stoppages due to unexpected breakdowns.

Third, limited production capacity and rare production lines can highly contribute to drug shortages. Limited production capacity influences the business decisions as some companies may entirely stop production of some important products which have low demand, and produce other profitable products instead, regardless of the therapeutic importance. Furthermore, if there is any shortage due to the inability of a company to produce a particular drug, other companies may not be able to ramp up the production

because of their limited capacity. If these companies decided on increasing production of certain products to address a shortage, it may result in further shortages of other medicines that share the same production line, as said by a top leadership at a local company during the interview (June 2019). In this context, a government official commented that toll companies suffer more from the problem of the limited production capacity because, after contracting with a particular manufacturer, this manufacturer may prioritize the production of its own drugs over that of the toll company (A government official 1, June 2019). In this case, the toll company tries to find another manufacturer and it may end up without finding an alternative.

Another key point is the scarcity of certain types of production lines such as manufacturing of lyophilized drug products. Lyophilization is a freeze-drying process which is used to remove moisture from thermolabile products, so it preserves the biological activity, reduces the weight, and extends the stability. Only one or two manufacturers have these lines, so they may not be able to meet the market need. Similarly, production of particular types of medicines requires highly specialized and complex manufacturing procedures, so they are devoted to specific production lines which are not available at all companies.

> "*Production of certain medications such as Penem antibiotics and Tamoxifen, which do not have a large market but they are very essential, require specific procedures according to GMP such as dedicated areas that cannot be applied by all companies. Thus, all companies contract with one or two manufacturers which can follow GMP, so they put pressure on these companies which could not meet the market need"* (A representative of a local company, June 2019).

The class of antibiotics mentioned by the interviewee, Penem, is used in the treatment of severe multidrug-resistant bacterial infections which is mainly used for critical cases in the Intensive Care Unit (ICU), while tamoxifen is a hormone therapy used in the treatment of

cancer. Given the importance of both drugs, the limited number of manufacturers which can produce them is alarming.

In view of a limited manufacturing capacity, multinational pharmaceutical companies implement quotas as they allocate certain quantities of products to each country, so if there is an increase in demand, they cannot cover it.

To sum up, interview results are in line with previous findings from the literature (Dill & Ahn, 2014; Bogaert et al., 2015; Fox et al., 2018). Manufacturing issues are a major cause of drug shortage, which results in production interruptions and delays. It may not be the most dominant reason for drug shortage in Egypt, but it still one of the main reasons. Quality issues and sudden line breakdowns may require a temporary change of manufacturing site or change in composition, a solution which needs approval from the health authority causing further delays. Besides, limited production capacity and scarcity of specific types of production lines lead to unavailability of some medicines which may be essential for patients. Therefore, MoHP may develop a national plan for the pharmaceutical industry by determining the priorities and types of production lines needed, then encourage companies to follow this plan by providing incentives and support to them, as suggested by senior leadership at FEDCOC.

5.2.3.2. Raw material issues

Industry representatives claimed that drug shortages can be linked with the underlying problems of raw materials. Global shortage of APIs and inactive pharmaceutical ingredients can result from natural disasters or from quality issues and manufacturing problems of raw materials. During the field study, a CEO of a local company expressed that the recent environmental clampdown in China resulted in the closure of thousands of raw material and chemical ingredient plants by the Chinese

government to tackle air pollution (CEO of a local company, June 2019). These closures are threatening supplies of APIs across the world because China is considered one of the important suppliers of raw material. In addition, many API manufacturers adopted a rationalization strategy to achieve higher efficiency and better competitive positioning, so they only produce a limited number of raw materials and ceased production of many other raw materials, which is in line with Bogaert et al.'s findings (2015). Accordingly, there is a reduction in the number of API suppliers and an increase in API prices which results in an increase in the production cost of medicines in Egypt.

Quality problems and non-compliance with GMP are highlighted by industry representatives as a fundamental cause of disruption in raw material production. Foreign raw material suppliers are not subjected to inspection by the Egyptian health authority, but CAPA prohibits importation from any suppliers for which a warning letter or an import alert has been issued by FDA or EMA. These warning letters and import alerts are mainly issued because of violations of or non-compliance with GMP. As reported by Fox et al. 2015, our field study findings lend support to the view that the drug shortage may be exacerbated if the non-compliant supplier was a sole supplier or if there is a limited number of suppliers around the world for this material.

> "*Over the past few months, most Valsartan suppliers were stopped due to impurities detected in raw material, and only very few suppliers – with higher prices and quality - have not experienced this problem*", (Representative of an MNC, June 2019).

Prohibiting importation of raw material from a certain supplier or ceasing production represents a problem for local manufacturers who then need to undertake a complex process to change the supplier. First, manufacturers should find, and contract with, another supplier which provides raw material at a reasonable price due to price restrictions in Egypt. Second, the company should obtain approval from CAPA to change the supplier

which requires conducting and submitting certain studies. Third, raw material should be analyzed in the national labs to obtain approval. Thus, if the company does not have an adequate inventory of raw materials, the medicine will be in shortage until completion of all the above procedures. In most cases, companies do not have sufficient inventory to cover market need for more than three months.

> *"We cannot buy and keep large stock of raw materials because the limited financial capacity and the high bank interest rate",* (A manager of the supply chain unit at a local company, June 2019).

It is underscored in this statement that economic aspects are closely related to inventory management practices. Thus, companies prefer to keep low inventory to cut costs which increase the likelihood of drug shortages.

It is clear from the above that shortage of raw material arises mainly from natural disasters, quality issues, and business decisions which most probably lead to shortage of finished pharmaceutical products, findings of the field study are consistent with earlier results (Fox et al., 2015; Awad et al., 2016; Bogaert et al., 2015; Birgli, 2013). Moreover, procedures for changing API supplier is time-consuming which worsen the situation since most API stock will be exhausted. Thus, the government may impose regulations that insist companies must maintain a certain inventory level of raw materials to avoid sudden shortage. Besides, MoHP should shorten the procedures required to change a supplier of raw materials.

