United States Drug Crises: Why Are There So Many Drug Shortages?

A Stakeholder Analysis

By Toni Schmittling CRNA, MBA

April 2016

Presented to the Faculty at the University of Michigan-Flint

In partial fulfillment of the requirements for the

Doctor of Anesthesia Practice Program

(Winter/2016)

Primary Advisor/First Reader:

Name: Yener Kandogan, Ph.D

Signature _____ Date 4/26/2016

Second Reader:

Name: Jane Motz, CRNA, DrAP

Signature _____ Date 4/26/2016

Table of Contents

Abstract

Purpose: The purpose of this capstone project is to explain from a market perspective the reasons for drug shortages that anesthesia, as well as the overall medical community, are experiencing. This capstone project will increase the anesthesia profession's awareness of root causes of sterile injectable drug shortages. The project will provide the anesthesia community with an understanding of the breadth of the problem, the underlying economical motivations, and the various stakeholders' positions.

Methods: Stakeholder analysis and pharmaceutical market evaluation were conducted by examination of current literature, white papers, subject-matter expert interviews, and government agency reports. Information collected is analyzed using economic market theories, carefully aggregated/categorized to develop a clear understanding of the current drug shortage crisis.

Results: Key stakeholders, drug manufacturers, government agencies' regulations, group purchasing organizations (GPOs), and raw material suppliers are cited most often as a "Primary Effects" or a root cause of the sterile injectable drug shortages. The "Secondary Effects" category does not cause drug shortages; they exacerbate existing shortages. Drug manufactures, healthcare facilities, and wholesaler distributors were implicated in the "Secondary Effects" category. Eight of the nine stakeholders were linked to "Safety Issues" related to drug shortages. Five stakeholders contributed to a category that addressed "Consequences of Drug Shortages". While these consequences do not play a role in the root cause of drug shortages, they have a significant effect on stakeholders and the market environment.

Conclusions: The sterile generic pharmaceutical market shortages are unlikely to equilibrate on their own. Complicated relationships among stakeholders and non-market issues impede the generic market from self-correcting. Therefore, some form of intervention is needed to resolve the shortages. Options will need to be carefully analyzed to avoid further market disruptions, as previous well-intended interventions to correct the market had unintended consequences.

Data Sources: Google Search, Google Scholar, PubMed, Government Archives, ProQuest Business, and Government Web Sites

Keywords: Drug shortages, anesthetic drug shortages, drug shortage causation, market failure, drug shortage explanations

Introduction and Background

The FDA defines drug shortage as "a situation in which the total supply of all versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level."[1] Over the past decade, the United States (U.S) has experienced a dramatic increase in the number of prescription drugs that have become inaccessible to the public. The crisis reached its peak in 2011 with 250 prescription drugs (hereafter drugs) on the shortage list; this is over four times the amount that was recorded in 2005 when there were 61 documented shortages.[2] Due to the escalating nature of the crisis and the detrimental impact on society as a whole, President Obama issued an executive order directing the Food and Drug Administration (FDA) to expand reporting of the potential shortages of certain drugs. Additionally, the executive order requires the FDA to expand its efforts for an expedited review of new manufacturing sites, new drug suppliers, and manufacturing changes to help prevent future drug shortages.[3]

The drug shortage has negatively impacted the healthcare community. From January 1, 2010 to August 26, 2011 the FDA tracked drug shortages. Of the 127 drugs tracked, 118 of those shortages, 93 percent, which were categorized as "medically-necessary".[1,4,5] A medically necessary drug product is a drug that is used to treat or prevent a serious disease or medical condition for which there is no alternative drug available in adequate supply, and which is determined by the medical staff to be an adequate substitute.[6] Currently, shortages are heavily concentrated in the area of sterile injectables (73%) cancer drugs, anesthetic used for surgery, emergency medicine, and electrolytes.[7-10]

The U. S. economy is based on a market system. Supply and demand is the driving force behind a pure market economy and government involvement (regulation) is generally minimal to nonexistent. Occasionally, government plays a part in influencing the market process.[7]

Generally, Prices in the market change to keep the quantity supplied and quantity demanded equal overtime. Prolonged shortages and surpluses are uncommon in most markets. In functioning and unrestricted markets, basic economic theory states that prices will fluctuate depending on supply and demand. In this capstone study, "market" here after refers to the pharmaceutical market.

The basic premise of supply and demand market forces is that if there is a shortage the natural tendency of market prices is to rise. The opposite occurs with a surplus, as market prices are expected to fall. The interaction of market supply and demand thus determines the competitive price at which there would be no long-term shortages or surpluses of goods. This is referred to as price equilibrium and market forces are in balance. [7] Once equilibrium is reached, there is no tendency for prices to rise or to fall. The equilibrium price equates quantity demanded with quantity supplied.[7]

The drug shortage is generally characterized as a supply-side issue.[8,9] There is not a sufficient supply of particular types (for example, sterile injectable generics) of drugs available to satisfy the demand for those drugs. The law of supply states that there is a direct positive relationship between the price of goods and the amount of those goods manufactures are willing to produce.[10] The price and the quantity supplied will move in the same direction. If the price increases, then it can be expected that quantity supplied will increase. In contrast, as prices fall, the quantities manufactures are willing to produce will decrease and subsequently the supply will be less.[10] If the price is too low, the quantity demanded by the consumers will exceed the quantity supplied.[10] In other words, this would cause a shortage of those goods.

Unlike other goods, pharmaceutical drug sales are affected by unique non-market factors such as government regulations, insurance coverage, and patent protection. These external

factors influence the supply and demand in the pharmaceutical market and they cause atypical results when compared to other markets.

Price elasticity is another factor that affects supply and demand. Price elasticity of demand indicates how responsive consumers are to changes in the price of the product. As a rule, the prices of non-essential goods are usually elastic and demand fluctuates significantly in response to price changes. The demand for most necessities, such as medications, is relatively inelastic and demand does not change significantly with price variations. The most important determinant of the price elasticity of demand is the availability of substitutes. When good substitutes (i.e. competitive products) are available for a particular drug a price increase will cause consumers to switch to other substitutes and demand would be more elastic.[10] This market reaction is especially true for pharmaceuticals.

Healthcare facilities have been affected by the drug shortages on multiple fronts. The financial impact, compounded by the detrimental health effects to patients, has the healthcare system reeling. The drug shortages have spiraled out of control and have had significant negative effects on healthcare facilities and patients. The drug shortage impacts on patients are numerous and not likely to change in the near future. When first-line drugs are in short supply, physicians are often confronted with limited treatment options since many drugs do not have suitable substitutes. For example, Cytarabine is the only known drug used to treat acute myelogenous leukemia (AML).[11] AML is a fast spreading cancer that can terminate a patient's life within three months if not treated. Without Cytarabine, the survival rate of AML is zero.[11] Problems also occur with the increased use of alternative drugs as replacement for the original, which creates an increase in demand for the substitute. Subsequently, increases in demand result

in shortages of substitute drugs.[8] This self-perpetuating cycle serves to exacerbate the drug shortage crises.

Problem Statement

The drug shortages are not resolving on their own and there is no indication that the pharmaceutical market will naturally equilibrate in the near future. The major shortages are concentrated on sterile generic injectable medications that have been around for decades and are used every day in the medical community. The questions to be answered are: Why are there so many drug shortages? How do drug shortages occur and why has the sterile generic pharmaceutical market not adjusted? When can the medical community expect some relief from the persistent drug shortages?

Aims and Objectives

Aims: The aim of this paper is to propose a comprehensive explanation of the drug shortages, safety factors and associated consequences of the drug shortages. This information will be compiled and evaluated formulating a clearer understanding of the drug shortages. Why do drug shortages occur? How do drug shortages occur? What are the repercussions of drug shortages?

Objectives: Stakeholders' interest and position are presented and compared to well-established economic theories in order to develop a comprehensive overview of potential causes and consequences of the drug shortages. Market factors that contribute or play an essential role in the drug shortages are investigated and explained.

Stakeholder Analysis and Literature Review

This paper explores the underlining reasons that have led to a nationwide drug shortage and focuses on generic sterile injectable drugs since they represent the largest share of current

shortages. It also explores the reasons why the U. S. pharmaceutical market has not self-adjusted. Understanding the key stakeholders' interests and positions is essential for analysis of the problem. Stakeholders' positions are examined with respect to their association to the current drug shortages.

Stakeholder analysis for this paper is the process of systematically gathering and analyzing qualitative information to determine interests and positions of key stakeholders in relation to the U. S. drug shortages. Key stakeholders are identified in **Figure 1**.

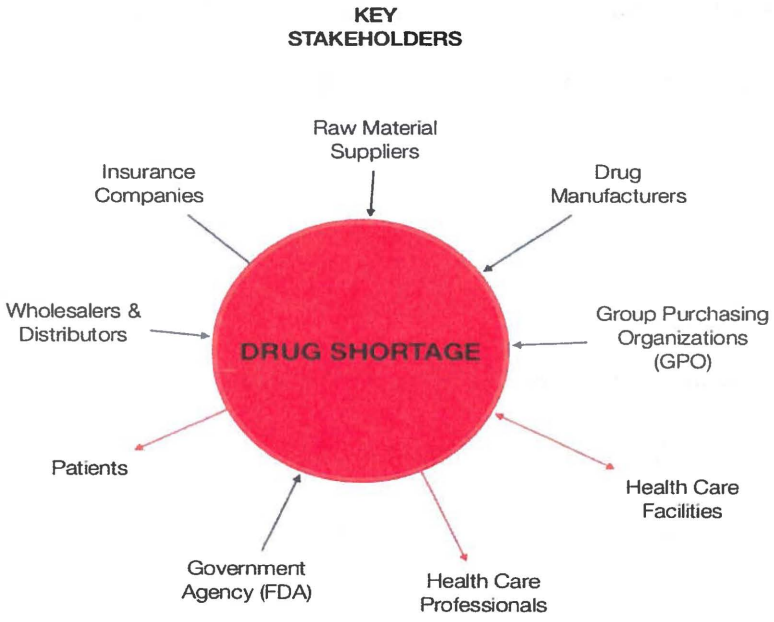


Figure 1. Key Stakeholders.

Drug Manufacturers

The pharmaceutical industry is comprised three main players: brand pharmaceuticals ("Big Pharma"), branded generics and generics. Brand pharmaceutical companies manufacture drugs that have trade names and are protected by patents. Patents allow companies to have exclusive rights for 20 years from the date of filing. However, it usually takes an estimated 7 - 9 years, to get FDA approval, before a drug reaches the market, thus decreasing pharmaceutical

companies' exclusive rights to market a specific drug.[12] After the patent expires, generic drug companies can petition the FDA to make and market a bioequivalent version of the previously protected medication. The generic drug company requests an "abbreviated new drug application" (ANDA). In this application, generic manufacturer must show that the new drug is the bioequivalent of the branded medication that is no longer patent-protected. From 2010-2015, brand pharmaceutical companies faced the largest patent expiration surge in history.[13] This phenomenon is dubbed the "patent cliff".[13] Once a patent expires, a drug's price can drop up to 90%.[13] A branded generic drug is the bioequivalent to the original but is now marketed by the original company's brand name or another company's brand name. The branded generic is priced higher than the unbranded generic but less than the previously patent protected brand drug.

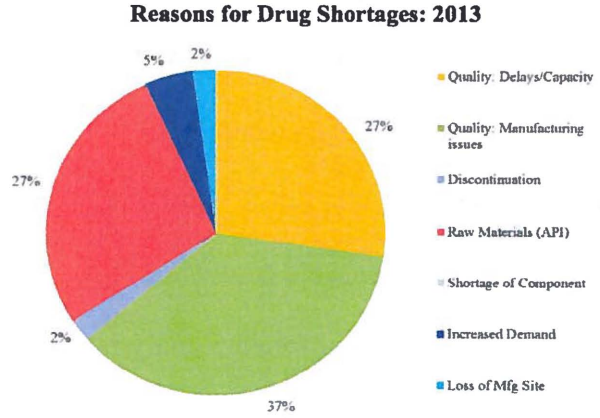
In past years, the pharmaceutical and vaccine markets have had sporadic shortages of individual drugs and intermittent shortages of several drugs belonging to a specific class.[14] Brand pharmaceuticals (patent protected drugs) account for 11% of drug shortages, with generic drugs (no patent or exclusivity) representing 83% of 2011 shortages.[15] The recent drug shortages, however, have been sustained and concentrated in the generic sterile injectable market.[14-17] According to the FDA in 2013, 80% of the drug shortages were confined to generic sterile injectable drugs.[18-20] In 2011, the IMS Institute for Healthcare Informatics analysis uncovered shortages of drugs: prior to the 1970s – 30 drugs; in the1980s – 58 drugs; in the 1990s – 37 drugs; in the 2000s – 38 drugs and in 2010 – 4 drugs.[15] The shortages tend to be older, less expensive generic drugs with 75% being introduced before 2000. Drug products that remain on the shortage list are concentrated in five areas: oncology, cardiovascular, central nervous system, anti-infectives, and pain.[15] Healthcare specialties of oncology, anesthesia, and emergency

medicine have been hit the hardest.[14,21,22] Intravenous electrolyte solution (.9 normal saline) shortages have affected all specialties across the board. Researchers at the IMS found that half of the generic injectable drugs in the United States were reported on the shortage list.[15,16,21,

Quality and manufacturing problems have been linked to the majority (64%) of the shortages of sterile injectable drugs.[18,23] A FDA "Drug Information Specialist" stated in an email correspondence:

> All sterile generic injectable drugs are not manufactured in the United States, some of these are manufactured overseas. I do not have specific percentages that are manufactured outside of the United States. Six manufacturers make up most of the market. These firms may do contract manufacturing as well as manufacture their own products[24]

Not all production disruptions result in shortages; however, all shortages are preceded by disruptions in manufacturing.[25] The chart below provides reasons for sterile injectable shortages:



source: FDA

Figure 2. Reasons for Drug Shortages: 2013

The generic drugs in the U. S. have very low profit margins.[20,26] These drug shortages are likely related to decreased incentives for the manufacturers to produce off-patent medications.[8] It has been suggested that the primary cause of generic injectable drug shortages is the lack of financial incentives for the industry to invest in updating manufacturing facilities and

to provide quality control systems.[25] Since profit margins are so low, manufacturers attempt to produce drugs as inexpensively as possible by using older and less efficient facilities that have antiquated equipment.[27] It has been proposed that shortages in the sterile generic industry are a consequence of extensive expansion in scope and volume of products without a corresponding expansion in manufacturing capacity.[28,21] Without expanding capacity, new more profitable opportunities force difficult business decisions resulting in a discontinuation or decreased production of the older and less profitable drugs.[21]

Biologic medications being replaced by biosimilars are examples of new opportunities. Biologic drugs comprise 22% of brand pharmaceutical drug sales and it is predicted to grow to 32% by 2023.[29] Biologics (large molecule products) are complex medications made of or extracted from living cells, blood components, and tissue. These medications treat life-threatening illness such as multiple sclerosis, anemia, hemophilia, cancer, diabetes, HIV, and rheumatoid arthritis. The FDA's definition of biologics is:

> Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.[30]

In the U.S., biologics had little competition until the Biologics Price Competition and Innovation Act (BPCIA) was included in the Affordable Care Act (ACA).[31] An interchangeable biological product is considered a biosimilar. Biosimilars are a relative new opportunity within the U.S. drug market. By the year 2020, it is projected that biologics will lose $100 billion in sales as patent protection expires and new biosimilars enter the market.[32]

The FDA defines biosimilars as:

> A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. [33]

The global biosimilar market is projected to be $20 billion by 2020.[34]

European countries have been using biosimilars since October 30, 2006. Biosimilars are not generics. Biosimilars must complete an extensive clinical comparability trial and are more costly to manufacture than other drugs.[35] For example, Zarxio is the biosimilar to Neupogen, which improves white blood counts to fight infections.[36] On September 3, 2015, Zarxio was the first biosimilar to appear on the U.S. market.[36]

The "patent cliff" increases the number of drugs available to the generic market.[13,37] Low profit margins of the older generic drugs have caused many drug companies to shift resources to higher profitable brand generics or new drugs that have recently come off patent. Another business strategy has been the development of "super generics". Super generics are generic drugs that are improved by manufacturers. These improvements may be due to the method of delivery, manufacturing processes, and/or reformulation technology. The super generic drugs enjoy a significant price premium.[26]

Many manufacturers produce low profit generic drugs in order to win group-purchasing contracts.[38] It is not a profitable endeavor; however, it allows the manufacturer to get their "foot in the door" in hopes of increasing the sales of pharmaceuticals that are more profitable. Manufacturers may view some generics as " loss leaders" and the cost of doing business.[20,38] A loss leader is a product that is sold at a loss to attract business.[39]

The trend of consolidation in the drug manufacturing industry has significantly decreased the number of players in the field.[1,17,19,20] The industry is concentrated with only six to seven main players making up 85-90% of the market.[19,40] According to the FDA, the top three manufacturers accounted for 71 percent of generic injectable drug sales in 2010.[21,41] In most cases, three or fewer manufactures supply a specific generic injectable drug.[14,15,19,20] The IMS Institute for Healthcare Informatics reported that in 2011, 168 products on the shortage list had no suppliers, 56 had one supplier and 23 had two suppliers.[15] This is partly due to company mergers which affect production capabilities if decisions are made to discontinue products and/or narrow product lines. The decrease in the number of manufacturers makes the market susceptible to drug shortages if there are any disruptions in production by the remaining manufacturers.

The generic pharmaceutical industry continues to consolidate with mergers and acquisitions. In February 2015, Pfizer announced its intention to acquire Hospira. The largest maker of sterile injectables in the world Hospira has two of the four applications for biosimilars pending the FDA's approval.[42] In September 2015, the deal between Pfizer and Hospira was completed. The acquisition of Hospira placed Pfizer in a dominant position in biosimilars. Pfizer stated: "We've created value for our shareholders … expected earnings per share (EPS) to grow… by strengthening our Global Established Pharmaceutical (GEP) business and positioning it for future growth."[43] In November 2016, Pfizer announced that it would buy Dublin-based Allergan with the intention of moving Pfizer's headquarters to Ireland for the purpose of slashing its U.S. tax bill.[44] The merger, barring any divestments, created the world's largest drug maker by annual sales of approximately $60 billion.[44,45]

Market consolidation may cause some drugs to be produced by only one manufacture. This has caused a sudden increase in market activity that has prices of single-supplier drugs skyrocketing. Tetracycline, a drug that entered the market in 1967, has increased in price from November 2013 - November 2014 from $.05 (.048493) per tablet to $ 8.59 per tablet (17,714% price increase).[46,47] Digoxin, a drug that has been used for decades to treat some heart conditions, experienced a price increase in one month from $131 per bottle to $989 per bottle (655% increase).[48] Another, perfect example of this is Duraprim, a 62 year-old drug that is used to treat life threatening parasitic infections (toxoplasmosis and malaria).[49] Turing Pharmaceuticals, a new start-up company, acquired the drug from Impax Laboratories.[50] The CEO, Martin Shkreli a former hedge fund manager, leveraged monopoly power to raise the price overnight from $13.50 to $750 per tablet.[49,50]

Lack of redundant capacity has also been cited in the literature as a problem.[40] This is defined as the availability of another line or facility to produce the same product if disruption of the primary production source should be disabled.[51] For example, some manufacturers operate one to ten facilities, which manufacture several product lines.[28] A specific drug can be produced on one or two of these lines (separate batches), which may continuously produce for hours to weeks.[25] Many facilities operate 24 hours / 7 days per week.[25,21] There are operational costs when switching from one drug to another.[14] Most facilities have been operating since the 1960s with minimal upgrades. From an economic point of view, low profit margins make upgrading aging facilities unattractive.[25] In addition, the manufacturing process for sterile injectable generic drugs is very complex and costly resulting in low profit margins.[1,8,21,40]

The regulatory compliance in the generic pharmaceutical industry has come under scrutiny. Compliance violations, both civil and criminal, have plagued the industry for years.

Current Good Manufacturing Practices (CGMP) are regulations enforced by the U.S. Food and Drug Administration (FDA).[52] The Consumer Protection Branch (CPB) is part of the Department of Justice (DOJ). The CPB enforces civil litigation and criminal prosecutions to protect the public health sector and consumers.[53] The FDA and CPB work closely together with a common goal of protecting the American people. Below are some examples of violations that were discovered by the CPB:[53] Ben Venue 2011 in a civil suit was convicted of 48 compliance violations that resulted in 40 recalls since 2002.[53] SB Pharmco, a subsidiary of GlaxoSmithKline (GSK), in 2010 pled guilty to felony charges related to the manufacture and distribution of adulterated drugs; a criminal offense that carried $750 million in fines.[53] In 2006, a criminal case against Ranbaxy, in which the company pled guilty to four felony counts of making false statements to the FDA, was fined $150 million.[53] Other companies that were indicted in criminal cases that incurred fines were Johnson & Johnson ($1.5 - 2 billion), Merck ($950 million), Eli Lilly ($1.4 billion), Abbott ($1.5 billion), Pfizer ($2.3 billion), and Purdue Pharma ($663 million)[54,55]

The FDA has been as a contributing factor to the drug shortages by holding the drug manufacturing industry accountable for regulatory and quality compliance. This has caused delays, interruptions, and prolonged facility closures.[8] Quality problems in manufacturing are accountable for a majority of the sterile generic drug shortages.[14] Regulatory and quality compliance issues increase the cost of production, forcing manufacturers to make difficult business decisions.[8] In 2011, one key manufacturer, Ben Venue Laboratories, made a business decision not to refurbish its manufacturing facility.[56] Deemed unsustainable for the long term, Ben Venue's management decision was based on the level of financial investment required to guarantee product quality.[56]

Changes in inventory practices can alter the availability of the drug supply. Manufacturers often decrease inventory by following "just-in-time" (JIT) inventory practices, which are meant to optimize cash flow and decrease the carrying cost of inventory.[1,19,21] The perfect JIT system would have zero inventories after meeting all of a company's demand. With JIT, there is a fine line between having too much inventory and not having enough. The "Goldilocks Principle" epitomizes the inventory condition; it needs to be "Just Right". With JIT it is difficult to adjust production volumes on short notice. Unanticipated changes in demand may occur without much advance warning. This leaves the industry vulnerable to interruptions in the flow of raw materials or other supply chain disruptions.[1,19]

In addition, disruptions in the supply of raw materials have been frequently cited as one factor responsible for causing delays in the drug manufacturing process.[8] In 2011, raw material availability was not a major cause of drug shortages with a reported incidence of only 3%.[28,57] However, in 2013, the FDA (Figure 2) noted that the supply of raw material was implicated in drug shortages 27% of the time.[58] Sole-source suppliers are particularly problematic; there may be several producers of specific drugs but only one supplier of the raw materials.[8,59] An interruption in raw material flow affects all manufacturers that require that essential component. Approximately 80% of the drug manufactures raw materials are imported from foreign suppliers.[8,60] This makes U.S. drug manufacturers dependent on the global supply chain and susceptible to economic changes in other countries.[61]

Group Purchasing Organizations

Most hospitals do not purchase drugs directly from manufacturers; they use Group Purchasing Organizations (GPO). GPOs collectively negotiate contracts with manufactures on behalf of their customers (hospitals). Most Hospital purchases (72%) are made through

GPOs[14,62] Consequently, GPOs have a tremendous amount of negotiating power.[14] The first hospital group purchasing organization established was the Hospital Bureau of New York in 1910. GPOs developed slowly and by 1962 there were ten.[63] By 1974, the number of GPOs had increased to 40, propelled by Medicare and Medicaid reimbursement changes.[64] In 1983, a revision to Medicare changed the payment structure from a "fee-for-service" (FFS) payment to a Prospective Payment System (PPS).[64] PPS provides a fixed payment per patient with a given diagnosis. The increased focus on cost stimulated rapid growth for the GPOs and by 2007 there were hundreds of healthcare GPOs. It is estimated that today there are over 600 GPOs.[64-67] The Healthcare Supply Chain Association (HSCA) differentiates GPOs:

> They vary greatly in size, type of ownership and services they offer. Some GPOs are owned by hospitals, while others do not have a link to the facilities they serve. Some GPOs serve non-profit organizations, others serve proprietary facilities and some serve both. Some GPOs offer hospitals the ability to purchase nearly every conceivable product, while others focus on specific products.[64]

The Office of the Assistant Secretary for Planning and Evaluation (ASPE) report states: "The GPO market is relatively concentrated with five GPOs commanding 85-90% of the market".[14,28,68] While another source states that there are seven large national GPOs in the United States.[69] In 2014, the United States Government Accountability Office (GAO) acknowledged that a small number of GPOs dominate the healthcare market.[67] There are also local and regional GPOs. However, their purchase volumes are insignificant compared to national GPOs.[69] Many of the smaller local and regional GPOs are actually members of one of the larger national "parent" GPOs.[70] This explains the large disparity in the reported numbers for GPOs.

Most GPOs charge administrative fees, which are percentages based on the size of the contracts. The drug manufacturers are charged these administration fees. The "pay to play" payment structure would be considered illegal kickbacks by other industries.

Medicare and Medicaid Patient Protection Act (MMPPA) of 1987 provides GPOs with "Safe Harbor Provision" protection from anti-kickback statutes. The MMPPA states:

> GPOs may be allowed to provide goods or services to a hospital or healthcare provider as long as both of the following two standards are met – (1) the GPO must have a written agreement with each hospital or healthcare provider, that provides for either of the following agreement: (a) The vendor from which the hospital or healthcare provider will purchase goods or services will pay a fee to the GPO of 3% or less of the purchase price of the goods or services provided by that vendor, and (b) In the event the fee paid to the GPO is not fixed at 3% or less of the purchase price of the goods or service, the agreement specifies the exact percentage or amount of the fee. (2) The GPO must disclose in writing to the hospital or healthcare provider at least annually, the amount received from each vendor with respect to purchases made by or on behalf of the hospital or healthcare provider.[64]

The GPOs negotiate the lowest possible prices with manufacturers. GPOs then sign long-term contracts with manufactures, locking in prices and restricting any price fluctuations in response to market conditions. "GPOs are a major, if not the primary, contributor to the market distortions in the healthcare industry in the United States" said S. Prakash Sethi, Ph. D. "Through exclusive contracting, which has given GPOs effective control of this industry, they have contributed to product shortages and disincentives for legitimate producers to manufacture and stock essential drugs."[71,19]

Literature varies extensively regarding impact of GPOs on drug shortages. In order for GPOs to secure low prices, a GPO must exercise some measure of monopsony power, which raises competition concerns.[72] An article by Blair and Piette has described GPOs as having monopsony power.[72] Monopsony is defined as a "market in which there are many sellers but

only a single buyer, who thus is able to control the price and availability of the goods offered".[73] When this occurs, one or a few, purchasers have so much power that they can command lower prices.

However, Lindsay writes in her paper regarding anti-trusts, that without a company controlling 35% of the market, monopsony is unlikely.[74] Literature also depicts the GPO industry as oligopolistic.[68,75,76] An oligopoly is defined as "a market structure in which there are only a few firms, each of which is large relative to the total industry".[7] Oligopolistic industries characteristically have three to four companies that control 50% or more of the market.[68] Baye explains in his book on Economics and Business Strategy, that the number of companies required is not exact and an oligopoly typically can occur when there are between two and ten companies.[7] The number of GPOs in the industry is reported to be greater than 600 but only 5-7 firms control 85-90% of the market. Dominance by a few rather than the total number in the industry is the determining factor in an oligopoly.[77] By definition, the GPO market would be considered oligopolistic.

Key characteristics of firms in concentrated markets include interdependence, strategy dependent, and high barriers to entry.[78] The Game Theory is used to model behavior in an oligopolistic environment.[7] In an oligopoly, each player (company) knows that its profit depends on actions of the other players. Collusion is a key characteristic of oligopolies.[78] Players collude so they can enjoy monopoly benefits. In an oligopolistic market firms may attempt to collude instead of compete.[78] When a few firms dominate the market, they can profit by "agreeing" to certain behavior that benefits the colluding companies at the expense of consumers and/or suppliers. Collusion is illegal in the United States. However, forms of collusion that are not

obvious (tacit) are very difficult, if not impossible, to prove. Companies may use nonverbal "signaling" to convey information.

