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A Quantitative Analysis of the Causes of Drug Shortages in Jordan: A Supply Chain Perspective

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Abstract

This study investigates the causes of drug shortage in Jordan. Based on thorough literature review, five causes related to supply chain were identified, namely regulatory and legislative processes, manufacturing-related issues, distribution factors, supply and demand imbalance, and human factors.

Data were collected from 221 professionals selected from Jordan Food and Drug Administration (JFDA), pharmaceutical manufacturing sector, hospital professionals, and other nodes in the supply chain including distributors and wholesalers. Multiple-regression analysis was used to test the hypothesized relationships. The results indicate that four causes are significantly related to drug shortages in Jordan, regulatory and legislative processes, distribution factors, human factors, and supply and demand imbalance. Manufacturing-related issues are not significantly related to drug shortages. Implications and recommendations for the decision makers are proposed on the basis of the study results.

Keywords: drug shortages, medications supply chain, causes of drug shortages, Jordan, empirical study

1. Introduction

Securing the supply of medications and ensuring meeting the needs of end customers in term of accessibility, quality, quantity, and cost of medications are at the top of any health care system priorities (Abdollahiasl et al., 2014). Pharmaceutical supply chain is susceptible to many risks leading not only to wasting valuable resources but also to disrupting the availability of medications resulting in the growing problem of drug shortages.

Complexities of the pharmaceutical supply chain make it difficult to identify the reasons for drug product shortages (Landis, 2002). The root causes of medication shortages are complicated and involve many factors at the different nodes of the supply chain; including manufacturing issues, regulatory and legislative issues, business and market factors, supply and demand issues, distribution factors, natural disasters, inventory issues, and the human factors. Additionally, each of these factors can be influenced by a number of sub factors. For example, manufacturing can be severely affected by the supply of raw materials and quality control issues. Business and market factors can be influenced by mergers and acquisitions and by labor disruptions. Regulatory processing can be affected by lengthy new drug approval procedures and natural disasters that include the breakout of pandemic diseases (Gu et al., 2011; Ventola, 2011).

Medications shortage has been identified as a chronic critical problem by many agencies and regulatory bodies, such as the American Food and Drug Administration (AFDA), American Society of Health System Pharmacists (ASHP), and the Institute for Safe Medication Practices (ISMP). This problem is emergent and is becoming increasingly uncontrollable due to the recent increase of the frequency of active shortages reported by the United State Government Accountability Office (U.S. GAO, 2014).

In 2004, Jordan Food and Drug Administration (JFDA) conducted a survey about drug availability and affordability in Jordan. The results showed that the median availability of generic medications surveyed in the public sector is 27.8% and 0% for originator brands. In contrast, the availability of those same drugs in the private sector was higher, with a median availability of 80% for generic medications and 60% for originator brand products (Conesa, 2009).

Therefore, the objective of the current research is to identify the causes of drug shortages in Jordan as a first step towards providing data to inform potential solutions. The research is survey-based and takes into consideration the data and opinions collected from the different parties in the drug supply chain, including: 1) the regulatory body represented by Jordan Food and Drug Administration (JFDA); 2) government entities including the Jordanian Ministry of Health; 3) professional unions, including the Medical Doctors Association and the Pharmaceutical Association; 4) the Jordanian

pharmaceutical manufacturing sector; 5) the suppliers, including drug distributors and stores as well as the regional offices of multinational companies in Jordan; and 6) the customers, represented by public and private sector hospitals. Few research papers have attempted to highlight drug shortages causes, mainly in developed countries. This research is significant and expected to contribute to the existing literature by identifying factors that contribute to drug shortages in Jordan. Drug shortages have profound human and financial consequences. The study offers original data that could be used to devise timely and cost-effective response plans to such shortages in Jordan.

2. Literature Review

2.1 Medications Supply Chain

Any supply chain infrastructure consists of a set of players involving manufacturers, suppliers, retailers and distributors. Information and resources are invested in different processes (sequence of events) across the supply chain in order to transfer raw materials and ready-to-use components into finished products or services to be delivered to the customers (Shah et al., 2004; Asamoah et al., 2011).

In the light of this description, a pharmaceutical supply chain can be defined as set of players/organizations and processes/operations, information, resources and services utilized in manufacturing, and distributing drugs across the different supply nodes (including primary manufacturing, secondary manufacturing, market warehouses or distribution centers, wholesalers, retailers and hospitals) to deliver the drug to the customers at the correct timing, to the right place, in the right quantity and quality at an acceptable cost (Shah, 2004; Kaufmann, et al, 2005).