5.2.3.3. Overdependence on importation

The evidence this field study found points to the excessive dependence on the importation of raw materials including pharmaceutical ingredients, chemicals, and primary and secondary packaging materials. This is confirmed by the results of Lofgren & Williams

(2013) and N Gage Consulting (2017). Similarly, representatives of local manufacturers and FDCOC stated that they import more than 90% of their production inputs.

> "*Absence of local manufacturers of raw materials in Egypt is the main reason for drug shortage leading to dependence on imports*", (Senior leadership at a local manufacturer, June 2019).

Considering the dependence on importation of raw material as one of the main causes of drug shortage indicates that the government should create incentives and encourage the establishment of plants for raw material production.

As well as the lack of domestic production of raw materials, there is a market gap in local production of high-tech medicines and biotechnological products, most of these products are imported as expressed by senior leadership at a local pharmaceutical company.

Dependence on imports requires companies to have sufficient liquidity and hard currency. Otherwise, they will not be able to import, as illustrated by senior leadership at a local company. This was evident in 2016 when, amidst the scarcity of hard currency in Egypt, most pharmaceutical companies were not able to import raw materials or finished products which resulted in a significant drug shortage.

Moreover, a government official infers that overdependence on importation exacerbates the problem because the local industry becomes very sensitive to the conditions of other countries (A government official 1, June 2019). For instance, revolutions in some countries lead to political and economic instabilities and negatively affects the business environment. Consequently, some pharmaceutical companies, which are considered a sole supplier for certain drugs, closed down. A government official said:

> "*After the revolution in Algeria, some products were in shortage in Egypt due to ceasing production in Algeria*." (A government official 1, June 2019).

Thus, closure of the company most probably will not only affect the drug supply in the country where the product is manufactured, but it will also affect the drug supply in other countries which depend on it.

Moreover, logistics related to importation may lead to interruptions in production and supply. A government official confirmed that a remarkable reason for drug shortages in Egypt is delays in the arrival of shipments. An MNC representative explained that some shipping issues lead to delays in shipment arrival such as the need for special containers for some products to meet specific storage conditions (June 2019). He added that special shipment procedures are not available all the time which could lead to further delays.

Furthermore, issues related to customs clearance such as missing documents delay product release, as highlighted by local manufacturers and importers. Coupled with missing documents, bureaucracy at the Egyptian Customs Authority results in more delays since they deal with pharmaceutical products as a normal commodity although it is a vital product affecting patient life. Senior leadership of a local manufacturer said

> *"Half of our production plans are suspended because the delay of customs clearance for raw materials"* (June 2019).

This infers that procedures for customs clearance and shipment release represent a fundamental cause of production interruptions and stock-outs.

Given that the pharmaceutical industry in Egypt depends on the importation of almost all components to produce medicines, drug shortage would be an expected issue because it cannot guarantee the availability of raw materials needed for production.

Briefly, it can be said that overdependence on importation increases barriers and challenges for the pharmaceutical industry in Egypt. It may adversely affect local companies and the ability of importers to meet the market need due to the unsustainable supply of imported raw materials as well as imported medicines. This unsustainable supply

may be due to external factors in other countries such as political and economic disturbances that hinder both the production of raw materials and medicines at these countries and exportation to Egypt. In addition, shipping issues and customs clearance causes delays in arrival and release of shipment which negatively influence the availability of drugs in the market. Therefore, the establishment of factories for the production of raw material should be a priority, and the government should push the industry into this direction. Besides, different ministries, MoHP and Ministry of Finance (MOF), should collaborate to encourage pharmaceutical industries and help them to overcome obstacles.

5.2.4. Causes related to distribution and supply problems

This field study also revealed that illegal distribution practices of either pharmaceutical companies or distributors to increase profits result in unfair distribution of medicines and an emergence of the black market, which deprives patients of medicines. During field research, a government official as well as a senior leader at a local manufacturer said that some pharmaceutical companies or importers sell products to warehouses, wholesalers, and distributors at higher prices (June 2019). In other words, companies do not confirm to the stipulated profit margins for distributors and pharmacies as per the Ministerial Decree 499/2012 and instead take the difference in price for their benefits, as confirmed by another government official:

> "*For some products which are in shortage, we found large stocks of them at companies' storehouses*", (A government official 3, July 2019).

Consequently, these illegal practices lead to further infractions from the distributors. Distributors or wholesalers sell drugs to pharmacies with a very low discount or no discount at all. Questionable practices in distribution even continue at the pharmacy level. A pharmacist said that the pharmacy might sell the drug products which are in shortage

only to acquaintances and patients who have expensive prescriptions (a Pharmacist at community pharmacy, July 2019). Moreover, the sold drugs cannot be easily tracked due to fake and false purchase orders and invoices.

> "*During the crisis of unavailability of Intravenous IV solutions and contraceptives, pharmacies were forced to buy these medicines at a discount of only 1% of their selling price compared to at least 10% which stated in Ministerial Decree 499/2012*" (Syndicate representative, June 2019).

This shows that most of these illegal practices, unfortunately, are adopted in the case of critical drugs due to the certainty that patients who need these drugs will buy them at any cost. For example, IV solutions are used in many critical cases so their shortage means severe medical complications that may lead to death.

Distributors themselves can initiate these malpractices. As proposed by ASHP, (2009) and Alruthia et al. (2018), this field study confirms that distributors and wholesalers may illicitly stockpile large quantities of important medicines which leads to a new shortage in the market or worsens an already existing shortage leading to monopolization and emergence of the black market.

> "*Although some drugs such as Mestinon and Devarol were in total shortage, there was a large amount of them in the black market*" (A senior leader at FEDCOC, June 2019).

This adds more evidence that the black market mostly targets patients who are in greatest need to medications such as those with Myasthenia Gravis (weakness in muscles) who need consistent doses of Mestinon, otherwise, they will not be able to swallow, move, or speak, and they may experience further complications that cause death.

This was confirmed by officials at MoHP as well as Syndicate representatives who illustrated that some of the top drug distributors in Egypt were accused of monopolistic practices and illegal price increases.