Dr. Sethi in his book "Group Purchasing Organizations: An Undisclosed Scandal in the U.S. Healthcare Industry" states that today most GPOs are privately held for-profit organizations. He further describes how these big corporate giants seem to put the financial interest of their owners above their clients to whom they owe their fiduciary duty.[68] Moreover, private ownership has permitted most GPOs' financial information to be withheld from the public. Sethi also remarked on how the "companies claim to save hundreds of millions of dollars", that he feels, has not been substantiated.[68]

Lawton Robert Burns, Ph.D., MBA, professor at the Wharton School and lead author of a paper prepared for the American Hospital Association (AHA) and the Association for Healthcare Resource and Materials Management (AHRMM) shares a different perspective. "Our study shows that not only do GPOs provide cost savings, but they help hospitals meet their need for physician preference items".[79]

In recent years, GPOs have been the focus of lawsuits from small manufacturers and have come under fire for unfair competitive behavior, which has initiated investigations by Congress (GAO).[75,79,80] The government investigation consisted of four Senate Judiciary Committee Hearings on GPO contracting practices and a succession of GPO performance reviews. The Senate requested that the GAO conduct the performance audits.[79] The critics of the GPO practices demanded the repeal of the safe harbor for the GPOs.[79,81,75]

Premier, a national GPO's, relationship with American Pharmaceutical Partners (APP) came under scrutiny in an article written by the New York Times (NYT). American Pharmaceutical Partners had a national contract with Premier serving 1500 hospitals.[68,82] In

APP's short history, it recalled 20 different drugs, and the FDA has warned the company three times to fix serious quality control problems.[82] Premier had a financial interest in APP's success as a drug company.[82] Premier received a percentage of the money that hospitals spent buying APP's drugs.[68,82] William J. Nydam, received stock options ($1.2 million) as an American Pharmaceutical director during the time he was executive Vice President of Premier.[82] Premier, by promoting the pharmaceutical company as one of its "elite" suppliers, literally turned a non-asset company into one that raised $144 million in its initial public offering.[82]

The NYT reported that Senator Kohl, chairman of the antitrust subcommittee, referred to the incident as "scandalous".[82] The NYT article was released March of 2002 and in April 2002 the Senate held a hearing to review GPO practices. During the hearing Senator Kohl demanded that within 90 days GPOs produce a code of conduct.[83] In response to the GAO investigations, the Healthcare Supply Chain Association (HSCA) made a decision to implement a code of conduct in an attempt at self-regulation. Furthermore, Premier, one of the largest GPOs, adopted additional principles to regulate contracting practices.[79] Critics to self-regulation argued that the code of conduct was voluntary, non-uniform, reversible, non-enforceable and did not carry any penalties for GPOs that were non-compliant.[79] The GAO reported the results of the audits that were performed in 2002 and 2003 and found that prices were not always lower when purchased by the GPO.[75] GPO prices were often higher than when hospitals independently negotiated with venders.[75,84] The latest GAO report (October 2014) looked at the funding structure of the GPOs. The GAO found that the literature and views of experts varied greatly. Consequently, the GAO investigation was inconclusive stating that there is very little empirical evidence available to either support or contradict claims one way or another.[85]

The GAO stated that revoking safe harbor could disrupt the healthcare supply chain in the short-term.[85] However, GPOs and hospitals are likely to adapt to the new market environment in the long-term.[85] It was decided that repealing the safe harbor provision would need further investigation and clearer understanding of the impact of the GPO funding structure and the implications to hospitals.[85]

Healthcare Facilities

The healthcare experts at the University of Pennsylvania-Wharton predict the trend of hospital consolidations will continue at a fast pace, particularly as health systems move more toward Accountable Care Organizations (ACO) in response to the Affordable Care Act (ACA).[86] It is well documented that the ACA has stimulated a wave of hospital consolidations as hospitals band together to gain power in an uncertain economic environment.[86-89] The ACOs tie reimbursement amounts to improvements in quality and reductions in the total cost of care. In order for hospitals to survive in a tough economic environment, there has been an increased number of mergers and acquisitions in attempt to gain market share, to take advantage of economies of scale, to improve leverage with managed care plans, to reduce administrative cost, to improve access to capital, and to limit duplication of clinical programs.[90] Data from the American Hospital Association (AHA) shows the number of hospitals in 1993 was 5,261, and by 2013 the number decreased to 4,974.[91] The biggest decrease was in the rural sector with the loss of 278 hospitals compared to 9 in urban areas.[91] The trend for independent hospitals is to be incorporated into healthcare systems that have an affiliation with academic medical centers.[87]

Similar to drug manufacturers, hospitals cut costs and control cash flow using "just-in-time" inventory practices. This inventory approach has exacerbated the drug shortages for

healthcare facilities because they do not have enough inventories to buffer against the impact of the unexpected interruptions in drug supplies.[8,21,57]

Furthermore, hospitals with good intentions may contribute to the drug shortages by stockpiling drugs that are or are rumored to be in short supply.[92,93] In 2011, a survey from the American Hospital Association indicated that 85% of hospitals purchased excess inventory in response or anticipation to drug shortages.[21,94] Hoarding in anticipation of or during a shortage can exacerbate the shortage and can cause a supply and demand mismatch.[59,92] Some hospitals, due to stockpiling or hoarding of drugs, may have an abundance, while other hospitals are unable to secure enough to fulfill daily requirements. Hospitals that stockpile can cause artificial shortages by draining the supply chain and can exceed manufacturers ability to meet the quantity demanded.[59] Additionally, holding excessive inventory increases hospital costs.[92] With the overstocking of inventory, drugs may expire and hospitals may be forced to discard expired drugs and thereby increase waste.

Unintended consequences may occur when hospitals are desperate to provide drugs that are no longer attainable through their customary supply chain process. In many instances, hospitals turn to compounding pharmacies.[95-97] The FDA defines compounding as "a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient".[98] The FDA states that compounding pharmacies play an important role helping people that have special needs. These needs may be due to an allergy to an inactive ingredient or for a patient that may require a route that is not available, such as in liquid or suppository forms. However, the FDA warns that, "consumers need to be aware that compounded medications are not FDA-approved; this means

that FDA has not verified their quality, safety, and/or effectiveness."[99] Since the drug shortage, a new troublesome trend has emerged as firms with pharmacy licenses are making and distributing drugs outside the traditional compounding boundaries.[99] These operations appear to be acting similar to manufacturers formulating large amounts of injectable drugs that transcend state boundaries.[95,99] In the U.S., it has been reported that there are 7,500 pharmacies that specialize in compounding.[95,100]

Multiple mishaps have been linked to the actions of compounding pharmacies in recent years. In 2012, an outbreak of fungal meningitis was linked to a compounding pharmacy in Massachusetts.[99,101] As of December 2012, tainted steroids were traced to 76 healthcare facilities in 23 states.[102] The steroid contamination at least 39 individuals, and there were 620 cases of meningitis and other illnesses reported.[102] It is estimated that 13,534 patients were exposed to contaminated drugs through epidurals, spinals, peripheral joint injections, or other therapeutic treatments.[103,104] The drug shortage has led to a steady increase in the use of compounding pharmacies.[105] The FDA does not review formulations for compounding and has no control of the quality and consistency of the process.[106]

When drug shortages occur, doctors, pharmacies, and hospitals have to modify therapeutic strategies. When a shortage of a primary drug occurs and if a substitute drug exists, the sudden increased utilization (unexpected demand) of the substitute drug can cause a secondary shortage of that substitute drug.[57,107] This leaves the medical community with limited or nonexistent treatment options.

The drug shortages have been devastating to healthcare facilities. Unexpected shortages and the large economic impact due to unanticipated costs have many hospital systems struggling to provide adequate patient care. The unanticipated shortage leaves little time for adjustments or

alternative plans. Communication is poor and sometimes nonexistent. In many cases, alternatives could have been put in place with prior knowledge of the impending shortages. In addition, a study by clinicians at the University of Michigan Health System (UMHS) found that annual labor cost for managing drug shortages were estimated at $216 million.[108] In addition to the labor cost Premier Healthcare Alliance estimated that acquisition of alternative therapies and more expensive drug substitutes could increase hospital cost $200 million annually.[109] The increased economic burden placed on already strained hospital systems could be disastrous for patients.

Healthcare Professionals

A healthcare professional for the purpose of this paper is described as any person that prescribes, dispenses, procures, or administers drugs in a therapeutic setting. This definition includes physicians, pharmacists, nurses, and other professionals. Each healthcare professional provides essential aspects in the pharmaceutical therapeutic milieu. One purpose unites all healthcare professionals and that is providing the most efficacious medical treatment possible. Drug shortages threaten that universal purpose in several ways. Drug shortages have plagued the medical community for a decade or more. The Institute for Safe Medication Practices (ISMP) surveyed in 2010 more than 1800 healthcare professionals regarding drug shortages[110] The survey responses were:

> Little or no information available about the duration of a drug shortage (85%)
> Lack of advanced warning from manufacturers or FDA to alert practitioners to an impending drug shortage and suggested alternatives (84%)
> Little or no information about the cause of the drug shortage (83%)
> Substantial resources spent investigating the shortage and developing a plan of action (82%)
> Difficulty obtaining a suitable alternative product (80%)
> Experience a significant financial impact (78%)
> Lack of a suitable alternative product (70%)

> Substantial resources spent preparing and/or administering the alternative products (69%)
> Risk of adverse patient outcomes (64%)
> Internal hoarding of medications associated with impending shortages (58%)
> Physician anger towards pharmacists/nurses/hospital in response to a drug shortage (55%).[110]

The survey respondents reported: near misses as approximately 35%; actual errors due to drug shortages were reported at approximately 25%; adverse outcomes varied per healthcare professionals responding to the survey, ranging from 18-33%.[110] In March of 2012, the American Association of Anesthesiologists (ASA) surveyed 3063 anesthesiologists representing 50 states and six nations.[111] Respondents reported that 67% of drug shortages had an impact on their patients with less than an optimal outcome; 52.8% experienced longer OR/recovery times; 27.5% patients complained; 0.2% resulted in patient deaths (6).[111] When respondents were asked what impact drug shortages had on his/her practice, survey results were as follows: 96.3% had to use alternative drugs; 50.2% had to change the procedure in some way; 7.0% had to postpone cases; 4.1% had to cancel cases.[111]

Shortages have forced pharmacists, physicians and nurses in many hospitals to make contingency plans for providing safe, effective therapies when required drugs are not available. Additionally, drug shortages increase the incidence of drug errors.[8,57,59,112] Mishaps and errors occur more frequently due to unfamiliarity with new agents, concentrations, and drug delivery methods.[8,57,112] Even when appropriate substitutes are available, clinicians may not be familiar with dosage conversions and patients may be over or under medicated.[112] Emergencies pose even higher incidences of error due to unfamiliar drugs being utilized in fast-paced crises.[112] Substitute medications can also have safety ramifications due to substitutes being less efficacious and/or increased risk of side effects.[8,110,113,114] Moreover, allocation of scarce resources in the form of rationing have occurred as a result of drug shortages. Physicians, pharmacists, and

clinicians have had to make difficult decisions concerning allocation of scarce resources. Rationing of medication has become a reality.[114,115,116]

There are emotional elements to the drug shortages such as frustration, anger, anxiety, and mistrust.[57,110] Shortages of chemotherapy medications have forced oncologists to make "tragic choices". Dr. Yoram Unguru, an oncologist and faculty member at the Berman Institute of Bioethics at Johns Hopkins University, stated, " It was painful. We kept coming back to wow, we've got that tragic choice: two kids in front of you, you only have enough for one. How do you choose?"[117] Tragic choices are described by Calabresi and Bobbitt:

> Distributions of scarce goods that entail "great suffering or death," Calabresi and Bobbitt explain, "arouse emotions of compassion, outrage, and terror," which reveal conflicts between, on the one hand, the source of the scarcity and the values used to determine the recipients of the scarce good and, on the other hand, "those humanistic moral values which prize life and well-being"[118]

Dr. Kamal Pohar, an urologist at Ohio State University's hospital, said, " I remember driving home, wondering if I was making the right calls for my patients." Dr. Pohar expressed his anxieties to the New York Times, "I can still feel the stress, I've never been faced with this before ".[117] Another doctor at a leading hospital admitted, "We've been forced into what we think is a highly unethical corner,"[117] Drug Shortages are extremely frustrating for everyone involved, pharmacists, physicians, nurses, and patients.[8] Furthermore, professional relationships can be compromised when misdirected frustrations turn to anger.[8]

Government Agencies and Regulations

The Food and Drug Administration (FDA)

The FDA was formed in response to the 1906 Pure Food and Drugs Act. Harvey Washington Wiley was head of the newly founded FDA, which provided unprecedented

protection to consumers at that time.[119] Through the years the FDA changed a great deal. Today's FDA is very complicated compared to its genesis in 1906. The FDA is currently housed within the Department of Health and Human Services (HHS). The HHS includes the Center For Drug Evaluation and Research (CDER) division. Drug shortage issues fall under CDER's jurisdiction.[120,121]

In 1999, CDER developed the Drug Shortage Program (DSP) with the intentions of monitoring and alleviating the impact of drug shortages.[122] The GAO found that until 2011 the FDA did not systematically maintain data on shortages.[123] In 2011, the FDA established a database containing shortage information. However, in 2001 due to an increase in the number of drug shortages (120 new shortages) the University of Utah partnered with the American Society of Health-System Pharmacists to establish the University of Utah's Drug Information Service (UUDIS).[123,124]

In 2012, the Committee on Oversight and Government Reform (HCOGR) presented a report to the House of Representatives entitled "FDA's Contribution to the Drug Shortage Crisis".[125] The report stated there was a dramatic drop in sterile generic drug production since Margaret Hamburg became commissioner.[126] Hamburg promised an aggressive enforcement effort to make sure that stringent manufacturing standards are met.[126] The first year Hamburg was in office warning letters sent to drug manufactures increased 42%.[125,126] The HCOGR alleged that the shortages were largely due to aggressive regulatory actions by the FDA.[125,127] FDA warning letters contained threats of legal action and seizure of products.[128,129] Letters sent out to manufacturers in some cases resulted in the companies halting drug production.[130,125] Four out of five U.S. generic injectable drug manufacturers were essentially required simultaneously to halt production in order to address FDA warnings.[126] The committee reported that FDA

regulatory activity shut down 30% of the total manufacturing capacity of four large producers of generic medications.[125]

Temporary closure of one manufacturing facility can lead to over burdening of other facilities and result in an inability to increase supply to meet the new demand. The HCOGR claimed that FDA warning letters increased 42% (474 to 673) between 2009-2010 and 156% (673 to1720) between 2010-2011.[125] However, this data is somewhat misleading. The statistics the HCOGR quoted is the total number of warning letters sent out from the FDA. The FDA statistics for warning letters exclusively from the CDER (division responsible for drugs) for 2009-2010 increased approximately 53% (112 to 171) and in 2010-2011 warning letters decreased approximately 37% (171 to 108).[128] CDER represented only 25.4% (171 of 673) in 2010 and 6.2% (108 of 1720) in 2011 of the total warning letters sent out by the FDA.[128]

The FDA was quick to refute the HCOGR allegation. Jeanne Ireland, FDA Assistant Commissioner for Legislation, wrote that the FDA was not the root cause of the drug shortage.[131,132] She stated that more than half of all the drug shortages were due to manufacturing quality and production problems.[131,132] FDA violations at the four largest generic injectable drug manufactures included the presence of endotoxins, glass and metal particulates contamination, aseptic manufacturing and crystal formation in injectable solutions.[133] Ireland also pointed out that the largest increase of warning letters in 2011 were sent to the Center for Tobacco Products (1040 of 1720) which accounted for 60% of the total warning letters sent out by the FDA.[128,131,132]

The Deputy Commissioner of the FDA and senior policy advisor to the Centers for Medicare and Medicaid Services, Dr. Scott Gottlieb, testified that outdated policies and inflexibility are major contributors to the drug shortage.[125] Dr. Gottlieb wrote:

> With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. The FDA and the manufacturers often don't understand the drug-production processes well enough to detect the root cause of problems. Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues – and the subsequent regulatory actions taken by FDA to address these problems – were involved in 42% of the drug shortages.[125]

The oversight committee questioned why the FDA mandated practically all of America's main manufactures of sterile generic injectables to upgrade facilities at the same time.[125] The HCOGR alleged that by forcing this remediation the FDA essentially decreased available manufacturing capacity by 30%.[125]

The FDA has limited control over manufacturing; it cannot require a manufacturer to increase capacity, capability, or redundancy.[134] The FDA cannot demand that a manufacturer make a specific drug, maintain a specific drug inventory level, or interfere with business decisions to discontinue specific drug lines.[134] The FDA also lacks the authority to require manufacturers to provide the agency with information about potential or current shortages and must rely on voluntary reporting[135] Furthermore, the FDA lacks the authority to impose penalties on companies that do not submit reports on discontinuations.[135] The FDA must approve all prescriptions drugs sold in the U.S. regardless of where they are manufactured.[136] This is to ensure safety and efficacy requirements. In an interview with Drug Controller General of India, Dr. G N Singh stated: "If I follow US standards, I will have to shut almost all drug facilities"[137] Dr. Singh went on to say, "The FDA may regulate its country, but it can't regulate India on how India has to behave or how to deliver."[138] He added, "We don't recognize and are not bound by what the U.S. is doing and is inspecting,"[138]

On October 31, 2011 President Obama issued an executive order expanding the FDA's influence. As follows:

Executive Order 13588:

Sec. 2. Broader Reporting of Manufacturing Discontinuances. To the extent permitted by law, the FDA shall use all appropriate administrative tools, to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease.