Therefore, any pharmaceutical supply chain has a unique nature due to the presence of different key players, integrated activities, complex information and high vulnerability to internal and external risks which makes managing and optimizing it a complex process that might affect the satisfaction of the customers (internal and external) as well as the safety of the patients (Asamoah, 2011; Abdallah, 2013).

Optimizing supply chains in pharmaceutical industry has become an important research focus (shah, 2004). Many practices were adopted to ensure the quality of the pharmaceutical supply chain. Adopting to such practices does not negate the risk of disruption of drug products flow from the original supplier to the customers as the pharmaceutical supply chain remains at risk due to internal (organizational and management related) and external (including, economic, environmental, political) risks (Abdallah, 2013; Breen, 2008).

Disruption may take an intense form leading to restricted or even stopped flow of medications through the pharmaceutical supply chain leading to a phenomenon called medications shortages, which in turn leads to increasing risk to the patient safety (Breen, 2008).

2.2 Medication Shortages Concept

Medication shortages meaning varies as a matter of perspective of the different players across the pharmaceutical supply chain (Fox & Tyler, 2003), and no harmonized definition for the concept was identified in the literature. Thus, it was crucial for the researchers to take into consideration all of these different definitions and to align them to ensure conclusive coverage of the concept.

From a manufacturer's perspective, medication shortage is viewed as a raw material unavailability related-issue or a sustained problem in the manufacturing process of certain products. Whereas wholesalers gave minimal importance to the reasons and duration of shortages, and focus on the difficulty of obtaining products (Fox & Tyler, 2003).

Organizations and health care providers from their side considered medication shortages as a supply related issue that affect patient care process and consequently their safety (Ventola, 2011). An example of such organizations is the ASHP which defined shortages as “a supply disruptions influencing prescribers practices including using alternative medications or influences pharmacy processes including drug products preparation and dispensing", whereas the FDA focuses only on situations where all sources of drug products and its alternative options (all clinically interchangeable versions of a regulated drug) used for treating or preventing serious or life-threatening diseases or other medical conditions are unavailable (FDA, 2013).

The international society for pharmaceutical engineering has adopted similar definition of the FDA with increased focus on balance between total supply and projected demand as well as current demand at user level (ISPE, 2013).

For the purposes of this research, the researchers will tackle the concept of shortages from a different perspective where shortages would mean any supply disruptions that result in the difficulty of obtaining or the unavailability of raw material as well as finished drug products and all of its clinically interchangeable versions of regulated drug alternatives, resulting in imbalance between total supply and current or projected demand of any medication used for treating or preventing serious or life-threatening diseases or other medical conditions, and affect the patient care process and consequently their safety, or leading to pharmacy processes alteration including drug products preparation and

dispensing, in addition to influencing prescribers practices including using alternative medications (Fox & Tyler, 2003; Ventola, 2011; FDA, 2013; ISPE, 2013).

2.3 Causes of Medication Shortages

It is unclear what factors lead to medication shortage; any expert refers to this crisis as multi-factorial and rooted in every phase of a drug life cycle (Gu et al., 2011).

An essential step toward solving the problem of medication shortages is to conduct a systematic investigation in order to provide a thorough understanding of this problem (Fox et al., 2009). Many trends that contribute to shortages were pointed out such as issues related to manufacturers including: raw material supply interruptions, economics and business decisions such as pharmaceutical mergers and acquisitions, the unanticipated shifts in market demand, Production and quality problems in the manufacturing process (e.g., contamination, and the presence of foreign particle) (Morrissey, 2012). Other causes include limited manufacturing capacity, and packaging component problems. These are the most common causes of drug shortages, accounting for nearly 46% of all drug shortages in 2011 as identified by the US- FDA (Gu et al., 2011).

Other possible causes include the potential impact of the falsified medicines directive, lack of market attractiveness for (older) medicines and stringent supply quotas imposed by pharmaceutical manufacturers (Cherici et al., 2011). Regulatory and legislative factors, the human factor particularly labor disruption, in addition to the imbalance between supply and projected demands are considered among the major causes for medication shortages (Morrissey, 2012; Cherici et al., 2011; Gu et al., 2011).