On the other hand, some distributors and wholesalers distribute medicines in a discriminatory manner, especially for drug products which were only recently recovering from shortage. They allocate larger quotas to pharmacy chains and big pharmacies, as mentioned by a government official 1 (June 2019). This unfair distribution may deprive some regions of certain types of drugs, and this result was emphasized by the Syndicate representative who said:

> *"Distributors and wholesalers sell medicines only to large pharmacies, leaving small pharmacies without some types of medicines"* (Syndicate representative , June 2019).

The head of a local company said that some key distributors, who have many branches, do not efficiently manage inventory. In other words, some branches may be overstocked while others are out of stock because the estimation of consumption rates may be inaccurate. Thus, unfair and inefficient drug distribution worsens the situation and causes drug shortages in some regions.

In addition, illegal exportation of medicines by any player in the supply chain is one of the causes of drug shortage in Egypt, as highlighted mainly by representatives of MNCs and distributors. In comparing with Birgli's findings (2013), it can be seen that the problem in Europe is the legal parallel exportation, but in Egypt, the problem is the illegal exportation.

> "*For particular products which were in shortage, companies increased the production to address this shortage, but, surprisingly, whatever quantity they produce, which is higher than demand, it disappears from the market*" (The head of business development in an MNC, June 2019).

Because of low drug prices in Egypt, some parties illegally export these medicines to neighboring countries that have the same drugs available at higher prices. An interviewee from MoHP explained that the Track and Trace project was initiated in 2016 by CAPA, but until now there is no real implementation of this project, which will help in tracking

drug products and preventing such illegal practices. This is also confirmed by Elkhouly, 2019, who in *Pharma Boardroom* states that the Track and Trace system is not fully implemented, adding that other countries as well as Egypt have experienced delays in implementation.

Another relevant point to consider is the supply chain management. An interview with a government official showed that limited financial resources and poor supply chain management within government hospitals and healthcare units leads to frequent supply interruptions (A government official 6, June 2019). Supply chain mismanagement includes poor demand forecasting, poor inventory management, and poor dispensing practices, all of which substantiates previous findings in research literature (Alruthia et al., 2018; Woodcock & Wosinska, 2013; Awad et al., 2016).

In light of all these, illegal practices during the distribution of drug products, which include monopolistic practices, illegal price increase, unfair distribution, and unlawful exportation, lead to the disappearance of drug products from the market and deprive patients of their right to access medicines. Besides, poor supply chain management and inefficient distribution can lead to supply interruptions. Thus, imposing strict sanctions for violations of regulations is necessary. Moreover, accelerating the implementation of the Track & Trace project would help in tracking drug products and prevent these illegal practices.

5.2.5. Issues related to consumption

Increased demand

It was found that increased demand for a specific drug in Egypt arises mainly when a company with a dominant market share cannot sustain drug supply at the same rates due to any obstacle. As a consequence, the demand for similar products produced by other

companies increases. Nevertheless, other companies may not be able to compensate for the shortfall and to meet the increasing demand due to limited production capacity, which fits well with previous findings (Fox et al., 2009; Jensen et al., 2002). Besides, companies may not have sufficient stock of raw materials or imported finished products to rapidly fill the market gap. As illustrated by industry representatives, because of manufacturing lead-time, additional supply would not be accessible immediately, so companies may fail to assist with covering a market shortfall.

> "*The time between placement of an order and arrival of the shipment is three months on average, and for certain products it may be six or eight months*", (The head of business unit at MNC, June 2019).

This means that a shortage may last for three months which can be disastrous for some types of drugs which have no alternatives, so each company should ensure a three-month inventory from either raw material in the case of locally manufactured products or finished drug products in the case of imported drugs to avoid sudden shortages, especially critical drugs.

False demand

The interviews with pharmacists at community pharmacies, as well as MNCs representatives, revealed that rumors about drug shortage and price increases could create false demand, which reflects findings in Bogaert et al. (2015) and Awad et al. (2016). When there is a slight reduction in the stock level held by distributors, distributors hold on to medicines and sell only a limited quantity to pharmacies, who in turn provide these drugs to patients in limited quantities. Thus, the patient becomes anxious about a perceived shortage and buys the medicine in a greater quantity than is needed. Furthermore, restoring availability after a period of drug shortage results in the same behavior described above.

> "*If there is a rumor about an expected shortage or a predicted increase in the drug price, pharmacy orders larger quantities, and patients try to get as much as they can of this drug*", (Pharmacist at a community pharmacy, July 2019).

False increased demand causes the continuation of shortage and worsens the situation because some patients may not be able to obtain their medications.

In brief, this field study provides evidence that the absence of a particular medication from the market increases the demand for similar products owned by other companies. This increase in demand may lead to a drug shortage because these companies cannot increase production due to limited capacity or unavailability of raw material. On the other hand, false demand is another issue that should be addressed to avoid the aggravation of the problem. Thus, upgrading and revamping of state-owned pharmaceutical companies to be the backbone of the government may be a solution to ensure the filling of market gaps.

5.2.6. Natural disasters and unforeseen incidents

In line with Woodcock & Wosinska (2013) and ASHP (2019), this field study showed that natural disasters may cause a shut down of many manufacturers and therefore affects the availability of drugs. A government official mentioned that the case becomes worse if there is a sole producer of certain medicine as happened in Egypt when a hurricane hit the United States of America which resulted in some companies ceasing production, from which Egypt imports some medications leading to drug shortage in Egypt (A government official, June 2019). Moreover, a senior leadership at a local manufacturer explained that natural disasters may limit the number of suppliers of raw materials, resulting in monopolistic practices from the remaining suppliers who increase the raw material prices which cannot be afforded by the Egyptian companies because of the fixed prices of medicines in Egypt as illustrated under [5.2.3.2].

Moreover, unforeseen and uncontrollable incidents such as fires that break out in pharmaceutical factories result in the destruction of production lines and a pause in

production. Rebuilding and reequipping the damaged area consume a long time and require huge financial capacity. A government official explained that fire destroyed the sterile area at SEDICO, which is one of the top companies in Egypt, leading to stopping production of many vital products such as insulins (A government official 3, July 2019). Thus, such incidents may lead to a prolonged deficiency of some medicines in the market, if other companies cannot compensate for the shortfall, a finding supported by Lyengar et al. (2016).