Sec. 3. Expedited Regulatory Review. To the extent practicable, and consistent with its statutory responsibility to ensure the safety and effectiveness of the drug supply, the FDA shall take steps to expand its current efforts to expedite its regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages.

Sec. 3. Review of Certain Behaviors by Market Participants. The FDA shall communicate to the Department of Justice (DOJ) any findings that shortages have led market participants to stockpile the affected drugs or sell them at exorbitant prices. The DOJ shall then determine whether these activities are consistent with applicable law. …[139]

The Medicare Modernization Act

The Medicare Modernization Act (MMA) of 2003 (implemented in 2005) has been cited repeatedly in the literature as a cause of the drug shortages. Basically, the MMA changed the formula for which Medicare and Medicaid Services (CMS) are reimbursed for Medicare Part B (outpatient program) drugs.[126] Before the enactment of MMA the cost for injectable drugs that were administered in an outpatient settings by physicians were reimbursable on a formula based on the "Average Wholesale Price"(AWP).[126] Oncologists prior to MMA used the "buy and bill"

reimbursement scheme to administer chemotherapy, which could be quite lucrative.[126] An oncologist buys the cancer medications, administers it to the patients and subsequently bills Medicare and insurance companies for the costs.[140,141] Medicare reimbursed physicians at 95% of the AWP. Due to unrestricted price setting by the manufacturers, an oncologist paid 66% to 88% of the drug price, resulting in Medicare overpayments of $1.6 billion annually.[141,142] Former White House advisor, oncologist Ezekiel J. Emmanuel, stated that essentially Medicare and insurance companies were charged using made-up "average wholesale prices".[140] The substantial markups in reimbursement of chemotherapy drugs have been a long-standing practice by private oncologists.[143] Oncologists countered in a report to United States General Accounting Office that Medicare's payment system does not sufficiently reimburse for the cost of administering chemotherapy.[144]

In 2005, the implementation of MMA changed the pricing reimbursement formula to average sales price (ASP) plus 6% markup to cover administrative costs.[140-142] Much of the literature points to the new reimbursement formula as a factor with unintended consequences that result in drug shortages. The MMA is referred to as a "price control" that prevents prices from rising in response to market changes.[141,145] Dr. Emmanuel reiterated that the MMA had unintended consequences of restricting price increases greater than 6% every six months.[140] A professor at Columbia Business School, Awi Federgruen, blamed drug shortages on government price controls that limit manufacturers profit margins to 6%.[146] In December 2011, Patrick Cobb, an oncologist from Montana, testified to the United States Senate Committee on Finance.[147] He believes that the MMA is responsible for the consolidation of the generic manufacturing market and therefore it is the root cause of drug shortages.[147] Furthermore, he testifies that the reimbursement system that was set up by the MMA is the underlying reason that

drug shortages occur.[147] Reporting MMA as a root cause is limited to literature focused exclusively on oncology drug shortages. However, in 2011 oncology drugs comprised only 16% of the total drug shortages.[15] A study by Evan A. Krasomil, (prepared for Senator Robert P. Casey, Jr) "Measuring the Impact of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 on Shortages of Sterile Injectable Oncology Drugs"[141] found:

> Contrary to the assertions made by Emanuel and others – that reimbursement rates are being prevented from rising by more than 6% every six months –rates for sterile injectables examined here, particularly generic, commonly rose by more than 6% between quarters. In some cases, reimbursement rates for a number of drugs examined here rose by hundreds or thousands of percentage points between quarters… Examination of changes in reimbursement rates following the implementation of MMA indicate that, contrary to what many who have written or spoken on the topic of oncology drug shortages state, the new rate formula of ASP plus 6 percent does not appear to be capping the rate at which reimbursement rates for drugs can rise. Indeed, the MMA formula uses the "average sale price"(ASP) of a drug to set reimbursement rates; this is a market driven formula dictated by the actual selling price of a drug, not- as it has often been characterized - a "Price control" set by the federal government.[141]

In a 2014, the GAO report to Congress regarding the impact of MMA on the drug shortages was evaluated. The GAO reported that four of the five manufacturers claimed that the change in Part B reimbursement did not play a major role in the cause of drug shortages[123] Additionally, it was stated that the change in Part B had a negligible effect because reimbursement was paid to the physicians and not the manufacturers.[123] Moreover, the preponderance of generic sterile injectables are utilized in an inpatient hospital setting and therefore not reimbursed under Medicare Part B.[123]

Drug shortages were also reported outside of the U. S. and Canada. Margaret McCartney, a general practitioner in Glasgow, stated in British Medical Journal (BMJ) that drug shortages were not only a United Kingdom (UK) problem but also a global problem.[148] McCartney went on to say, "This global problem needs a global solution. A stable supply of (usually) cheap

useful drugs should be an international priority, and if free markets can't manage it then we need a system that can."[148] A survey conducted by the European Association of Hospital Pharmacists (EAHP) revealed that drug shortages are widespread, and affect virtually every European nation.[149] The survey showed drug shortages throughout all medical categories.[149] Some Europeans are concerned because the drug shortages in Europe seem to be moving in a ominous direction including more critical drugs such as antibiotics, cancer drugs, anesthetics, and emergency medicines.[149] A 2015 study, Insights into European Drug Shortages: A Survey of Hospital Pharmacists, discovered a majority of the respondents identified anti-infective medications in conjunction with cancer drugs as being affected most by the shortages.[150] Generic, less expensive injectables were predominant in the drug shortage categories.[150]

Patients

The impact of the drug shortages on patients has been well documented.[22,94,151] The patients have had to contend with delayed treatments, canceled surgeries, inadequate clinical outcomes, and increased risks including death.[94,110] Drugs including antibiotics, anesthetics, chemotherapeutic drugs, and cardiac medication are just a few of the medications that are in short supply. When generic drugs are unavailable, expensive brand name drugs, that are not as effective, may be used as substitutes. Insurance companies may not cover the substitute medications because they are not considered the first-line treatment.

Patients may incur higher treatment costs due to drug shortages. Patients' clinical outcomes also have been affected by using replacement drugs that are not as efficacious as the first line therapy.[8,110,113] In 2011, at least 15 deaths and several adverse outcomes have been attributed to the drug shortage.[113,152,153] Frustration, anger, and betrayal permeate the literature with anecdotal accounts of personal tragedies and challenges. Mary Greene, assistant director of

development services at Columbia Law School, could not find treatment for her bladder cancer due to the unavailability of BCG, a cancer medication.[154] Greene scoured the Internet until she was able to find isolated doses at various hospitals. Greene told the Wall Street Journal, "This totally took me by surprise. It was the very first time I had to think about the drug companies as failing the people that they're supposed to be there for."[154]

Wholesalers/Distributors

Wholesalers purchase drugs from manufacturers and distribute them to pharmacies hospitals, and other healthcare facilities. In addition, they may provide other services such as repackaging of pharmaceuticals and drug buy-back programs.[136] Manufactures supply pharmaceuticals to wholesalers and self-warehousing chain pharmacies.[136] The typical pharmaceutical flow through the pharmaceutical supply chain as explained by a Kaiser Family Foundation paper stated:

> Pharmaceuticals originate in manufacturing sites; are transferred to wholesale distributors; stocked at retail, mail-order, and other types of pharmacies; subject to price negotiations and processed through quality and utilization management screens by pharmacy benefit management companies (PBMs); dispensed by pharmacies; and ultimately delivered to and taken by patients.[155]

The wholesale market has experienced a period of consolidation, which has left three of the largest national drug wholesalers (AmerisourceBergen, Cardinal Health, and McKesson) with 90% of the market share.[155] Regional and secondary wholesalers comprise 10% of the market share.[136] In the past, pharmaceutical wholesalers traditionally functioned to receive products from manufacturers, warehouse the products, and manage the inventory.[155] Today, wholesalers have expanded into specialty drug distribution, electronic order services, reimbursement support, repackaging of pharmaceuticals, and drug buy-back programs, as previously mentioned.[155] In the generic market, the wholesalers have more bargaining power than they do with the brand

pharmaceuticals. This is due to the ability of wholesale distributors to drive market share or to increase the volume sold.[155] The pharmaceutical supply chain is complex and the flow of money among various entities makes it difficult to follow the money trail.[61] There can be substantial disparity in the price that different purchasers pay for the same drugs.[155]

Drug shortages have created an environment that is conducive to gray markets. Gray markets are supply channels that are unofficial and not authorized by the original manufacturer. Gray markets may also be referred to as "parallel markets".[156,157] During drug shortages, hospitals are unable to get scarce drugs through the normal supply channels. Gray markets can emerge in markets where products are scarce. During drug shortages, secondary wholesalers buy all available drugs on the shortage list taking advantage of the opportunity to sell the drugs at extremely high prices. As the number of drugs in short supply increased, hospitals began receiving calls from secondary wholesalers that were interested in selling specific drugs (at inflated prices) that hospitals were unable to find elsewhere.[158]

In 2011, Premier Healthcare Alliance surveyed all of its acute-care hospitals inquiring about unauthorized offers to sell drugs that were in short supply.[156] Within a two week period, 1745 examples of gray market offers were reported from 42 acute-care hospitals.[156] Of the 1745 drugs offered, all were on backorder from the manufacturer and unavailable to hospitals through any other legitimate channel.[156] The largest markups were the ones needed to treat the critically ill patients. Figure 3 from Premier Healthcare Alliance shows drug markup versus drug/care categories.[156]

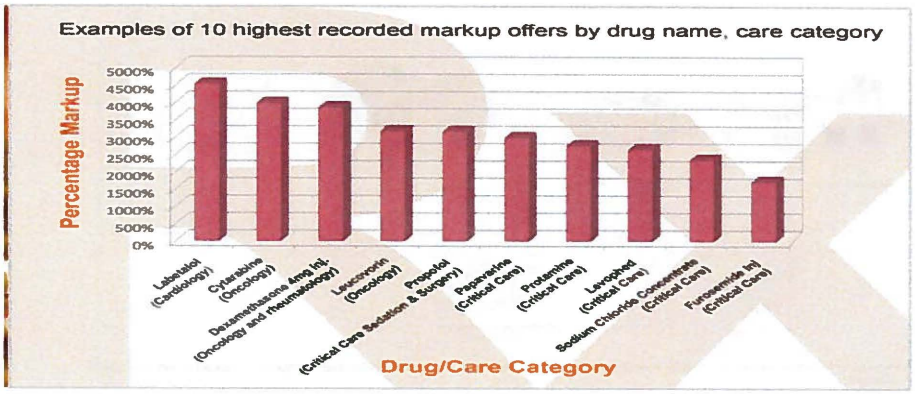


Figure 3. Highest Drug Markups[156]

Findings from the House Committee on Oversight and Government Reform (HCOGR) reported that some injectable drugs "leak out" into gray market distributions and never reach the intended healthcare providers.[158] The gray market distribution consists of a number of different companies that buy and resell drugs to each other (with markups at each phase of the journey) before they reach their ultimate destination of the healthcare provider.[158] In addition, the HCOGR report found that:

> "Fake Pharmacies" Acquire Prescription Drugs from Authorized Distributors and then Sell Them Into the Gray Market…
> "Drug Brokers" Recruit Pharmacies to Purchase Drugs for the Gray Market…
> Gray Market Business Practices Are Widespread…
> Gray Market Drugs Are Marked Up as They Quickly Pass from Owner to Owner…
> Gray Market Companies Sometimes Charge Hospitals Significantly Different Prices for the Same Drug Product on the Same Day…[158]

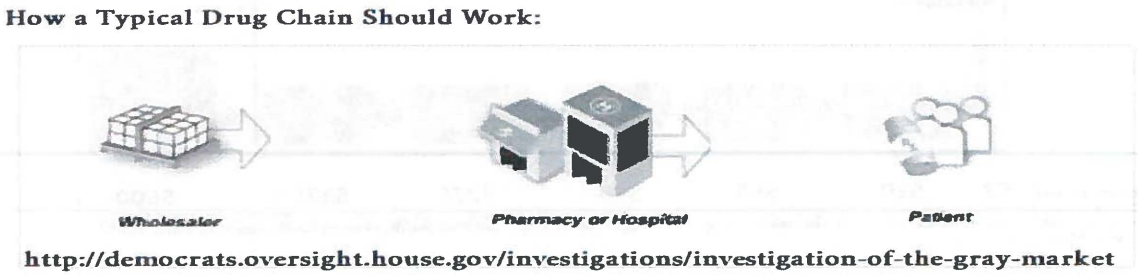
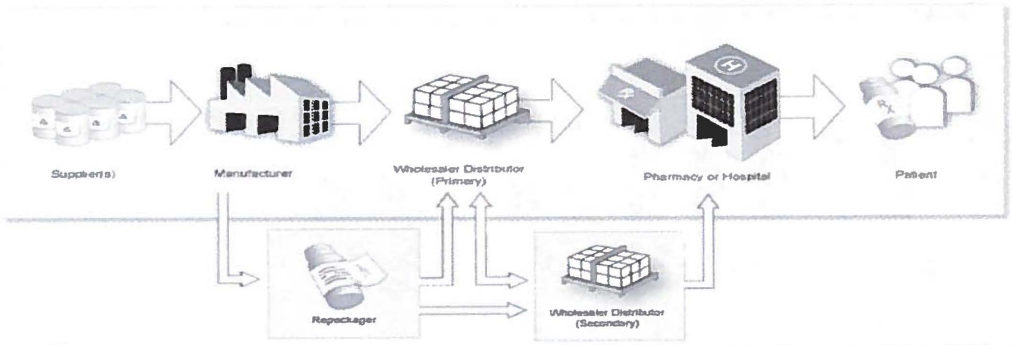
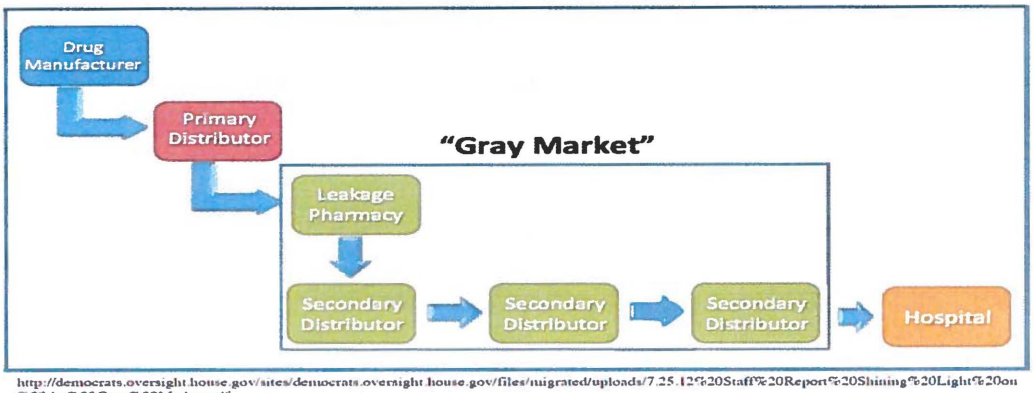