Based on this review, we classified the causes of drug shortages into five main factors: regulatory and legislative processes, manufacturing-related issues, distribution factors, supply and demand imbalance, and human factors (Morrissey, 2012; Cherici et al., 2011; Gu et al., 2011; Cherici et al., 2011; Ventola, 2011; Fox et al., 2009). It should be noted that previous studies on drug shortages did not address human factor as a cause of shortages. Our study is the first empirical study that includes human factor among factors causing drug shortages. These factors and their effects on drug shortages will be discussed in the hypotheses development section.

3. Research Framework and Hypotheses Development

3.1 Research model

The current study adopted quantitative design using hypotheses testing approach to identify the effects of the different supply chain disruption factors on drug shortages in Jordan. The research model was developed by proposing a direct relationship linking potential-supply chain related causes of drug shortages (independent variables) with drug shortages in Jordan (dependent variable). The research model is depicted in Figure 1 below.

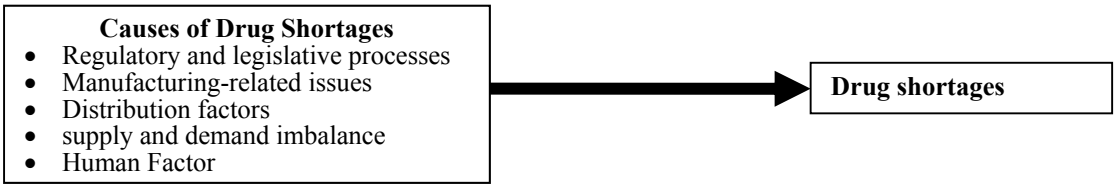

Figure 1. Research framework

3.2 Hypotheses Development

3.2.1 The Effect of Regulatory and Legislative Processes on Drug Shortages

Drugs are strategic products in any health care system and are thus highly regulated and under tight control of public regulatory authorities. To protect the integrity throughout the pharmaceutical supply chain, regulations should cover many areas of operations to ensure quality and successful product manufacturing as well as maintaining an oversight on the drug distribution system (Koh et al., 2003; CDA, 2010). However, regulations can lead to drug shortages due to stringent quality requirements, which may be perceived as major and costly constraints by manufacturers and wholesalers (McKenna, 2011).

The challenge of quality assurance remains at the top of the causes of drug shortages in any health care system. Increased governmental oversight represented in far reaching regulations regarding quality control issues and good manufacturing practices lead to increase cost and time to approval decisions for Abbreviated New Drug Applications (ANDA), supplemental applications, and approval processes of new facilities due to risk mitigation (McKenna, 2011; ASHP, 2010). Accordingly, manufacturers regard regulatory as limiting of their ability to develop reliable production schedules, which could be confounded by internal policies and insufficient resources (Shah, 2004; Fox et al., 2009;

ASHP, 2010; Gu et al., 2011; Ventola, 2011).

Complex and lengthy new drug approval processes, perceived unfairness of the pricing parameters imposed by regulatory bodies, and low profit margins can be detrimental factors, which may limit manufacturers' options and direct their decisions toward eliminating a production line and pursuing manufacturing certain drug products (Schweitzer, 2013).

Additionally, continuous information flow is an essential component of an integrated supply chain. The lack of an advanced warning system within the pharmaceutical supply chain about potential shortages and anticipated market withdrawals were considered significant contributors to drug shortages (ASHP, 2010; Ventola, 2011). Moreover, the lack of statuary authority with the ability to enforce notifications actively and maintain the flow of information and active communication channels between the different players across the pharmaceutical supply chain can also contribute to drug shortages (GAO, 2014).

H1: The more regulatory and legislative constraints, the more drug shortages

3.2.2 The Effect of Manufacturing-related Issues on Drug Shortages

According to Ventola (2011), manufacturing-related causes of drug shortages are multi-factorial and account for 23% of the causes of drug shortages. Decisions made by manufacturers may vary from dropping out the market permanently or temporarily, making reductions in production of certain drugs, shifting production from one line to another or reallocating resources to other products (Fox et al., 2009). Factors leading to such decisions may include lack of financial incentives in the form of insufficient profit margins, the introduction of competing generic products, market share fluctuations, patent expiration, drug-approval status, regulatory compliance requirements, high cost to correct manufacturing problems, legal liabilities, or mergers in the pharmaceutical industry (Fox et al., 2009). These factors can influence manufacturers by encouraging them to maintain lower inventories of low profit drugs or even push toward market withdrawal altogether and accordingly increasing frequency of drug shortages (McKenna, 2011).