Accordingly, natural disasters and uncontrollable incidents can adversely affect production processes as well as companies' ability to meet the market need.

5.2.7. Exaggeration of the drug shortage problem

As was mentioned in the introduction, drug shortage is a global problem, and countries are experiencing the problem at different levels. It was interesting to find out that the drug shortage problem in Egypt may appear more significant than is actually the case. This exaggeration, mainly, results from mass media, patient culture, and physician behavior.

Mass media

Mass media has a substantial role in shaping society. Some interviewees emphasized that the media tends to exaggerate the drug shortage problem due to vested interests and political bickering.

> "*Media exploit any problem of the drug shortage for propaganda purposes, even if the drugs are not that much important*" (Senior leadership at FEDCOC, June 2019).

Media exaggeration spreads panic among people which affects the attitude of patients because they tend to overstock medicines which worsens the problem, as explained by the

Syndicate representative and a government official 1 during personal interviews (June 2019).

Accordingly, the media's portrayal of drug shortage is disproportionate to the actual size of the problem. Instead of raising concerns among patients and amplifying the problem, the media should play its role in raising awareness about dealing with drug shortage and improving society culture.

Patient culture and physician behaviors

Interestingly, it was found that incorrect perceptions about analogue and alternative drugs may amplify the problem. As illustrated during interviews with pharmacists, a syndicate representative, and a government official, patients in Egypt are used to buying medicines with their trade names and if the drug is not available and the pharmacist attempts to sell a similar product, the patient refuses to take any other medicines besides that prescribed by the doctor.

> "*Patients when asking for a drug and before I say a word, they say: do not give me a similar product*", (A pharmacist at a community pharmacy, July 2019).

This shows how patients are insistent on a specific drug that is in shortage despite the availability of other similar products. This wrong culture and behavior may inflate the size of the drug shortage problem in Egypt.

Unfortunately, some physicians may be behind the insistence of patients on a particular medicine even if it is in shortage, as highlighted during personal interviews with pharmacists at community pharmacies, as well as a senior leadership at FEDCOC. A local company representative argued that a physician's insistence on prescribing a specific drug might be due to their lack of knowledge about other trade names. In contrast, a syndicate representative and pharmacists claimed that doctors might make deals with pharmaceutical companies to prescribe their products, so they refuse to prescribe an alternative (A

syndicate representative, June 2019 & a pharmacist at community pharmacy, July 2019). Whatever the reason behind the physician's refusal to prescribe other similar or alternative medicines, this behavior places greater burdens on patients to find the specific drug and worsens the problem. Thus, some interviewees suggested that MoHP should issue guidelines to regulate the prescribing of medicines by doctors.

These results lend support to Abdelrahman et al's (2016) findings that many patients have wrong perceptions about similar and alternative drug products, and that some physicians may refuse to prescribe alternatives. As a consequence, many complaints about drug shortage may be wrongly raised despite the availability of their analogues, inflating the drug shortage problem.

5.3. Current actions

In response, the government has exerted many efforts to mitigate drug shortages. In 2012, the government established the Drug Shortage Department (DSD) to ensure drug availability and to overcome any shortage. DSD is one of the departments within CAPA, and it does not have the power to decide on various issues independently, instead it refers each problem to the concerned department. It achieves its mandates by working closely with manufacturers helping them to overcome problems and to restore drug availability. Similarly, it communicates with other manufacturers to increase production and to fill the market gap. Besides, it accelerates the procedures of drugs that are in shortage through communication with departments within CAPA and with other regulatory entities. However, and as illustrated earlier, the cooperation between different departments and entities is still not sufficiently effective, and some officials are not adequately responsive.

A government official explained that CAPA created a hotline (+20225354150) which works 24 hours a day. Through this hotline, citizens can report any shortage or ask

about any drug (A government official 1, June 2019). DSD informs patients about other similar medicines that they can use instead, or directs them to pharmacies where they can find their medication. Nevertheless, the interviewees at community pharmacies said that they had not heard about this hotline before. Furthermore, an interviewee from FEDCOC explained that this hotline does not work efficiently because calls may not be answered, or patients may receive inappropriate information due to unqualified persons answering the calls (An interviewee from FEDCOC, June 2019).

As mentioned earlier, a monthly bulletin about drug shortages is issued, where similar and alternative drug products are stated. Unfortunately, this bulletin was periodically published until 2016, and now it is still issued but not published. An official commented that announcing drug shortages should be handled with care because it may lead to further shortfall (A government official 1, June 2019). On the other hand, a representative of a local company said that, because of the large number of drug shortages in 2016, the government preferred not to publish the bulletin to avoid public criticism and anger, especially as people were unaware of how to deal with drug shortages (A representative of a local company, June 2019). Similarly, a syndicate representative commented:

> *"Drugs in shortage are not announced by the government, you can know them from the market", (*A Syndicate representative, June 2019*).*

Now, DSD depends on informing the main distributors about the available similar or alternative products to be used instead of drugs in shortage. Thereafter, this information is circulated by distributors to pharmacies and then to patients. An interview with a government official revealed that there is a current plan to develop a mobile application whereby all citizens can be informed of drugs that are in shortage and to know what other options they can use instead. In addition, citizens can report any shortage using this mobile

application. However, until the activation of this mobile application, publication of the drug shortage bulletin is important in managing drug shortages because it informs physicians, distributors, pharmacists, and patients about similar and alternative drug products, so some shortages might be resolved and the severity of others might be decreased.

Recently, DSD adopted new approaches to predict drug shortages instead of depending on citizens' complaints to determine shortages. Prediction depends on keeping track of the drug inventory at the major distributors; if the stock level covers less than one month of market need, provided there is a problem that hinders the production of this product, it is considered a shortage. This prediction and close monitoring are applied mainly on particular classes of drug products such as lifesaving products, blood products, M.S. drugs, oncology medicines, contrast agents, ICU medicines, and insulin. The close monitoring includes the importation of raw material and manufacturing of medicines and even its distribution to ensure proper coverage of all aspects and. regions across the country.

> *"Recently we noticed that DSD has become proactive, they ask periodically about the stock level and the consumption rate of some products, and in some cases provide support to complete the procedures*.", (The head of a business development unit at a MNC, June 2019).