Figure 4. How Typical Drug Chain Should Work



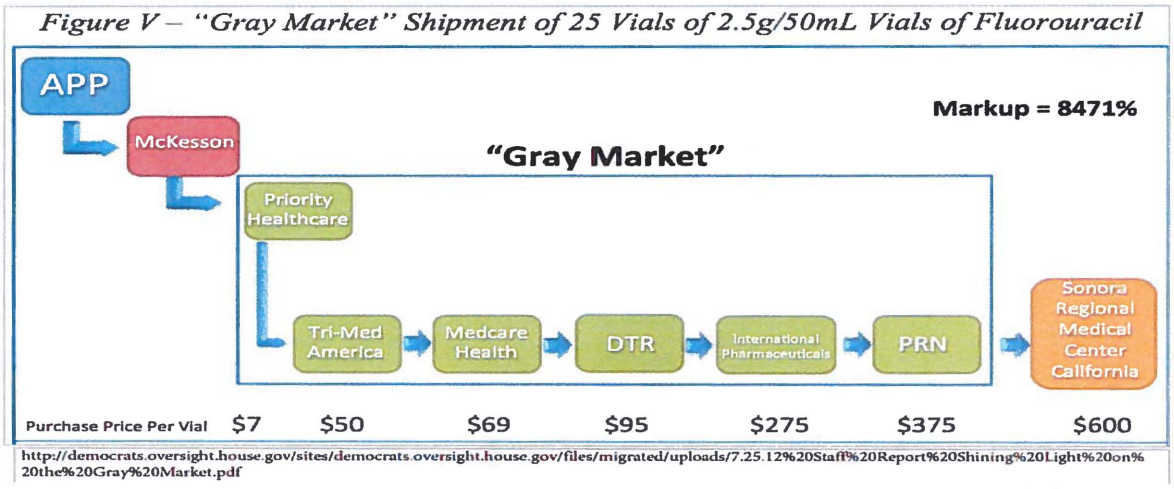
http://democrats.oversight.house.gov/sites/democrats.oversight.house.gov/files/migrated/uploads/7.25.12%20Staff%20Report%20Shining%20Light%20on%20the%20Gray%20Market.pdf

Figure 5. How the Current Drug Chain Works



http://democrats.oversight.house.gov/sites/democrats.oversight.house.gov/files/migrated/uploads/7.25.12%20Staff%20Report%20Shining%20Light%20on%20the%20Gray%20Market.pdf

Figure 6. Gray Market Product flow



http://democrats.oversight.house.gov/sites/democrats.oversight.house.gov/files/migrated/uploads/7.25.12%20Staff%20Report%20Shining%20Light%20on%20the%20Gray%20Market.pdf

Figure 7. Example of a Fluorouracil Shipment Through the Gray Market

Other concerns about gray market drugs relate to the safety of the products. Due to the unpredictable path the injectable drugs follow, it would be impossible to know if the drugs were stored or handled appropriately. The Fox Chase Cancer Center in Philadelphia told the HCOGR committee, " If I can't be absolutely sure of the integrity of the drug, then I can't administer it to a patient."[158] A drug from the gray market doesn't have the same quality assurance; there is no way to insure a drug's legitimacy or its pedigree. The FDA describes a drug pedigree as:

> A drug pedigree is a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them. Under the pedigree requirement, each person who is engaged in the wholesale distribution of a prescription drug in interstate commerce, who is not the manufacturer or an authorized distributor of record for that drug, must provide to the person who receives the drug a pedigree for that drug.[159]

Making the gray market drug problem even riskier is the possible introduction of counterfeit drugs into the gray market drug distribution chain. Counterfeit drugs are defined as drugs that may not have active ingredients (AI), may have too much or too little AI, wrong AI, or fake packaging.[160] According to the FDA, there is a greater chance of introducing counterfeit drugs into the supply chain when there are multiple wholesalers.[161] Primary and regional wholesalers work directly with manufacturers and are not usually a source of entry for counterfeit drugs.[162,163] Conversely, secondary wholesalers buy and sell drugs based on market shortages and surpluses.[162] Secondary wholesalers do not work directly with manufacturers.[162] They also package and repackage drugs thus providing opportunity for the introduction of counterfeit medications into the system.[162] It has been reported that 40% of all drugs in the U.S. are made overseas.[160] In addition, 80% of all active ingredients for drugs are imported from foreign manufacturers located in more than 150 countries.[164] Rogue wholesalers have found ways to exploit the system to manipulate their way into the distribution chain. In addition to the

harmful affects on patients, the counterfeiters are able to exploit healthcare systems and patients by charging exorbitant prices.[162] Counterfeit drugs have increased the cost of healthcare while endangering the lives of patients. The drug shortages have encouraged the influx of counterfeit prescription drugs into the United States.

Insurance Companies

A literature research review considering insurance companies' role in the drug shortages did not expose any direct or indirect association. However, insurance companies may affect the patients' access to affordable medication since the insurance companies may not pay for alternative therapies.[165] Increased cost for substitution drugs may or may not be covered by third-party payers. According to a survey by the National Community Pharmacists Association (NCPA), 52% of respondents reported that insurance companies do not cover alternative treatments and the patient bares the brunt of paying for the substitute drugs.[165] The survey respondents reported that 66% of patients go without their prescribed drugs as a result of the drug shortage.[165]

Raw Material Suppliers

The American drug supply chain is complicated and dependent upon a global supply of raw material.[60,61] Drug manufacturers may be reliant on a single supplier of an active ingredient for a particular drug.[8,123] While there may be multiple manufacturers making the same medication, the dependence on one source for raw material makes the upstream supply chain tenuous.[8,160] Quality control presents a challenge due to the vast number of outsourced suppliers located in hundreds of foreign countries.[123,160] Testimony to the GAO manufacturer representatives stated that the unavailability of raw material or AI has been the cause of some drug shortages; however, it was a small percentage.[123] FDA data analysis revealed that between

2011-2013 unavailability of raw material accounted for 9% (see Figure 8) of drug shortages.[123]

Figure 8. Reported Causes of Drug Shortages from January 2011 through June 2013

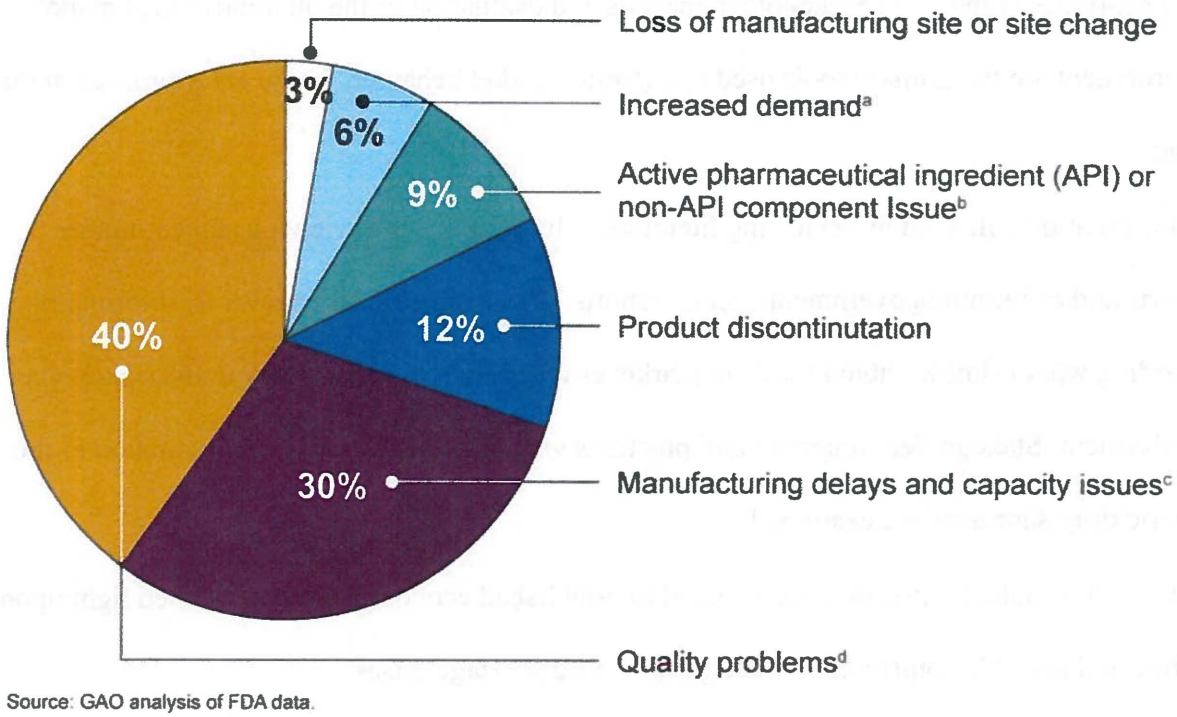


Figure 8. Causes of Drug Shortages January 2011 Through June 2013

Erin Fox, Director Drug Information Service University of Utah Healthcare, in a presentation focusing on drug shortage "Myths vs. Reality" stated that unavailability of raw material is rarely the cause.[166] Raw material shortages may be due to numerous factors, including political conflicts, natural disasters, environmental factors, trade disputes, and degradation or contamination during transport.[8] Packaging components and repackaging problems could also interfere with the supply of available raw material. However, after extensive research, it does not appear that the lack of raw material is a major factor in drug shortages.[28,166]

Methodology and Study Design

This qualitative explanatory paper attempts to clarify conditions that have led to critical drug shortages in the U. S. Stakeholder analysis and evaluation of the pharmaceutical market environment are the primary tools used to examine market behavior. These are examined in three stages:

1. Information collected by reviewing literature, white papers, interviewing subject-matter experts and examining government agency reports. The research concentrates on information regarding what is known about the drug market environment, market behavior and stakeholder involvement. Stakeholders' interests and positions via "stakeholder analysis" in relation to the generic drug shortages are examined.

2. Each stakeholder's position is compared to established economic theories to shed light upon its role and possible contribution to the generic drug shortage crises.

3. Findings of the stakeholder analysis and market evaluation are summarized and added to the conclusion section, thus forming a clearer explanation of the drug shortage.

Conceptual Framework:

U.S. Drug Shortages: Stakeholders' Analysis and Market Evaluation

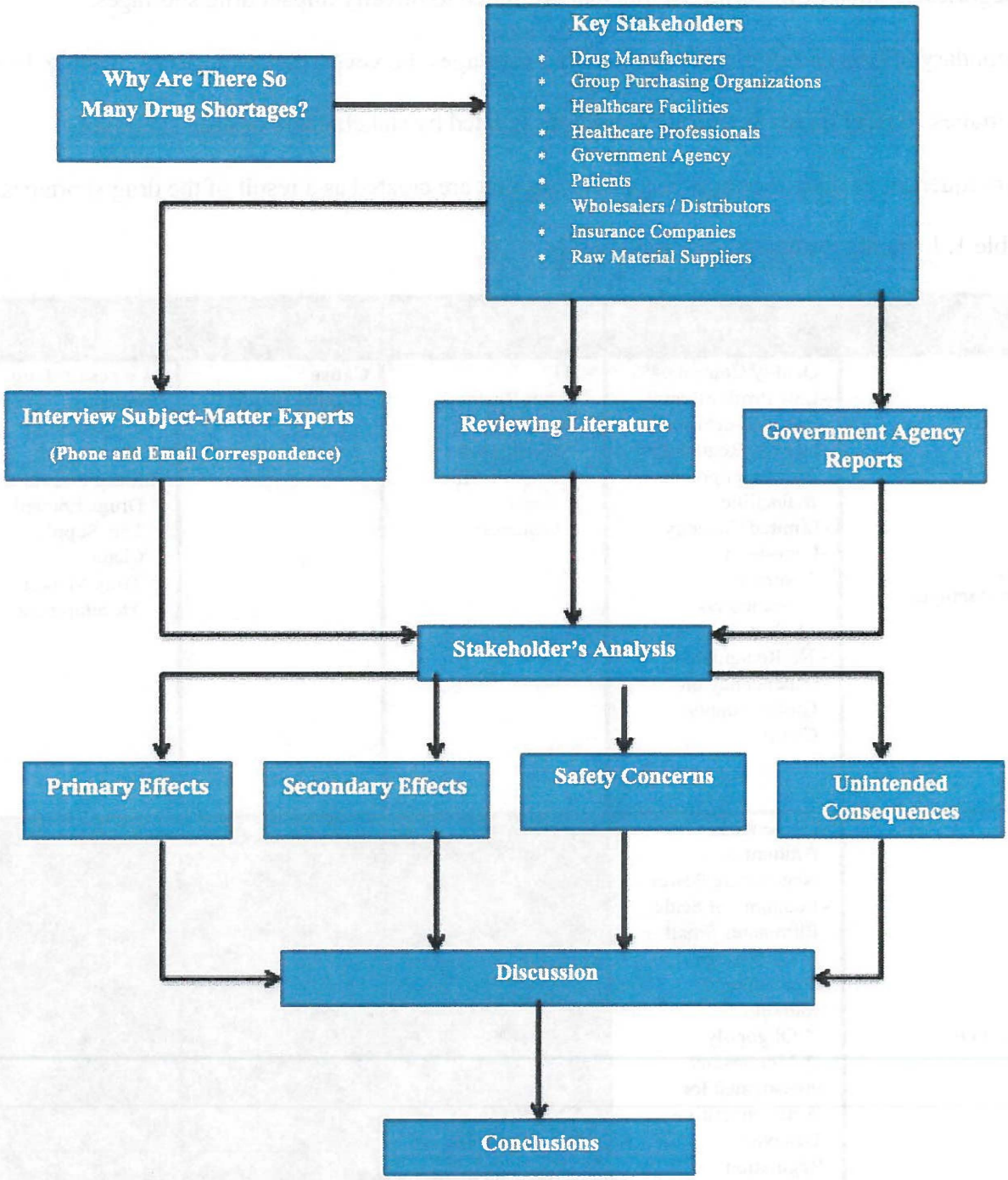


Figure 9. Conceptual Framework: U.S. Drug Shortages: Stakeholders' Analysis and Market Evaluation

Results

Material accumulated from the literature review and stakeholder analysis fell into four categories. Primary effects are factors that are stated to directly impact drug shortages. Secondary effects do not directly impact drug shortages; however, they exacerbate existing drug shortages. Safety issues are unsafe conditions created by stakeholders or drug shortages. Consequences of drug shortages are conditions that are created as a result of the drug shortages.