According to the FDA, product discontinuation was number one cause of shortages, accounting for 12% of the shortages reported between January 1, 2011 and June 30, 2013. This is especially the case when discontinuation decision pertains to generic drugs (ASHP, 2010). One reason behind this is the nature of generic drug market, which is dominated by few manufacturers. Consolidations in the pharmaceutical industry also have left only few manufacturers to operate (Kaiser, 2011). New quality requirements imposed by FDA and diminishing demand are two other causes for drug discontinuation and accordingly drug shortages (Kaakeh, 2011). Moreover, the manufacturer inability to fill in when competitors lack capacity to meet unanticipated clinical demands (Jensen et al., 2002; Fox et al., 2009; Schweitzer, 2013). Indeed, profit margins remain a major factor for discontinuation decisions of products with low profitability or low sales. Generic drug prices are controlled by many factors such as the number of manufacturers, the level of competition, the profit margins, and stringent regulation by health authorities (Fox et al., 2009).

In a market economy, there is nothing that can force manufacturers to resume production. Ethical obligations toward patients may necessitate the production of a certain product regardless of their low or negative profit margins. Incentives including tax credits may encourage manufacturers to resume the production of low profit margin drug products like generic drugs, or drugs which lack the economies of scales in their production.

Disruptions of the supply of raw materials are also frequently responsible for drug shortages. This problem will have an increasing impact when a single supplier is monopolizing the raw materials sourcing. This might even force the manufacturer to take the decision to discontinue production (Fox et al., 2009). Raw material importation from other countries may be affected by natural disasters. Trade disputes and political instabilities including armed conflicts and political upheaval can also influence raw material supply (Ventola, 2011).

Suboptimal quality of raw materials is a major concern and accounts for 50% of all causes of raw material shortages (FDA, 2013). This was the leading cause of the Chinese active pharmaceutical ingredients (APIs) shrinkage by 50% in 2010, according to FDA. Current Shortages may result from impurities, microbial and chemical contamination. Botanical sources of raw material may get contaminated or can be influenced by climatic changes. Likewise, animal sources may be affected by diseases resulting in impaired raw material sourcing (Kaakeh et al., 2011).

H2: The more manufacturing-related constraints, the more drug shortages

3.2.3 The Effect of Distribution Factors on Drug Shortages

Manufacturer's distribution can be restricted by inventory practices of health care facilities, such as just-in-time inventory, which may result in little or no inventory cushion at the health care provider to address the threat of short-term shortages (Fox et al., 2009). Other practices including depending on sole source and forcing bundled purchasing may also lead to shortages. In addition, the nature of contractual agreements with different entities at the

local, regional, and global levels (e.g. Group Purchasing Organization) may influence drug distribution systems and consequently affect drug availability (ASHP, 2010).

Poor communication can take place here as well, in cases where systems for product allocation might suffer from inability to address shortage problems due to the lack of reliable information on resumed product availability (Senators & Robert, 2011).

Once the product gets into the wholesale distribution channel, the manufacturer loses control and they lack the ability to track product and consequently allocate the available supply to fill the gaps (Verrastro, 2012). Manufacturers from their side may contribute to medication shortages due to adopting certain practices that allow them to retain control over the market such as holding back supplies and stopping shipments of products when they meets their sales quota and consequently disrupt medication distribution channels (ASHP, 2010).

Unclear medications procurement procedures and protocols is another system limitation, which may contribute to medication shortages, such as the inability to set clear criteria to determine competitive pricing procedures, which would facilitate establishing multiple contracts for a specific product to eliminate the influence of a primary supplier (ASHP, 2010). Other concerns include the presence of grey market (i.e., distribution channels other than those authorized by the manufacturer) and price escalations for products in short supply (ISMP, 2011).

H3: The more distribution constraints, the more drug shortages

3.2.4 The Effect of Supply and Demand Imbalance on Drug Shortages

Occasionally, the demand for a drug can surpass supply beyond expectations or production capacity due to variety of reasons ranging from new clinical practices, unexpected demands due pandemic diseases, natural disasters, political instability, business decisions, or interruptions of raw material and finished product supply (ASHP, 2010; Gu et al., 2011). Unpredictable factors that may lead to a sudden increase in demand and consequently drug shortages include: new indication approval for an existing drug product, therapeutic guidelines modifications, epidemic conditions or spread of diseases (Fox et al., 2009). Unexpected demand due disease outbreak may quickly disrupt the regular supply chain (Nakamura & Stein, 2011). Natural disasters such as fires, hurricanes, tornadoes, and floods can cause major damage and whole product manufacturing disruption as happened in Puerto Rico (Jensen et al., 2002), resulting in production disruptions (Thompson, 2011). Other natural disasters may contribute to the problem by creating unexpected demand for drugs needed by the disaster victims (Ventola, 2011).