The recent actions taken by the government are recognized by many stakeholders. Nevertheless, some industry representatives see that the government is mainly concerned with particular products, which were chosen on the basis of previous experiences of shortage. On the other hand, there is a handful of products which seem to be less critical, but they are important for a wide range of the population. Thus, such tracking should be applied to all drug products.

Furthermore, to avoid the emergence of the black market and to track the distribution of medicines efficiently, CAPA only allows pharmacies owned by the Egyptian Pharmaceutical Trading Company, which is an affiliate of Holdipharma, to sell important drugs which were in shortage and had restored their availability. Another key point to notice is that the tracking system does not depend on a well-established and robust system because the track and trace project is not implemented until now, so instead it depends on sending data from the distributor to the DSD.

In an attempt to avoid delays in analysis at the national labs, CAPA inspectors mark the samples of drugs, that are already in shortage or expected to be in shortage, by a specific stamp to prioritize them in the analysis, as highlighted by government official during the field study (July, 2019). It is a good sign that the government is now considering the importance of communication between different governmental entities.

In addition to the previously mentioned actions, the government issued some decrees to help in easing the drug shortage problem. For instance, and as reported previously, the Prime Minister Decree number 32/2016 and the Ministerial Decree number 26/2017 were issued to increase the prices of many drugs that were in shortage after devaluation of the Egyptian Pound. Furthermore, to increase the number of competitors in the pharmaceutical market, and as illustrated before, Ministerial Decree 645/2018 was issued to allow more products to be registered without adhering to the limited number of drugs within the "box". CAPA officials determine a list of pharmaceutical molecules, which are in shortage, to be registered according to this decree. A lot of criticism has been directed to this Ministerial Decree. For example, the criteria by which CAPA selects certain molecules to be registered without a limited number is vague.

> "*Surprisingly, we found some molecules in the drug shortage list, and we already have a stock of them, and they will be expired soon because they do not have a market*", (CEO of a local company, June 2019).

In addition, a government official argued that this system could not force companies to register and produce particular molecules (A government official 2, June 2019). In other words, companies prefer to choose profitable and easily manufactured molecules, and they leave other important molecules. He further said

> "*We received around 90 registration applications for a non-steroidal drug, which has other alternative products in the market. On the other hand, oncology drugs for example has a very limited number of applications*" (June, 2019).

A local manufacturer representative illustrated that although this ministerial decree allows the registration of more products, the registration process itself takes at least three years, and during this time needs most probably will change, so decree 645/2018 will not be effective in addressing drug shortage (An interviewee from local industry, June 2019). Accordingly, reviewing the status of products that are already in the box either registered or under registration and trying to solve the problem facing these products can efficiently and rapidly address some drug shortages. In contrast, allowing more products to be registered will increase the burden on the registration department and lead to more delays. Therefore, decree 645/2018 seems to be ineffective in solving the drug shortage problem.

Briefly, it can be said that the government exerted some efforts and endeavors to mitigate drug shortage. The main efforts include establishment of DSD to help companies to overcome obstacles and to speed up the procedures within the government. Moreover, DSD receives complaints about drug shortage and attempts to solve them. Recently, it created a watch list of specific classes of drugs to closely monitor their manufacturing and distribution, so it can predict their shortage in advance and can control their distribution. However, despite the actions taken by the government, more efforts are needed to

effectively mitigate the drug shortage. In comparison with actions taken by other regulatory bodies such as the FDA, EMA, Health Canada, TGA, and Brazil, it can be noted that a task force that involves multiple stakeholders – not only government officials - should be established. Besides, a national strategy to deal with drug shortages may be developed to determine the role and responsibility of each stakeholder. A notification system for anticipated or current drug shortage may be created to allow immediate actions to address the shortage. Finally, the communication of drug shortage information to a healthcare provider is important to manage drug shortage and minimize health hazards.

Chapter six: Conclusion and mitigation measures

6.1. Conclusion

The study attempts to explore how and to what extent the government can mitigate and tackle the drug shortage problem in Egypt. The study objective was achieved by determining the causes of drug shortages, the impact of the current regulations and policies on drug shortages, and the current actions taken by the government to resolve the problem. The drug shortage problem has received increasing attention in recent years due to its dire consequences on patients and health systems. Despite the considerable amount of literature on the drug shortage problem, only a few studies were performed in developing countries, specifically in the Arab world and Egypt, which has a different political, economic and legislative context. The significance of this study is that it provides a better understanding of the drug shortage problem in the Egyptian context, which allows for the proposal of tailored and effective solutions to address the problem.

A qualitative research design was adopted to fulfill the objective of the study by conducting in-depth interviews and reviewing secondary data for the purpose of triangulation. In reference to the research questions, and in accordance with the conceptual framework, the findings of the study are divided into the government's definition of the drug shortage, causes of drug shortages, and the government's efforts to mitigate the problem.

It has been found that the Egyptian MoHP does not have a clear published definition for drug shortage. However, it can be concluded that the government considers a drug shortage when the drug license holder fails to meet patients' needs. Turning to the causes of the problem, the study has shown that the causes are intertwined and wide-reaching.

First, despite the goal of the regulatory bodies to ensure the availability of safe, effective, and affordable medicines to patients, it was shown that bureaucracy and some policies might adversely influence the availability of drugs. Complicated procedures and excessive bureaucracy are mainly attributed to overdependence on external committees and lack of the following: adequate communication among departments, an effective automation system, trust in companies due to malpractices of some companies, and deterrent sanctions, all of which may lead to delays in obtaining approvals, and hence interruption in the drug supply. Similarly, delays in analysis undertaken in the national labs and excessive sampling result in postponed release of production batches, which adversely affect drug availability in the market. Moreover, some regulations and policies have been found to contribute to the drug shortage. Significantly, drug pricing policy seems to be the main cause for ceasing production of some products which have a low-profit margin. Other regulations dealing with marketed drug products such as drug variation guidelines and importation regulations can profoundly affect drug availability. It is also worth noting that there are no specific regulations and guidelines to address drug shortages.