Table 1. Lists the results on each stakeholder.

	Primary Effects	Secondary Effects	Safety Issues	Consequences of Drug Shortages
Drug Manufactures	-Quality Control 64% -Low Profit margin -Business decisions -Heavily Regulated -Aging equipment & Facilities -Limited Capacity -Long-term Contracts -Concentrated Market - No Redundancy -Dependency on Global Supply Chain	- JIT - Better Business Opportunities * Biosimilars * Patent Cliff * Super Generics	**Cause** -Quality issues	**As a result drug shortages:** *Compounding Pharmacies * More Counterfeit Drugs Entered The Supply Chain * Gray Market Development
GPOs	-Tremendous Amount of Negotiating Power - Economy of Scale Eliminates Small Manufactures -Concentrated Market * Oligopoly * Monopsony -Investigated for Anticompetitive Behavior -Regulation Protects GPO from Anti-kickback Statutes (MMPPA)	None Reported	None Reported	None Reported

	Primary Effects	Secondary Effects	Safety Issues	Consequences of Drug Shortages
GPOs	-Long-term Contracts, Locking Prices -High Barriers- Entry			
HEALTHCARE FACILITY	None Reported	- JIT -Stockpiling Hoarding -Substitute Drug Use Causes Shortage of Substitute Drugs	**Cause** -Increased Errors -Buy Drugs from Compounding Pharmacies -Buy Gray Market Drugs - Increased Risk of Procuring Counterfeit Drugs - Modified Therapy May Provide Substandard Care	**As a result drug shortages:** - Increase Cost of Care * Managing Drugs * Procuring Drugs * Overstocking Drugs Cost & Waste of Expired Drugs * Increased cost Associated with Compounding Pharmacies usage
HEALTHCARE PROFESSIONALS	None Reported	None Reported	**Cause** - May be forced to Give Substandard Care - Increased Chance * Making an Error * Having to Make "Tragic Choices" * Having to Ration Tx	**As a result drug shortages:** - Increased Emotional Stress: * Anger * Frustration * Anxiety * Mistrust

	Primary Effects	Secondary Effects	Safety Issues	Consequences of Drug Shortages
GOVERNMENT AGENCIES	FDA * Increased Regulatory Enforcement * Forced Shut Down of 30% of Capacity (Manufacturing) * Threats of Legal Action Resulted in Halted Production In Some Companies * Inflexibility & Outdated Policies * Limited Control Over Foreign Suppliers MMA - Changed Formula Reimbursement From AWP to ASP + 6%"Price Control" * Referred to as "Price Control" * Only Reported With Cancer Drugs - Study: ASP is Market Driven Not "Price Control" - GAO: Report on MMA * Manufacturers View: MMA as Not A Major Factor * Reimbursement Provided to Doctor Not Manufactures * Major Portion of Sterile Generic Injectables are Used in Inpatient Settings & Not Subject to Medicare Part B	None Reported	FDA *Failed to keep adulterated drugs from the market *Failed to protect the public from drug shortages *Over enforced regulations that are ineffective and unable to ensure quality. * Failed to strategically resolve compliance problems, shutting down 30% of generic manufacturing capacity as a result.	None Reported

	Primary Effects	Secondary Effects	Safety Issues	Consequences of Drug Shortages
PATIENTS	None Reported	None Reported	**Affected by** - Delayed Tx - Poor Clinical Results - Increased Risks * Side Effects * Drug Errors * Death - Victim of Rationing - Exposed to: * Gray Market Drugs * Poss. Exposure to Counterfeit Drugs	**As a result drug shortages:** -Increased: * Out-of-Pocket Cost * Delay Tx * Cancelled Surgeries
WHOLESALE/ DISTRIBUTORS (secondary wholesalers)	None Reported	-Secondary Wholesalers * Exacerbate Shortages by Buying All Available Drug in Short Supply (Stockpiling and Hoarding) then Diverting To Gray Market Distribution Channels	-Secondary Wholesalers * 10% of the Market * Makes Supply Chain Susceptible to: - Gray Market Distribution - Counterfeit Drug Incursion - Stockpiling & Hoarding - Threaten Drug Integrity by Using Unconventional Routes to End User -Keeping Drugs From Reaching Intended End User * Denying Patients And Hospitals: - Expeditious Delivery of Drugs -Largest Markups: Drugs For Critically Ill Patients	**As a result drug shortages:** - Some Secondary Wholesalers Became the Gray Market

	Primary Effects	Secondary Effects	Safety Issues	Consequences of Drug Shortages
INSURANCE	None Reported	None Reported	- Patients may go Without Meds If Third Party Payers Refuse to Pay for Alternative For Treatments	
RAW MATERIAL SUPPLIERS	- Dependence on Global Supply Chain for Raw Material - Outsourced Suppliers In 150 Different Countries - Averaged 9% (2011-2013) Primary Cause of Drug Shortages - Quality Difficult to Control With Many Global Suppliers - Raw Material May Only Have a Single Supplier - Several Manufactures May Depend on the Same Supplier for Raw Materials	None Reported	- Quality of Raw Material May be Difficult to Monitor	None Reported

Table 1. Stakeholder Analysis Drug Shortage Results

After an extensive literature review, government reports, subject expert testimonies, and interviews, four of the nine stakeholders fell into the "Primary Effects" category. In Table 1, drug manufacturers, government agencies' regulations, GPOs, and raw material suppliers are cited most often as a primary or a root cause of the sterile injectable drug shortages. Of the four stakeholders designated as primary causes of drug shortages, drug manufactures were most often cited as the root cause. Over-aggressive government agencies' regulations and enforcement activities are cited for shutting down or holding up production at drug manufacture sites. GPO research material lacked empirical support, however, it was frequently cited as a root cause. Lack of raw material is named least often as a root cause of the sterile generic drug shortages.

Review of the literature placed drug manufactures, healthcare facilities, and wholesaler distributors in the "Secondary Effects" category. The JIT inventory process was asserted to exacerbate shortages in both manufacturing and healthcare facilities. While stockpiling, hoarding and diverting are attributed to secondary wholesaler distributors. When first line drugs are unavailable, healthcare facilities inadvertently cause secondary drug shortages of substitute drugs. Business decisions focus on opportunities that yield better profit margins exacerbating drug shortages by producing less or eliminating drugs in short supply.

The "Safety Issue" category includes both stakeholders that cause the safety issue and stakeholders that are affected by the safety issue. Eight of the nine stakeholders are associated with safety issues. Patients are the only stakeholders that are exclusively affected by safety issues. The other seven stakeholders are contributing causes of safety issues. Safety issue conditions may be inadvertent, unintended, or forced on stakeholders. However, stakeholders are responsible for safety issues that originate in their domain. Only the GPOs were excluded from the "Safety Issue" category.

As a result of drug shortages several ancillary conditions developed. While these conditions do not play a role in the root cause of drug shortages they have a significant affect on stakeholders and the market environment. Five stakeholders are assigned to the "Consequences of Drug Shortages" category. Manufactures are responsible for supplying the market with generic drugs. As a result of the industry's inability to fulfill that obligation several conditions have developed such as the expansion of compounding pharmacies, gray markets, and increased opportunity for counterfeit drugs to enter the supply chain. Healthcare facilities have incurred significant expenditures relating to the procurement, management of alternative therapies,

increased stocking and wastage cost (stockpiling and hoarding), and the use of compounding pharmacies when other choices are unavailable.

Clinical situations that are less than optimal expose healthcare professionals to emotions such as increased anxiety, frustration, anger, and mistrust. Drug shortages place healthcare professional in circumstances that are clinically substandard. Patients incur treatment delays, cancelled surgeries, and increase cost as a result of drug shortages. As a result of drug shortages, secondary wholesaler distributors use drug shortages to their advantage by procuring and diverting drugs that they eventually sell at significantly increased prices.

Discussion

Why are there so many drug shortages in the U. S.? The answer is complex and involves many factors. Four out of nine stakeholders are reported as primary causes of the drug shortages. Particularly, Drug manufacturers, government agencies' regulations, GPOs, and raw material suppliers are cited most often as "primary or a root causes" of the sterile injectable drug shortages.

Drug manufacturers

Stakeholder investigation of generic drug manufacturers as the source of drug shortages appears like a logical place to begin. Information collected about generic drug manufactures can be classified into four different categories: Primary Effects, Secondary Effects, Safety Issues, and Consequences of Drug shortages (Table 1).

The generic drug market in 2013 was valued at $168 billion and expected to reach $283 billion by 2018 growing at a compound annual growth rate (CAGR) of 11%.[167] The majority (80%) of shortages are concentrated in the sterile injectable generic market despite the fact they comprise only 29% of the entire generic market.[5] It is interesting to note that these sterile

injectables are older drug products and have very low profit margins. The demand for these drugs remains steady and is the foundation of many clinical specialties. Market forces apply downward pressure on the prices of these generic drugs. Market forces include GPOs, government policies, insurance reimbursement plans, intense competition among generic manufactures, and large healthcare systems' buying practices. A declining supply of a drug does not necessarily result in an increase in price of that respective drug. The generic market historically has been relatively unresponsive to price changes.[1,168]

Intense competition for big institutional contracts with group purchasing organizations (GPOs) has caused many generic companies to commit to long-term agreements. Moreover, the conditions of the generic manufacturing facilities have been described as timeworn with need of updating.[25] When unanticipated interruptions of production occur and a facility is already operating at capacity without redundancy, there is little chance of increasing capacity to meet unanticipated demand. With a limited number of manufacturers supplying a specific generic injectable, when one manufacturer develops a problem, it is not possible for the other manufacturers to make-up the manufacturing shortfall. Due to low profit margins, there is no incentive for other manufacturers to "fill the gap" between supply and demand. Long-term contracts make it impossible for the manufactures to increase drug prices; thus, short-term adjustments are difficult or nearly impossible to make under uncertain circumstances.

It is well documented that the generic companies have limited capacity.[21,25] The generic pharmaceutical subsector lacks the capacity to manufacture both the older less expensive generic drugs and newer more profitable drugs under these competitive circumstances.[14] Management makes business decisions based on allocating resources so that profit maximization is in the best interest of the company. When newly off-patent drugs become available, the generic companies

are faced with difficult decisions. The strategy to capitalize on the newly patent-free blockbuster drugs has the generic companies eliminating older generic lines that have been manufactured for decades. When decisions to narrow product lines are made and discontinuation of less profitable sterile generic injectable are eliminated from the portfolio, the market is often left with one supplier of the those medications.

Consolidation has been noted in the sterile injectable generic market with only seven primary manufactures and with the top three accounting for 71% of the market. It is not unusual to see consolidation take place in mature markets; however, the hyper-consolidation in the sterile injectable generic sector has many in the medical field concerned. Recently there have been isolated price increases of some older generic drugs.[46,47] These significant increases occurred when there is only one manufacturer supplying a specific drug. When only one supplier is producing a sterile generic injectable drug, a monopoly situation may exist if no substitutes are available for that drug. This gives the manufacturer monopoly power over that specific drug.

While some price increases may be the effect of drug shortages and hyper-consolidation, the New York Times reported that price increases may be the result of a business strategy of acquiring old neglected drugs and selling them as high-priced "specialty drugs".[49] A new business strategy to make unprofitable products profitable is not unusual. However, when ethical and moral norms are compromised, it is extremely unpopular and controversial.[118,169] Is the market attempting to equilibrate? The manufacturer increases the profit margin to such a degree that other manufactures enter the market, thus creating competition and putting downward pressure on prices until the market reaches equilibrium. This is the way the market is expected to work over the long run. Market forces are not sensitive to peoples' health, ethical

and moral obligations, and emotions. This is one reason the market is unable to equilibrate on its own.

It is well documented that quality is a major factor in the current drug shortages.[18,23] It is difficult to understand why such an exacting manufacturing industry does not have tight quality control systems. The evidence is clear that the generic pharmaceutical industry is lacking good quality control. Installing tight quality control processes may initially increase the cost of doing business. However, to avoid civil and criminal fines, increasing quality control is a necessity. While a tighter quality control process will decrease the number of legitimate errors missed, it may increase the number of inappropriately identified errors, which will also increase the cost of doing business. This may be a challenge for generic pharmaceutical companies due to such low profit margins on their products. Under these market conditions it is not surprising that manufactures are unable or unwilling to invest in new equipment and quality control systems to meet the FDA's Current Good Manufacturing Practices (CGMP).

Government Policies and Regulations

The pharmaceutical industry is heavily regulated. One purpose of government regulations is to protect consumers from the abuse of a firm's market power. The FDA regulates food and drug producers placing emphasis on purity, labeling, and product safety. If this is the case, then why is a heavily regulated industry having major difficulties meeting and sustaining quality control? One possibility that may explain this situation is that regulations are not being enforced appropriately. Another explanation is that regulations do not ensure quality outcomes. It is also possible to have a combination of both, inappropriate enforcement and ineffective regulations. The literature suggests that it is the combination that is most likely. Over-regulation that is too restrictive will have negative economic consequences on the industry as a whole. Inflexible,

outdated regulations that are not updated and revised can impose unnecessary burdens on the regulated industry in question.

With globalization of the pharmaceutical industry, it is virtually impossible for the FDA to exert its regulatory power over 150 countries that supply the pharmaceutical industry. Many of these countries function with less sophisticated manufacturing and regulatory systems. This presents a conflict since the U.S. generic drug manufacturers outsource many different drug components to foreign suppliers. This includes 300,000 foreign facilities that export FDA-regulated products to the U.S..[164] The FDA has not kept up in the globalization movement and does not have methods, authority, or resources to function in this new environment.[61] The GAO in 2009 estimated that it would take nine years for the FDA to inspect all the foreign companies on the list.[170] The list of companies and facilities has grown since 2009. According to FDA data, drugs were manufactured in more than 100 countries in 2009 compared to 150 countries in 2013. [170] Due to lack of FDA resources, the foreign sector supplying the generic drug manufacturers lacks oversight and is under regulated.

Since drug shortages are not unique to the U.S., it seems appropriate to develop some form of global partnership to manage and mitigate the uncharted waters of regulated globalization of the pharmaceutical industry and its supply chain. Due to loose control over foreign contractors and questionable quality control at generic manufacturing sites, there have been many mishaps and drug recalls. This produced a knee-jerk reaction from the U.S. government and the FDA. Increasing oversight, the FDA focused on the sterile generic drug manufacturers. This activity essentially halted production in four out of the five major generic drug manufacturers. This action decreased production capacity 30% for the entire sterile generic pharmaceutical market.

Appropriate regulatory oversight is imperative. As shown in the U.S. and global drug market, either too much or too little regulation can have devastating and far-reaching effects.