H4: The more supply and demand imbalance, the more drug shortages

3.2.5 The Effect of Human Factors on Drug Shortages

Labor Disruptions are considered among the factors that contribute to the problem of medication shortages by affecting the productivity of the manufacturing sector negatively (Gu et al., 2011).

Lack of communication and advance warning system may increase frustrations with drug companies that fail to disclose the cause and the duration medications shortages (ISMP, 2010). One step toward reducing the tension and the dissatisfaction of health care providers is by understanding the reasons behind drug shortages, the role each discipline has in managing shortages, and establishment of an effective method of communication between disciplines (Gulbis et al., 2013). However, lack of collaboration and employee involvement difficulties may impede such efforts. Trust is essential to create healthy relations among managers and employees engaged at different levels of the supply chain. As shortages start to occur, it can be highly frustrating and influences the satisfaction of health care providers due to frequent stock depletion of critical drugs, and the need to scramble to find, prepare and use the appropriate substitute (Briggs et al., 2003; Campbell et al., 2011; Marvin et al., 2013). Frustration is not the only emotional consequence of lack of cooperation and human integration, but it also may lead to anger, anxiety and mistrust between manufacturers, pharmacies, prescribers, patients and providers (Mayer, 2012).

Additionally, lack of skilled labor in terms of knowledge and training in placing orders, inventory management, using electronic systems may contribute to drug shortages. Moreover, Patient behavior such as tending to accumulating medication and dispense same medication from multiple sources, or due to lack of knowledge or fear of shortages may affect medication shortages. Likewise, Physician knowledge and lack of good practice guidelines including the lack of knowledge about medication alternatives, formulary, and lack of treatment guidelines may also increase drug shortages.

H5: The more human factor constraints, the more drug shortages

4. Methodology

4.1 Data Collection

A total number of 400 questionnaires were hand distributed randomly to a sample of professionals carefully selected to

represent the aforementioned nodes of the pharmaceutical supply chain in Jordan. Stratified random sampling was used, as differentiated information is needed regarding different strata perspectives within the population. The population for this study represented all employees with responsibilities related to drug supply chain in Jordan. Respondents were selected from 1) the regulatory body represented by Jordan Food and Drug Administration (JFDA); 2) government entities including the Jordanian Ministry of Health; 3) professional unions, including the Medical Doctors Association and the Pharmaceutical Association; 4) the Jordanian pharmaceutical manufacturing sector; 5) the suppliers, including drug distributors and stores as well as the regional offices of multinational companies in Jordan; and 6) the customers, represented by public and private sector hospitals.

First, all permissions were sought from the selected sites to be surveyed. Then the questionnaire was distributed to the selected sample personally and in some cases by e-mail. An explanation of the implication of each question was provided. Some respondents refused to fill out the questionnaire in the presence of the authors due to time limitations. In such cases the questionnaire was left for a period of time, usually one week. Respondents were asked to read and follow the instructions mentioned on each question carefully. They also were advised not to read all items at once, instead they were advised to answer each question then move to the next. Confidentiality was assured to all participants. Respondents were selected if they met at least three out of four of the following criteria 1) main health care decision makers, 2) possess considerable knowledge about medication supply chain in Jordan, 3) have spent at least one year in his or her position, and 4) represent one of different nodes in the pharmaceutical supply chain.

Two hundred and thirty two professionals of those surveyed responded and provided data. Eleven responses missing basic information regarding the type of the institution, job title, or years of experience were excluded. A total of two hundred and twenty one questionnaires were used for subsequent data analysis. The total response rate was approximately 55.25%. Primary data collection and interviews were performed over a period of one month starting from April, 2014. The cross-sectional study questionnaire was distributed over a period of three months, starting from June, 2014, and ending on September, 2014. Sampling time included the time for obtaining the approval and expert panel revisions at the hospitals surveyed.

The final sample was represented as follows: JFDA accounted for 20.4% of total respondents, the manufacturing sector accounted for 23.3%, hospital professionals accounted for 23.1%, professional unions accounted for 12.4%, suppliers and distributors accounted for 11.2%, and customers accounted for 9.6%.