Second, the economic environment in Egypt, particularly after the devaluation, has influenced the ability of pharmaceutical companies to operate commercially in Egypt. Many companies ceased production of some drugs, which saw rising production costs but fixed sales price, resulting in low-profit margins or even incurred losses. Given that the pharmaceutical industry depends on importation of 90% of production inputs, scarcity of hard currency hindered the importation of raw materials and therefore also the production. All these factors lead to market turbulence and a challenging business environment resulting in greater shortages.

Third, multiple issues related to the manufacturing process can lead to disruptions in production and drug shortage. For example, quality issues and machinery breakdowns may lead to a sudden and prolonged interruption in production. Limited production capacity and scarcity of particular types of production lines were also determined to be a cause of drug shortage. Furthermore, issues related to raw materials can stop production such as a global shortage of raw materials, the limited number of API suppliers and production rationalization, or prohibition of the importation of raw materials from some API suppliers based on FDA and EMA warnings and alerts. Due to low drug prices, some companies tend to import lower grades of raw materials with lower costs, which increases the likelihood of production disruption due to quality problems. It might be said that overdependence on importation remarkably influences the sustainability of production, mainly because of shipping and logistics problems, contractual problems and hard currency issues, as well as the political and economic environment in other countries.

Fourth, distribution and supply problems notably have been found to influence drug shortage in Egypt. It has been noted that illegal practices such as the stockpiling of medicines, illegal exportation, and unfair distribution are behind the unavailability of medicines. The absence of the implementation of the drug tracking system facilitates the continuation of such practices that exacerbate the drug shortage problem.

Fifth, it has been observed that increased demand as a cause of drug shortage is mainly due to interruption in the production of other similar products. Companies may not be able to ramp up production to compensate for the shortfall because they cannot deviate from their production schedule or due to limited production capacity.

Sixth, whilst natural disasters and uncontrollable conditions feature rarely, they could potentially have a severe impact on drug availability.

It is interesting also to note that two main factors exaggerate the problem in Egypt. The first is the behavior of the mass media which tends to sensationalize the problem, thus causing panic and driving patients to stockpile medicines. The second is the prevalent perception of patients and physicians regarding drug analogues and alternatives. It has been noticed that patients refuse to take any other medication except that prescribed by the physician even if it has the same active ingredient, which increases complaints of drug shortage. Furthermore, some physicians may be unaware of, and therefore cannot prescribe, alternatives to medicines that are suffering a shortage. All these factors may generate more panic and exaggerate the problem.

It can be concluded that the causes of drug shortages in Egypt are multifaceted and include economic issues and consequently low-profit margin, the illegal practices of distribution, manufacturing problems and quality issues, bureaucracy, complicated procedures and delays, increased demand, and unforeseeable events. Coupled with these causes, mass media reporting and physicians' and patients' incorrect perceptions about drug analogues and alternative can amplify the problem.

The actions taken by the government are essential to mitigate these causes and their impacts. In an attempt to tackle the problem, MoHP has established the Drug Shortage Department which is concerned with all issues related to drug shortages. DSD works closely with manufacturers to resolve problems and to speed up the procedures at the MoHP. It established a hotline to receive patients' complaints about drug shortages. Moreover, DSD developed a watch list of drug products that are life-saving and essential to patients. The products in the watch list are monitored regarding their importation, production, and distribution. In response to economic changes, the government increased the prices of many drugs to facilitate more profitable production. Besides, more

cooperation between the three regulatory bodies was introduced to accelerate the resolution of drug shortages. The aforementioned efforts exerted by the government have improved the situation and decreased the number of drug shortages, especially during the last year. However, there are more many actions that can be taken to mitigate the problem and decrease its severity and negative consequences.

6.2. Mitigation measures

Based on the findings of this study and countries' experiences in mitigating drug shortage, the following gaps are identified and some measures are provided to help in mitigating the problem according to the Egyptian context.

Table 3 Suggested mitigation measures

a) Enhancing the sustainability of production of medicines by improving profitability	
Gap to be addressed	Drug pricing mechanisms are considered a constraint on the pharmaceutical industry due to the low prices set by the government, especially after devaluation and increased costs.
Mitigation measure 1	**1Implement a fair and clear drug pricing policy** which suits with the Egyptian settings. This policy should **depend on the actual cost of the drug product regardless of the presence of a cheaper similar drug product in the market**. By considering costs during the pricing process, companies may be encouraged to invest more in the quality of their products which in turn may decrease shortages resulted from quality issues.
Obstacles to be considered	Lack of trust between government and companies because some companies may exaggerate the cost of their product. Thus, a regular monitoring system for prices of major production inputs may be developed, and deterrent sanctions should be imposed if any violation is detected. Additionally, companies should provide original purchase invoices for production inputs as evidence for the requested price.

Mitigation measure 2	**Prioritize reviewing the current drug prices** to fit with the economic changes in Egypt to prevent further shortages and encourage many companies to resume the production.
Obstacles to be considered	Public anger and criticism may be an obstacle for the government to increase drug prices. However, avoiding raising prices of drugs may impact the availability of medicines, so the government should either increase drug prices or afford the increase in costs itself instead of industry and patients, and this may be achieved by mitigation measure no.3.
Mitigation measure 3	**Accelerate and prioritize the implementation of a comprehensive health insurance system** where the country will cover the cost of treatment and out-of-pocket payments will be eliminated**.**
Obstacles to be considered	As illustrated in section [4.1.1], the government already has developed a plan to fully implement this system over fifteen years, so prioritizing the implementation of such a large project to help in mitigating drug shortages requires a reallocation of the budget and a political well.
Gap to be addressed	Increased costs of imported production inputs while drug prices are fixed
Mitigation measure	Implement a **differential exchange rate** where the most essential goods could be assigned a favored exchange rate, and luxurious commodities may have a higher rate, which helps reduce production costs and maintain affordable prices for medicines.
Obstacles to be considered	Customers of luxurious commodities may oppose this decision, so the difference in the exchange rate should be rational.
b) Improving collaboration between various stakeholders	
Gap to be addressed	The current entity handling drug shortages is the DSD at CAPA, and other stakeholders are not involved officially in addressing drug shortages. Besides, DSD is not empowered to take decisions independently.
Mitigation measure	Establish **a standing task force or a multi-stakeholder steering committee for drug shortage** which includes representatives from, pharmaceutical regulatory agencies, Ministry of Health, Ministry of Finance (Custom Authority), professional associations of physicians and pharmacists, and any other party that might be part of the problem. This committee aims to determine the root causes of drug shortages and work jointly to resolve any current or anticipated shortage.