Another important component of FDA regulations is the efficiency of the regulations themselves. It has been suggested that the FDA regulations and enforcement methods are rigid, unbending, and out-of-date. Good manufacturing regulations when followed by the drug manufacturer should produce a quality product. Regulations should add value to the product and process. This should not be a burdensome procedure that only increases the cost of production without ensuring an increase in quality. The U.S. generic drug industry seems to have a plethora of regulations without the concurrent increase in quality. Regulations need to be evaluated and updated to meet the needs of a changing industry. As all industries tighten their belts and become more efficient in order to survive in today's competitive environment, it is essential that the FDA do the same.

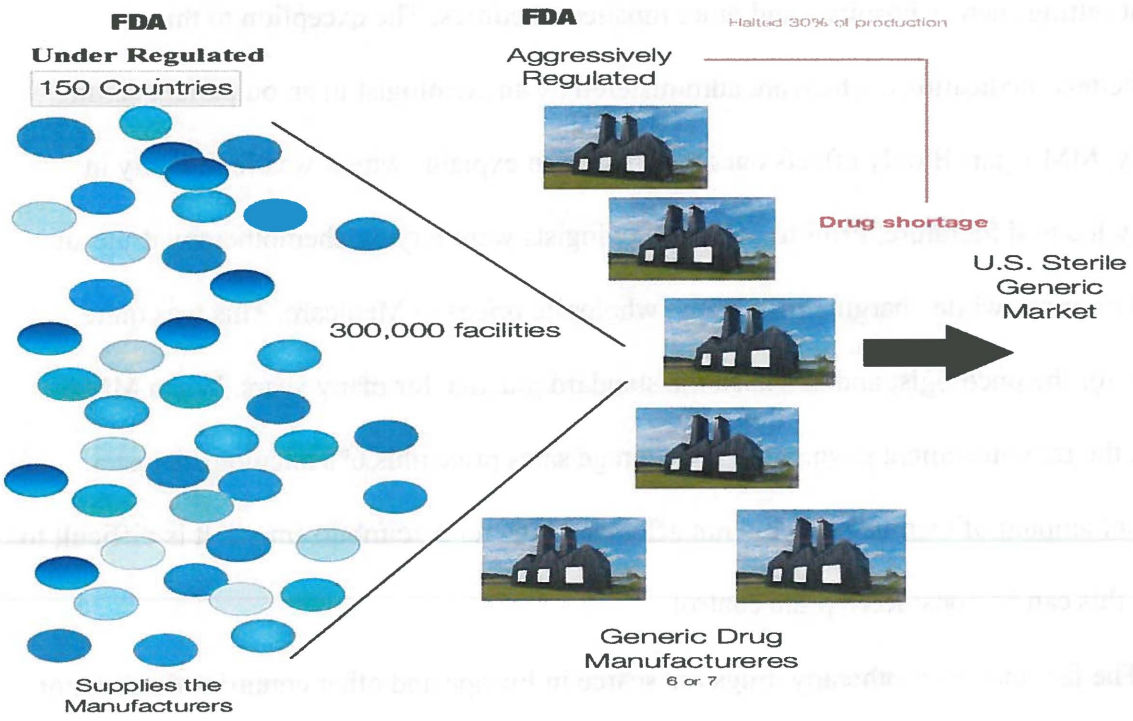


Figure 10. FDA Global Manufacturer Suppliers Under-Regulation vs. FDA Generic Manufactures Aggressive Regulation

Sometimes governments place limits on how prices are allowed to increase or decrease and these mandates can affect market equilibrium.[7] Government regulations that control the price of a product and do not permit the price to increase as demand increases will result in a product shortage.[171] The Medicare Modernization Act (MMA) has been reported in the literature as government "price control" that has resulted in drug shortages. Interestingly after researching and reviewing many articles, one common theme emerged. Only articles regarding chemotherapy drugs seem to make this allegation. Chemotherapy shortages comprised only 16% to 28% (2009-2014) of the total drugs involved in the shortages. What about the other 72% to 84% of drugs reported in the shortages? Why has MMA not been as a root cause for the majority of all sterile generic injectable drug categories in short supply?

Medicare Modernization Act part B is warranted in an outpatient setting. This is an important piece of the puzzle. Sterile injectable drugs for the most part are utilized in an inpatient setting such as hospitals and other inpatient facilities. The exception to this is chemotherapy medications, which are administered by an oncologist in an outpatient setting. Basically, MMA part B only affects oncologists, which explains why it was found only in oncology focused literature. Prior to MMA, oncologists were buying chemotherapy drugs at discounted prices while charging marked-up wholesale prices to Medicare. This was quite lucrative for the oncologist and had been the standard practice for many years. When MMA changed the reimbursement payment to the average sales price plus 6% oncologists lost a significant amount of income. This did not affect manufactures reimbursement. It is difficult to see how this can be considered price control.

The fact that chemotherapy drugs are scarce in Europe and other countries that are not affected by U.S. reimbursement policies also infers that MMA is not the cause of drug shortages.

The drug shortage timeline does not support MMA as a cause of drug shortages. The MMA was implemented in 2005. In 1999, CDER developed the Drug Shortage Program and in 2001 due to an increase in the number of drug shortages (120 new shortages) the University of Utah partnered with the American Society of Health-System Pharmacists to establish the University of Utah's Drug Information Service. This is well before MMA was enacted.

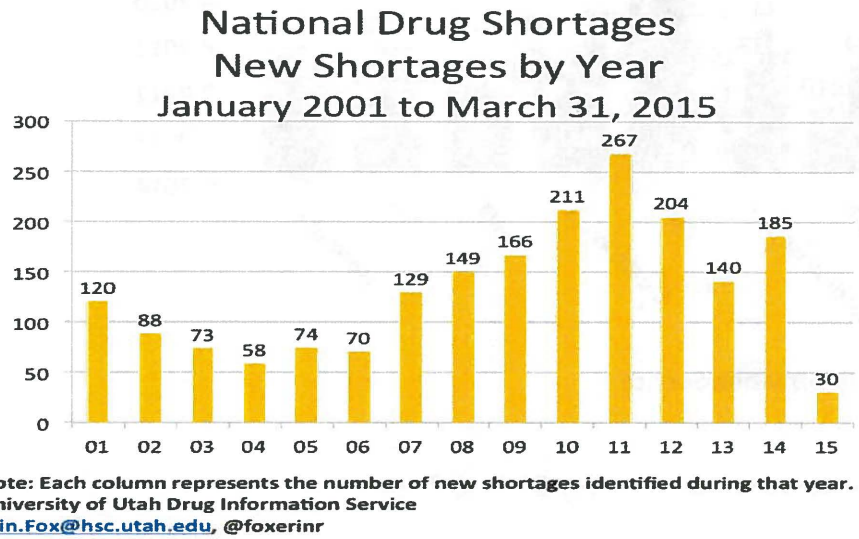


Figure 11. New National Drug Shortages January 2001 to March 31, 2015

There are additional changes in reimbursement that do not support MMA as a root cause. In 2012, Congress mandated a budget sequester that Medicare Part B be cut by 2%.[172] Since 2012, oncologists have been reimbursed at ASP plus 4.3% (down from 6%).[172] If MMA is a root cause of chemotherapy drug shortages, one would expect that a decrease in reimbursement would exacerbate the chemotherapy drug shortages. That is not the case as shown in **Figure 12**. When comparing 2011 (6.0% reimbursement) to 2012 (4.3% reimbursement) there was a 58% decline in chemotherapy drug shortages. In 2011 compared to 2013, there was a 73% decrease. When 2011 is compared to 2014, a decrease of 62% is noted. Consequently, MMA as a root cause of drug shortages, including chemotherapy drugs, cannot be substantiated.

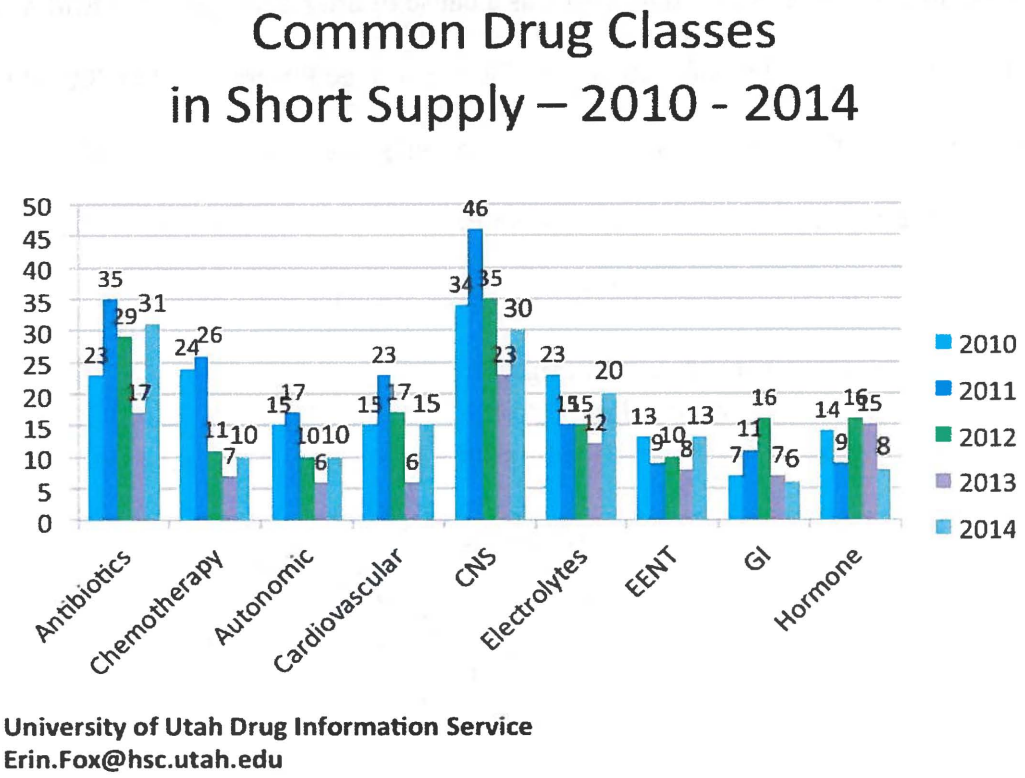


Figure 12. Common Drug Classes in Short Supply 2010 to 2014

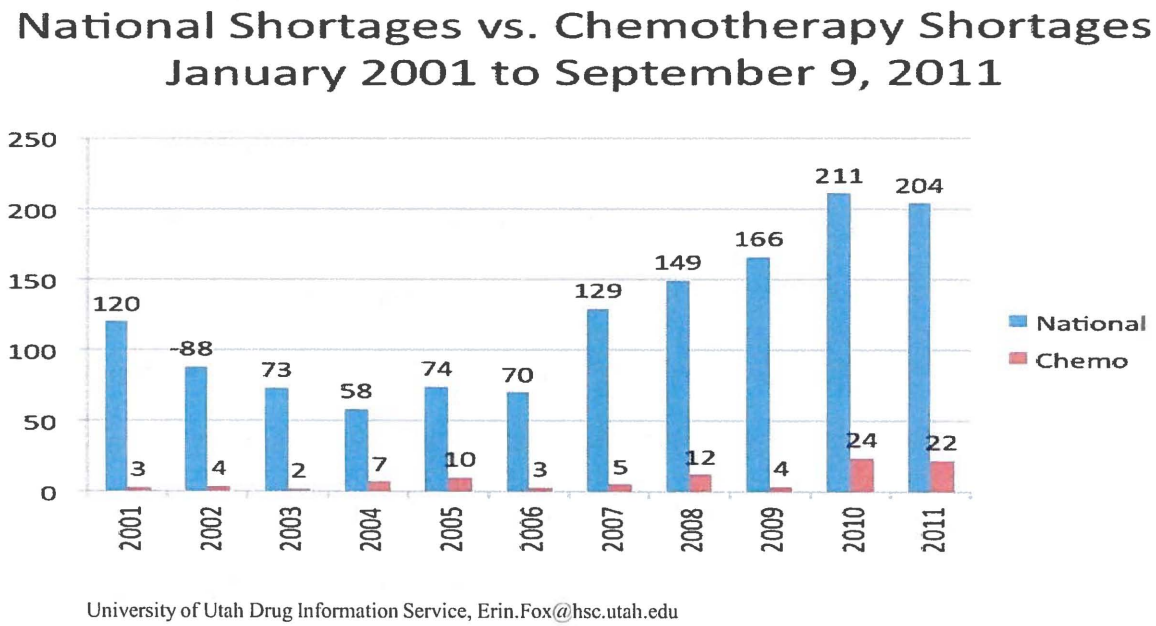


Figure 13. National Shortages vs. Chemotherapy Shortages January 2001 to September 9, 2011

GPOs

Confusion, controversies, and accusations permeate the literature, expert witness interpretations, and government hearings. Even the number of GPOs in existence is questionable. Some sources claim that there are 600-900 GPOs in operation and others claim that the GPO market is consolidated with only a small number controlling 85-90% of the market. The explanation for the great disparity in numbers seems to be that regional and local GPOs belong to parent national GPOs. Of the six largest GPOs, four are private and two are publicly held. There is little doubt of the aggregate buying power of the GPOs. The tremendous buying power has come into question in the procurement of generic sterile injectable drugs. GPOs use the principle of economies of scale to negotiate lower prices for its members. Small generic drug manufactures may be excluded because they cannot produce the economies of scale needed by the GPOs. This is perceived as an exclusionary practice and anticompetitive behavior. This buying practice may have caused market consolidation by eliminating small sterile generic drug manufacturers. This consolidation contributes to the vulnerability of the sterile generic supply.

GPOs put downward pressure on the drug manufacturers to obtain the lowest price on the sterile generic injectables. Once the prices are locked in long-term contracts, they become sticky and are not able to fluctuate with supply and demand. With incumbent GPOs enjoying the large market share and long-term member contracts, it is difficult to break into the GPO market. Additionally, the drug companies manufacturing sterile generic injectables are also concentrated. Long-term contracts to supply incumbent GPOs inhibit new entries into the GPO market. With economies of scale that have already been established, it is challenging for new companies to gain market share. Loyalty schemes, strong brand names, and long-term relationships among GPO market leaders discourage new entrants into the market. Hence, barriers to entry are high.

It appears that GPOs do exert some monopsony power because suppliers of generic drug manufactures have very little choice but to sell to one of the few major GPOs that supply 85 to 90% of the market. Without a contract with a major GPO, a generic sterile injectable drug manufacturer does not have a market to sell its product. The GPO leverages that power to drive down the price of the sterile generic injectables. Driving prices down to benefit consumers, hospitals, insurance companies, and governments appears to be a worthy goal. However, the very low profit margins on generic sterile injectables may have unintended consequences that contribute to the national drug shortages and stimulate considerable consolidation of the sterile generic market.