4.2 Structure of the Questionnaire

The questionnaire development process began with interviews with some key players in the pharmaceutical supply chain and a review of the literature (including primary research, reviews, and government publications) on the causes of drug shortages. As a result, the questionnaire was structured with two main sections; section one included demographic data including the institution type, job title, professional rank, and years of experience. Section two included question items related to the five causes of drug shortages as well as to the construct representing drug shortages. Respondents were asked to indicate their agreements or disagreements with statements provided based on 5 point Likert scale.

A total of 11 question items were adapted from the literature to measure regulatory and legislative processes construct (Gu et al, 2011; ASHP, 2010; Ventola, 2011; Fox et al, 2009; Shah, 2004; McKenna, 2011). A total of 20 items were adapted from the literature to measure the construct of manufacturing-related issues (Fox et al., 2009; ISPE, 2013). For distribution factors construct, 18 items were adapted from the literature (Ventola, 2011; Fox et al, 2009; ASHP, 2010; ISPE, 2013). A total of 6 question items were adapted for the supply and demand imbalance construct (Thompson, 2011; Ventola, 2011). To measure human factor construct, 5 question items were developed by the researchers. Finally, drug shortages construct consisted of 8 question items adapted from the literature (Ventola, 2011; Fox et al., 2009; ASHP, 2010; ISPE, 2013). The full questionnaire is available from the authors upon request.

4.3 Research Validity

Validity tests are used to test the goodness of a concept measurement or method (Sekeran & Bougie, 2010). For the purposes of this research, face validity, content validity, and construct validity were tested.

Face Validity is defined as the ability of the instrument, subjectively viewed by experts, to measure what it is suggested to measure (Sekaran & Bougie, 2010). Initially, the questionnaire was judged by four unbiased experts in supply chain in order to assess the relevance and suitability of the questions proposed in this survey. Subsequently, the survey instrument was pilot tested with 20 professionals from the different nodes of the medication supply chain using in depth interviews and cognitive feedback. In addition, these professionals were asked to complete the questionnaire and comment on the different scales used, assess the easiness and the clarity of the questions, and evaluate if the questionnaire is user friendly. Based on this two-tier assessment, the necessary corrections, adjustments and modifications were implemented to the questionnaires to improve face validity and minimize the survey completion time.

Content validity is concerned with ensuring the adequacy of an instrument to conclusively cover the concept (Sekaran & Bougie, 2010), and is tested by examining the fit between the content of the instrument and the literature reviewed on the topic (causes of drug shortages). The fit between drug shortages causes identified through reviewing the literature and the ones included in the instrument were assessed. Different search terms (medications shortages causes, drug products shortages, drug shortages effect, medications unavailability) were used to identify drug shortage factors in the related peer-reviewed literature, which were categorized into five major groups, under which numerous sub factors can be grouped. These five major categories were considered to encompass the leading causes of drug shortages. Content validity was based on the assumption that the more comprehensive inclusion of drug shortages causes, the better the ability of the instrument to measure the causes of drug shortages. Additionally, the questionnaire was reviewed by five professors in Business Administration and was revised as needed.

Construct validity measures how well the instrument design is tapping the concept of concern as theorized (Sekaran & Bougie, 2010). For the purposes of this research, construct validity was established through Exploratory Factor Analysis (EFA) using Varimax rotation with principal components method. We ensured that all items related to each construct loaded onto the factor representing that construct with eigenvalue greater than 1 and factor loadings greater than 0.45 (Hair et al, 2010). To assure the appropriateness of the factor analysis, Kaiser-Meyer-Olkin (KMO) test for assessing sampling adequacy and Bartlett's test of sphericity to test for homogeneity of variances were performed for the measurement scales (Hair et al., 2010). The results of KMO test showed that the statistics for all the scales were greater than 0.50, and Bartlett's test of sphericity showed significant statistics for all the scales ($p < 0.05$) indicating that factor analysis was appropriate. Nineteen question items did not meet the adopted criteria and were deleted. The EFA results are available from the authors upon request.

4.4 Reliability Test

The reliability of the measurement scales was tested using Cronbach's alpha coefficient. The closer Cronbach's alpha is to 1.0, the better the consistency of the items in the scale and the more reliable the questionnaire (Gliem, & Gliem, 2003; Sekaran & Bougie, 2010). The recommended minimum acceptable limit of Cronbach's alpha is 0.70 (Hair et al., 2010). Values of alpha for all the research constructs exceeded 0.70 indicating high internal consistency as shown in Table 1 which reports mean values and standard deviations of the study constructs as well.