	Because the causes of drug shortage are multifaceted, the committee could allow a suitable interaction between multiple stakeholders and to share the responsibility to ease the problem. Such task force and steering committees were successfully implemented in the USA, Canada, and the EU
Obstacles to be considered	The reluctance of some stakeholders to cooperate and improper enforcement of decisions taken by this task force may be an obstacle. Thus, this task force should be institutionalized and empowered. The enactment of Law No. 151/2019 for establishing the Egyptian Drug Authority, as described in section [4.2.1], would be a great opportunity to formulate this standing task force under the structure of this authority. The establishment of this task force may be achieved by a Prime Minister's decree because it comprises of representatives from various ministries, and to allow mandatory enforcement of its decisions.
Gap to be addressed	Lack of guidelines on how to deal with drug shortages.
Mitigation measure	Develop a strategic plan or a **protocol to determine the role and responsibility of each party** to mitigate drug shortages, identify a proper response for each type of shortage, and streamline procedures within institutions and organizations. The Australian model may fit the Egyptian context in this regard because the DSD already has a Watch List of critical drugs which is part of the Australian model, so we could build on what already achieved in Egypt.
Obstacles to be considered	Proper implementation of this protocol/plan may be an obstacle. Therefore, this protocol should be issued by the above-mentioned standing task force or by the Prime Minister to be mandatory for all parties. DSD may play a role in monitoring and evaluating the implementation of this protocol/plan.
c) Improving reporting system and communication of drug shortage information	
Gap to be addressed	Lack of a notification system for supply disruptions
Mitigation measure	Create **a notification system which requires companies to notify drug authority in advance** about supply interruption, delays, discontinuation or manufacturing change leading to a drug shortage. Also, companies should explain the causes of supply interruption and the timeline for resolution. This may allow better anticipation of drug shortages, and faster response to avoid the

	shortage. This measure was successfully implemented in the USA, Canada, Australia, the EU, and Brazil.
Obstacles to be considered	Companies may be reluctant to notify about supply interruptions, so a ministerial decree may be issued to make it mandatory. Additionally, the drug authority may publish the names of license holders who are not compliant with this regulation. Furthermore, according to the Australian and Brazilian experience, civil penalties in the form of fines may be imposed if deliberate repeatable non-compliance is demonstrated.
Gap to be addressed	Lack of a communication system for drug shortage information
Mitigation measure	**Create a tool to communicate drug shortage information**, this tool may be a searchable online format or a mobile app, which will allow proper management of the patient case by predetermining other alternative therapies.
Obstacles to be considered	Communication of drug shortage information, especially anticipated shortages may worsen the situation because of the malpractice of distributors and patients who may stockpile these medicines, so the track and trace project should be implemented in parallel to prevent such practices in addition to raising the awareness of Egyptian citizens about dealing with drug shortages.
d) Developing mechanisms to prevent sudden shortages due to raw material issues	
Gap to be addressed	Overdependence on the importation of production inputs and high-tech medicines.
Mitigation measure	**Encourage the establishment of manufactures of raw materials** and high-tech medicines to decrease the dependence on imports.
Obstacles to be considered	Lack of experience in Egypt for this industry, so the government may encourage partnerships with foreign companies to help local companies produce these products.
Gap to be addressed	Lack of legislation requiring companies to maintain a proper level of drug inventory.

Mitigation measure	Introduce **legislation obliging companies and importers to keep a particular level** – determined according to the therapeutic importance- **of stock** of either imported raw materials or imported finished products to avoid sudden interruptions due to importation problems.
Obstacles to be considered	This may be opposed by companies because this will increase costs. Thus, applying a fair pricing system is the key.
e) Enhancing proper distribution of medicines	
Gap to be addressed	Malpractices such as medicine stockpiling, the black market, and illegal exportation cannot be easily detected by the current system**.**
Mitigation measure	Accelerate **the implementation of the Track and Trace project** which has been initiated by MoHP since 2016. This project will allow more effective control for illegal practices during the distribution and allow better inventory management and fair distribution.
Obstacles to be considered	The difficulty of implementation of this project as it requires all companies to apply a specific coding system for their products. Thus, the implementation requires a proper collaboration between government and companies to accelerate the implementation and to consider it as a top priority.
f) Encouraging the development of plans to be adopted by companies to prevent shortages	
Gap to be addressed	Lack of proper planning in some pharmaceutical industries to prevent shortages.
Mitigation measure	**Encourage companies to develop and implement a drug shortage plan** by which they identify risks to their supply chain and maintain a proper stock of raw material and outline procedures for handling issues that may lead to drug shortages.
Obstacles to be considered	Lack of experience and knowledge of some companies may be an obstacle. Therefore, MoHP, the Ministry of Trade and Industry, and the Chamber of the Pharmaceutical Industry may cooperate to help pharmaceutical companies to develop and implement these plans.
g) Development of Mechanisms to encourage companies to produce drugs which are in shortage	
Gap to be addressed	Lack of mechanisms to encourage companies to ramp up the production to address a drug shortage.
Mitigation measure 1	Establish **incentives to encourage companies to produce drugs which are in shortage and recognize** these companies by publishing their names as **partners**

	in mitigating drug shortage. On the other hand, introduce penalties for any party in the supply chain, which intentionally caused a drug shortage.
Obstacles to be considered	Companies may be reluctant to cooperate because they may not be able to sell their products if other companies produced the same product at the same time, so the government should ensure that the company will not end up with expired products, and this can be achieved by communicating the trade name of its product to physicians and pharmacists as a substitute for that in shortage.
Mitigation measure 2	Direct public sector companies to produce medicines which are in shortage and increase their efficiency to achieve a better competitive position.
Obstacle	Insufficient financial capacity to upgrade and revamp their facilities may hinder companies' ability to sustain the production. Therefore, these companies need effective management to determine gaps and find solutions to increase their profitability.
h) Raising awareness of society about drug shortage	
Gap to be addressed	Wrong perceptions of society about analogue and alternative drug products.
Mitigation measure	**Raise awareness of society about drug shortage** and illustrating the meaning of similar drug products (analogue) and alternative drug products which may prevent the amplification of the problem. This may be achieved by the media.
Obstacles to be considered	People may not trust the government, thus the government should declare its efforts in mitigating drug shortages and its plans to mobilize the entire country for one goal of alleviating drug shortage.