Table 1. Means, standard deviations, and cronbach's α-coefficient

Variable	Mean	S.D.	Cronbach's alpha
Regulatory and legislative processes	3.23	0.737	0.821
Manufacturing-related issues	2.79	0.788	0.946
Distribution factors	3.06	0.967	0.822
Supply and demand imbalance	3.50	1.107	0.820
Human factors	3.76	1.299	0.720
Drug shortages	3.65	1.523	0.752

5. Results

To test the study hypotheses, multiple-regression analysis was applied. Normality of data is a prerequisite for regression analysis. We used Skewness and kurtosis tests to check the normality of the data. The values for skewness ranged between -0.177 and -0.485, while the values for kurtosis ranged between 0.090 and 0.267 indicating that the data are normally distributed and suitable for multiple regression analysis (Hair et al., 2010).

An inherent problem associated with multiple regression analysis is multicollinearity which is caused due to high correlations among independent variables and leads to unreliable results of regression analysis (Hair et al., 2010). A widely used technique to test for multicollinearity is variance inflation factor (VIF). The results showed that VIF values for the independent variables did not exceed 1.329 indicating that the results were not affected by this problem.

The independent variables were entered into the regression model with drug shortages as a dependent variable. The results of the multiple regression are reported in Table 2. The value of R of 0.525 indicates high correlation between the independent variables and the independent variable. Coefficient of determination, R^2, shows that 27.6% of the variance in drug shortage is explained by the five causes included in our model. The adjusted R^2 of 0.267 indicates that the R^2 is slightly decreased due to the number of independent variables and the sample size. The F-value of 30.576 is highly significant ($P < 0.001$) indicating that there is a significant effect of the five causes taken together on drug shortages in Jordan.

As for the effect of the individual causes, regulatory and legislative processes showed the highest significant effect on drug shortages; therefore hypothesis H1 was supported.

Distribution factors and human factors were also highly and significantly related to drug shortages in Jordan. Additionally supply and demand imbalance showed significant effect on drug shortages. Therefore, hypotheses H3, H4, and H5 were also supported.

Manufacturing-related issues did not show significant effect on drug shortages (β = 0. 0.056; $p > 0.05$), therefore hypothesis H2 was rejected.

The results indicate that the more or higher the causes of drug shortages, the more or higher the drug shortages in Jordan. As for the relative importance of the four causes on drug shortages, regulatory and legislative processes showed the highest effect ($\beta = 0.269$; $p < 0.001$), followed by distribution factors ($\beta = 0.221$; $p < 0.001$). Next was human factors ($\beta = 0.149$; $p < 0.01$), and lastly supply and demand imbalance ($\beta = 0.106$; $p < 0.05$).

Table 2. Multiple-regression analysis of drug shortages

Variables	Model Coefficients	*t*-value	*p*-value
(Constant)	0.900		0.000
Regulatory and legislative processes	0.269	5.533	0.000
Manufacturing-related issues	0.056	1.184	0.237
Distribution factors	0.221	4.506	0.000
Supply and demand imbalance	0.106	2.183	0.030
Human factors	0.149	3.230	0.001
R	0.525		
R^2	0.276		
Adj. R^2	0.267		
F	30.576		0.000

6. Conclusions and Implications

6.1 Conclusions

Medication shortages remain a persistent problem worldwide, which poses a significant threat to patients' care process quality including patient's safety threats, economic pressure and extra expenditures of health care facilities to address shortages. Such situation may lead to frustration among the different health care providers.

Although previous studies have provided an insight about the size and the impact of the problem on the health care system worldwide, this problem was never addressed in Jordan. Addressing the causes of medication shortages have special importance as an essential and maybe solely way to control the situation by developing a better understanding of it. This research extended the scope of shortage causes to include a new category addressing human factor or behavior as a contributing factor to medications shortages. Other factors causing medication shortages were adapted from the literature and included regulatory and legislative processes, manufacturing-related issues, distribution factors, and supply and demand imbalance.

The findings from this research identified main causes for drug shortages in Jordan. Regulatory and legislative processes were found the most contributing cause to medical shortages. Issues within this factor include lack of coordination in controlling inventory between central medical stores, regional medical stores and health facilities especially in the public sector. Also, it includes unfair pricing parameters, lengthy new drug approval process, and lack of automation in inventory control in the regional medical stores and health care facilities stores in both the public and private sectors.

Distribution factor was also identified as a contributor to the medication shortages. Some related issues associated with the distribution factor include depending on a sole supplier monopolizing supply, poor communication between central supply store and regional supply stores and hospital, Poor ordering practices, hoarding caused by rumors of an impending shortage, and unexpected delivery delays that may affect inventory level.

Human factor was also perceived as a significant contributing factor to medication shortages in Jordan. This factor includes patient behavior and their tendency to accumulate medications and to dispense medications from multiple sources. Additionally, Physician knowledge and lack of good practice guidelines including the lack of knowledge about medication alternatives, formulary, and lack of treatment guidelines contribute to the human factor effect on medication

shortages in Jordan. Moreover, human-related constraints such as lack of skilled labor, lack of knowledge and training in placing orders, inventory management, and using electronic systems explain the high effect of human behavior on medication shortages.

Supply and demand imbalance was also found as a significant factor contributing to medication shortages. This could be explained by Interruption of raw material and finished product supply, Pandemic diseases leading to unexpected demand, new clinical practices such as new indication for using a drug, and political instability in the region that contributes to increased demand.

Manufacturing-related issues were not significantly related to medication shortages in Jordan. This result could be justified by at least two reasons. First, pharmaceutical manufacturing companies do not distribute medications directly to hospitals and health care facilities. They rather outsource this function to specialized distributors. Second, raw materials are mainly purchased from international suppliers in sufficient quantities and reliable deliveries. Substitutes of the raw materials can be easily found in the international markets with prompt delivery if needed.

6.2 Implications and Recommendations

Based on the results of this research, a number of implications and recommendations for decision makers, and professionals are proposed:

Establish a national reporting system of medication shortages. The Jordan Food and Drug Administration (JFDA), in collaboration with professional associations, should encourage health care providers including physicians and pharmacists to report product shortages to the JFDA, which should provide special education and training on how to do this reporting.

The JFDA as a statuary body should enforce the establishment of a national notification system of drug shortages. All stakeholders including the JFDA, manufacturers, wholesalers, joint procurement departments (JPD), hospitals, and health care providers should have formal communication channels regarding such drug shortages, including advanced notifications about expected future shortages.

Manufacturers, especially generic products manufacturers, should increase their share of the national market rather than focus on exportation, and accordingly develop mechanisms to improve their forecasting of local demand for their products. They should also develop strategies to enhance stakeholder's awareness about their capacities.

The JFDA, wholesalers, and distributors should conduct proactive analyses of foreign markets drug products in order to enhance the ability to anticipate product shortages from foreign sources.

Automation of inventory management using special software and centralized databases, especially in regional and institutional warehouses of the Ministry of Health, and oversight of the central warehouses over the regional outlets is houses.

Increasing inventory levels of medically necessary products is essential. This should be done throughout the supply chain by all stakeholders.

The automation of medications dispensing systems at public and private sector health care facilities to minimize waste and ensure patient safety.

Develop a work plan to increase cooperation between the public and the private sectors to enhance drug availability by integrating public and private distribution channels.

Apply unified national patient records at all health care facilities in the public and the private sectors using the unique national number to prevent patient accumulation of the same medication from multiple sources and accordingly eliminate this type of waste.

Establish guidelines for managing shortages including contingency planning and procedures to identify the available alternatives proactively based on the recommendations of the clinical guidelines for a given indication. This can be enabled by the establishment of a readily accessible centralized source of information on alternatives for specific drugs experiencing shortages.

JFDA and ministry of health in addition to royal health care awareness society, manufacturers, in collaboration with other stakeholders including hospitals, other health care organizations, and professional organizations (e.g., medical specialty societies, pharmacy associations) should educate practitioners, and sometimes patients, on issues related to drug shortages including:

- Establish group societies to raise awareness on rationale drug use among consumers and patients, as a part of public education campaign, to correct their behavior toward medication including their tendency to dispense medications and accumulate them to minimize waste and consequently medications expenditures, patient safety,

and possibly their satisfaction with health care provided when they learn about their medications alternatives.

- Raise awareness of health care providers on using generics as the best alternative with similar efficacy of the originators through conducting seminars and developing supporting brochures.

6.3 Research Limitations

Although this research provided a closer look at the contributions of the different nodes of the pharmaceutical supply chain in Jordan, it has some limitations. For example, the response rate was relatively low especially from the pharmacists within the sample. The survey was only distributed to the manufacturers who agreed to participate in the study and the number of respondents working at these facilities was controlled by the administration. Finally, the list of shortages from the joint procurement department, supply and purchasing department and hospitals systems were not available or not accessible.

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