Source: developed by the researcher.

In addition to these measures, other actions may be taken to I**mprove workflow within the MoHP and to avoid unnecessary delays such as:**

- Impose **strict sanctions** to deter violations of rules, which may prevent malpractices of some companies and build trust between the government and companies.
- Implement an effective automation system which allows proper communication between departments and eliminates the redundancy of work and speeds up the procedures.

- Build capacity and increase employees efficiency to decrease dependence on external committees, thereby reducing long queues.
- Rationalize the frequency of sampling based on the company's history and its compliance with regulatory standards to avoid delays in the national labs.
- Review drug variation guidelines taking into the consideration implementation of the notification system for some types of drug variations, and the implementation of grace periods to execute the new change requested by the company.
- Provide guidelines for the importation to avoid personal judgments and sudden prohibition for importation of raw material.

From the proposed mitigation measures mentioned above, it can be concluded that solutions are as complex and intertwined as the problem itself. Thus, a holistic approach may be adopted to address this problem and reduce its severity, duration, and likelihood. The drug shortage problem is a very pressing issue and should be placed on top of the government's policy agenda.

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Appendices

Appendix 1: The appendix number (2) in Ministerial Decree 425/2015

The table clarifies the boxes of similar products, and each box includes a group of dosage forms.

1	**Box I**	Solid unit dosage form (traditional (Conventional) immediate release)	Tablets (Sugar - Film Coated)	Hard Gelatin capsules	Dragees (Tablet in French)	Caplets	Lactabs	Pilules (Pills / Capsule)	Spansules (Sugar coated Pills /Capsule)
			Lozenges						
			Gums						
			Soft Gelatin capsules						
2	**Box II**	Solid Unit Dosage Form (Fast Immediate Release)	Quick Tablets	Flash Tablets (DISOLVE IN MOUTH only)	Oro-disintegrating	Melt tablets	Oro-Dispersible Tablets		
			Chewable Tablets						
			sublingual Tablets						
			Buccal Mucoadhesive Tablets (Buccal Mucoadhesive Tablets(prolonged only in mouth for local effect or systemic effect)						
			effervescent Tablets	Disintegrating Tablets	Dispersible Tablets				
			Effervescent Granules/Powders	Powder in Bottle (each dose will be reconstituted at time of use	Powder / Sachets				
3	**Box III**	Solid unit Dosage Form (Modified release)	SR, CR, MR, XR Capsules / Tablet	Depotabs	Retard Capsules / Tablet	Enteric Coated tablets			
			Modified Release Powder/Granules in Sachets	Modified Release Powder/Granules in Bottle (each dose will be reconstituted at time of use					
4	**Box IV**	Oral Preparation (Liquid-semisolid-Powder/ Granules for Reconstitution)	Solutions	Syrups	Oral drops	Elixirs	Drinking ampoules	Powders /oral (Solution)	Powders/ (Emulsion / Susp.)	Emulsion	Suspension	Oral Gels	Oral Jellys
			Modified Release Oral Preparations										
5	**Box V**	Buccal Preparation	Oral Paste										
			Oromucosal Gels										
			Oromucosal Sprays										
			Gargles	Mouth washes									
6	**Box VI**	Sterile Preparation (injections)	Solutions	Suspensions	Emulsions								
			Irrigation Solutions (LVP)										
			Modified release Injections	oily injections									

a

7	**Box VII**	Implants					
8	**Box VIII**	Sterile Preparation (sterile Prefilled Injections)	Prefilled Syringes				
			Pen Filled Preparations				
			cartridges				
9	**Box IX**	Traditional topical Preparation	Topical Cream				
			Topical gels/Emulgel				
			Topical ointments				
			Topical solutions	Topical lotions (if solution)			
			Topical Emulsions	Topical lotions (if Emulsion)			
			Topical Pastes	Poultices (Cataplasm)			
			Topical Nail Preparation				
			Topical Paints				
			Topical Shampoos				
			Topical Plaster				
			Topical Liniments				
			Roll on (Pack)				
10	**Box X**	Non Traditional Topical Preparations	Topical Sprays (Pressurized)				
			Topical Foams				
11	**Box XI**	Transdermal Systems	Transdermal Patches (Transdermal Plaster)				
			Medicated dressings				
			Transdermal Semisolids				
12	**Box XII**	Vaginal & IUD Preparations	Vaginal Creams				
			Vaginal ointments				
			Vaginal Foams				
			Vaginal Ovules/Pessaries	Vaginal Capsules	Vaginal Tablet		
			Medicated IUD				
			Vaginal Rings (Diaphragm)				
			Vaginal Sponges				
			Vaginal Douches				
13	**Box XIII**	Rectal Preparations	Rectal suppositories	Rectal Tablets	Rectal Capsules		
			Rectal Creams				
			Rectal ointments				
			Enemas				
14	**Box XIV**	Eye/ear Preparations	Solutions	Viscous Liquids (Soln)	Drops	Suspensions	Viscous Liquids (Susp)
			Gels				
			Ointments				
			Ocular Injections				
			Ocuserts				
			Creams (Not Found)				

b

			Sprays (Not Found)	
15	**Box XV**	Nasal Preparations	Nasal Drops	Nasal Solutions
			Nasal Sprays	
			Nasal Viscous Liquids	Nasal Gels
			Nasal Ointments	
			Nasal Creams (Not Found)	
16	**Box XVI**	Inhaler	Rota Tabs	
			Capsules	
			Solutions	
			Powders	
			aerosols	
17	**Box XVII**	Nebules	Respules	
18	**Box XVIII**	Oral Soluble Films		