Raw Material Suppliers

There are few industries that have not been touched by increasing globalization and the pharmaceutical industry is no exception. However, globalization of raw material has presented a few challenges to the pharmaceutical manufacturers. Tracing the route that pharmaceuticals take from raw material all the way to the end-user is complicated. Weaknesses in the supply chain with poor transparency, tainted, expired, or counterfeit drugs that enter into legitimate distribution channels can damage reputations and more importantly cause harm.[173]

Several misadventures in the upstream supply of raw material have led the FDA to concentration on security and safety issues related to the drug supply chain. In 2008, corrupted raw material imported from China was used in the manufacturing of heparin, a widely used blood thinner. The tainted raw material was implicated in the death of 81 people and injured another 785 reported by the FDA.[174] The heparin recall affected over 10 countries. The Supply Chain Security Act (DSCSA) of 2013 mandates steps to be taken in order to build "an electronic interoperable system to identify and trace certain specific drugs as they are distributed in the

United States."[173] The DSCSA will be implemented over a period of 10 years.[175] The track and trace portion of the DSCSA is a requirement and responsibility of the entire supply chain. In the past, manufacturers only needed to ask the name of the raw material from suppliers.[176] This was considered enough for "source" identification.[176] The DACSA holds manufacturers fully responsible for the raw materials that go into their products.[176] The DACSA mandates that by 2017 manufactures must serialize and place unique identification numbers on drug packaging.[173]

By law, wholesalers will not be able to accept products that do not meet the serializing identification number protocol.[173] Managing and balancing the supply chain of custody will be challenging and expensive. Only the future will tell whether DACSA will strengthen the supply chain and eliminate its weaknesses. Raw material shortages account for only 9% of the drug shortages averaged over three years. However, this attention has highlighted vulnerabilities in the supply chain. Figure 14. Exhibits primary root causes and how they contribute to quality issues.

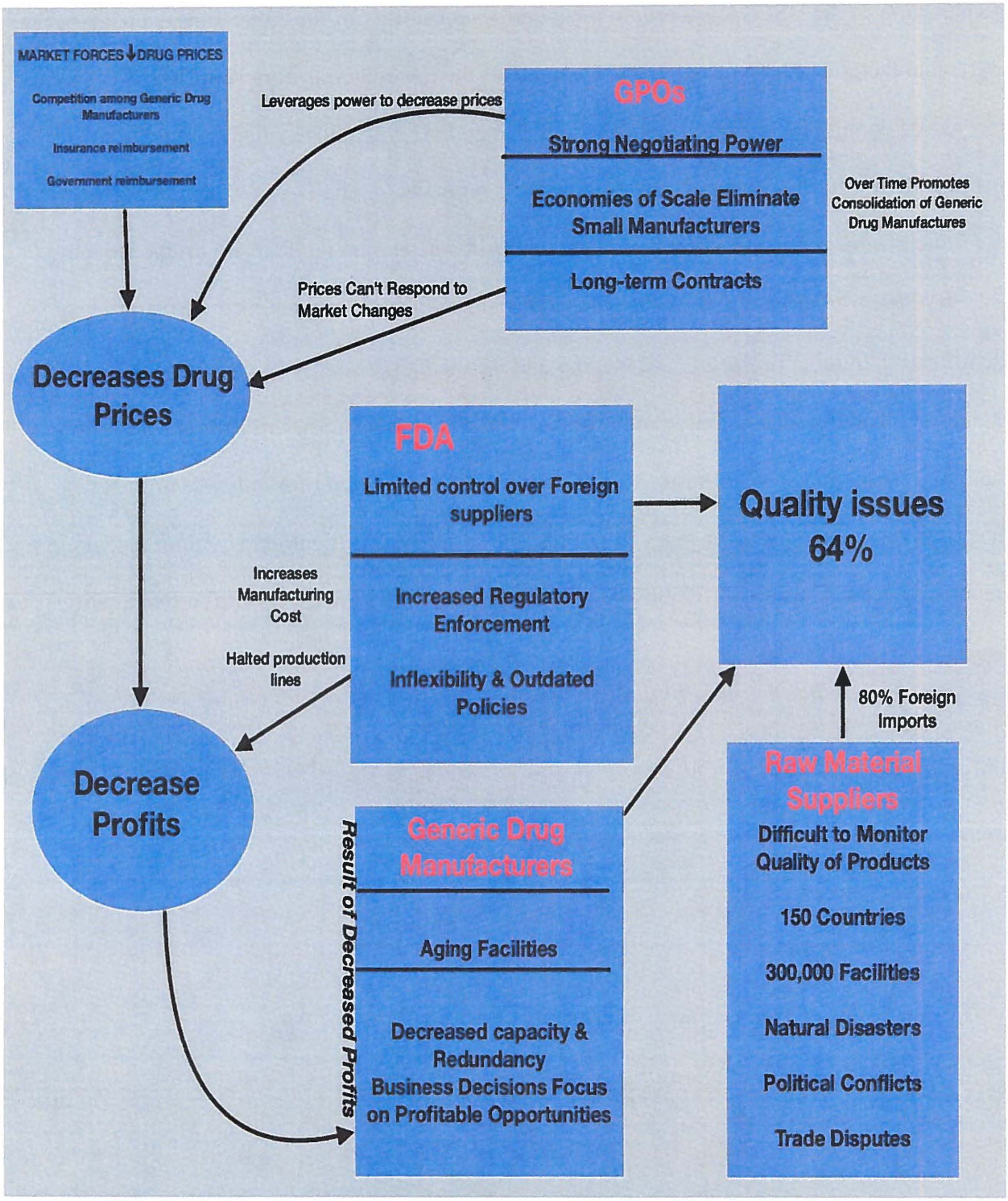


Figure 14. Primary Root Causes and How They Contribute to Quality Issues

Healthcare Facilities

Both vertical and horizontal consolidation trends in the healthcare market are well documented.[86,177] Consolidation does not appear to play an important factor in the sterile generic drug shortages. Increasing market share by consolidating hospital systems fosters a corresponding increase in market buying power. However, most hospitals do not acquire pharmaceuticals directly from the manufacturers; they use GPOs to negotiate the best prices.[14] Through GPOs the hospital systems have a tremendous amount of buying power since a small number of GPOs control 85 to 90% of the market, as previously discussed.[14,28,68]

Inventory practices such as just-in-time may intensify drug shortages by decreasing the buffer a hospital has against any disruption in the supply chain. This is a secondary affect and not a factor in the original root cause.

Stockpiling is associated with causing artificial shortages and draining the supply chains.[59,178] In industrialized countries during stable economic periods, it is expected that scarcity of commodities will be rare.[179] "Hoarding exists when consumers' current inventory of an item exceeds its inventory in previous periods while the expected consumption rate remains constant"[179] The biggest threat is consumers' concerns and overreaction. The pharmaceutical industry agreed that it would not be able to keep up with demand if consumers started hoarding and panic buying.[180] The Vice President at McKesson Corporation warned, "If people believe there will be a disruption, then there will be a disruption."... "People react out of their perceptions and create reality,"[180] The mere mention of a shortage can actually cause panic buying and hoarding; thus creating an artificial shortage. Overbuying and stockpiling of drugs by hospital pharmacies may in some instances create secondary shortages. By amassing a large amount of inventory in anticipation of increased demand of substitute drugs, hospitals may

actually cause drug shortages of substitute medications. In addition, ordering excessive amounts of drugs that are in short supply can exacerbate the problem by causing distributive inequities.

Compounding pharmacies do not play a role in creating drug shortages. Some argue that they actually help by providing an alternative to commercial drug manufacturers. The Association of State and Territorial Health Officials (ASTHO) suggests that compounding pharmacies have been singled out as a means to increase drug availability during the shortages.[181] While the potential to lessen the impact of the drug shortages is possible by utilizing compounding pharmacies, the lack of FDA oversight and historical mishaps make using compounding pharmacies a risky venture. The Drug Quality and Security Act (DQSA) enacted November 27, 2013 established opportunities for large-scale outsourcing facilities that compound sterile drugs to voluntarily register and be subject to FDA oversight.[182] However, compounding pharmacies will continue under the oversight of the state boards, which will strive to increase communication between federal and state entities.[182]

Healthcare Professionals

There is no documentation in the literature that supports or implies that healthcare professionals contribute to the root causes of drug shortages. Documentation suggests that healthcare workers suffer emotionally due to added stress. Ethical dilemmas related to the allocation of scarce resources that determines life and death place healthcare professionals in an insufferable position. Drug shortages impact the healthcare professionals' ability to deliver quality healthcare. With scant options due to drug shortages, choices are made to use expensive alternatives that may or may not be as effective. Therefore, healthcare professionals may unwittingly, given the limited therapeutic choices, raise the cost of healthcare.

Wholesalers Distributors

Wholesalers play a fundamental role in the sterile generic drug supply chain. There is no supporting evidence that wholesalers play a major role in drug shortages. Although, the development of gray markets may exacerbate the drug shortages. By diverting drugs from the principal-users to secondary wholesalers and fake pharmacies, the drugs reside in the supply chain longer and may need to be disposed of due to limited shelf life. By delaying drugs from getting to the end-users and increasing drug wastage, the gray market exacerbates the drug shortages on two fronts while also increasing the cost of healthcare. Many end-users do not buy drugs from gray market wholesalers because the drug pedigree cannot be verified. Without a proper pedigree, the drugs legitimacy cannot be substantiated.

Three conditions must exist for gray markets to develop.[183] First, the gray market must have a supply source.[183] Second, barriers must be low enough to move products from one supply route to another.[183] Third, price differentials must be large enough to provide incentives for gray marketing.[183] All three of these conditions are met by the current drug shortages. Network wholesalers monitor the market looking for indications of new drug shortages. They monitor trade and government websites and watch for major recalls with the intention of buying as much as possible of a drug in short supply.[184] Once they acquire the scarce medication, they stockpile and hoard the medication that they will later sell at inflated prices. Weakness and loopholes in the supply chain present low barriers to gray market profiteers allowing gray market medications to leak into the drug supply chain. The drug shortages provide profit-making opportunities for gray market profiteers. Some refer to the profiteers as "price gougers" and "scalpers".[158] An article in the Canadian Medical Journal titled: 'Prices Gone Wild: Grey Market 'Scalpers'

Scoring Windfall in American Drug Market" stated that there is no federal law against price gouging.[185]

Patients

The impact of the drug shortages on patients has been well documented.[22,94,151] The patients have had to contend with delayed treatments, canceled surgeries, inadequate clinical outcomes, and increased risks including death.[94,110] Patients' clinical outcomes also have been affected by using replacement drugs that were not as efficacious as the first line therapy.[8,110,113] In 2011, at least 15 deaths and numerous adverse outcomes have been attributed to drug shortages.[113,152,153]

Insurance Companies

Health insurance companies do not play a major role in the root causes of the drug shortages. The economic impact is focused primarily on the patient with healthcare systems also absorbing costs for alternative medication not covered by insurance companies. However, health insurance may play a role in contributing to drug price inelasticity. Health insurance limits consumers' incentives to be concerned about costs associated with the use of medical services.[186] Insurance coverage lowers an individual's risk and consequently increases the demand for pharmaceuticals. By spending someone else's money for drug purchases, individuals become less price sensitive. Consumers also lack the appropriate knowledge to make sound economic and medical decisions.[186]

Conclusion

The U.S. is a leader in technology, finance and business, entertainment and higher education. The U.S. has drugs that can treat erectile dysfunction, grow longer eyelashes, and paralyze muscles to prevent wrinkles. However, many drugs that are medically necessary to

treat life-threatening illnesses are in short supply. Why? Understanding the problem and all its complexities is the first step. Economic and stakeholder analysis is the key. The overlapping relationships of the four stakeholders that are identified as "primary" root causes of the drug shortages are complicated. The market will not recover on its own due to non-market forces, normative ethics, moral obligations, and human emotional factors. The new question becomes what adjustments need to be implemented that will solve the drug shortage problem without upsetting and distorting the generic market even more. There is not a quick fix. While solutions will take time to emerge, mitigation of "secondary effects", "safety issues", and "consequences of the drug shortages" can alleviate some of the symptoms but will not cure the sick market.

The drug shortages are unlikely to resolve in the near future. The FDA, drug manufacturers, and healthcare facilities are doing what they can to mitigate the impact of drug shortages. The roots causes are complicated and not easily remediated. Future research should focus on how to incentivize manufacturers to produce older sterile generic drugs. Generic drug manufacturing companies have a fiduciary responsibility and obligation to make a profit thereby increasing the wealth of the shareholders. Making these drugs profitable is the only way that private companies can rationalize producing these older generic drugs in lieu of other profit making opportunities.

Government subsidies, tax breaks, and other incentives should be explored. Increasing supply by extending shelf life should also be investigated. A FDA study found that as many as 90% of drugs were still efficacious after their expiration dates.[187] Many of these drugs were found to be safe and effective years after the manufacturer's expiration date. One drug was found to be as effective 15 years after the expiration date.[187] Globalization is a theme that keeps recurring throughout this study on drug shortages. Perhaps more effort should be focused on a

global solution since drug shortages seem to be a global problem. Organizations such as the World Health Organization (WHO) or the United Nations (UN) should make an effort to unite and explore joint solutions to the mutual problem of drug shortages.

Limitations of this paper are as follows. The research is based on data that is dynamic and in many cases subjective. Minimal empirical data was available for analysis. Analysis, opinions, and conclusions are based on information that was accessible at the time. As drug shortages evolve, new information continues to become available enhancing awareness and shedding light onto the drug shortage problems. Continued research is essential to move forward.

Bibliography

1. Koh H. *Testimony of Dr. Howard Koh*. Washinton DC: US House of Representatives; 2011. Examining the Increase In Drug Shortages.
2. Hamburg MA. *Report to Congress: First Annual Report on Drug Shortages for Calendar Year 2013*: Food and Drug Administration; 2014. First Annual Report on Drug Shortages.
3. White House. *Executive Order 13588 -Reducing Prescription Drug Shortages*: White House; 2011. Executive Order 13588.
4. Kweder S. Prescription Drug Shortages: Examining a Public Health Concern and Potential Solutions. *FDA.gov*. December 15, 2011. Available at: http://www.fda.gov/NewsEvents/Testimony/ucm282956.htm. Accessed February 12, 2016.
5. Food and Drug Administration. Introduction and Background Table of Contents: A Review of FDA's Approach to Medical Product Shortages. *FDA.com*. November 3, 2011. Available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm277745.htm#characteristics. Accessed February 26, 2016.
6. FDA. Text Version: Drug Shortages Infographic. *FDA.com*. April 7, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm441585.htm. Accessed June 12, 2015.
7. Baye MR. *Managerial Economics and Business Strategy*. Fifth ed. New York: McGraw-Hill Irwin; 2006.
8. Ventola CL. The Drug Shortage Crisis in the United States Causes, Impact, and Management Strategies. *Pharmacy and Therapeutics*. 2011;36(11):740-757.
9. Chisholm-Burns MA, Vaillancourt AM, Shepherd M. *Pharmacy Management, Leadership, Marketing, and Finance*. Vol 1. 2nd Edition ed. Burlington: Jones & Bartlett Learning; 2014.
10. Gwartney JD, Stroup RL, Sobel RS, Macpherson DA. *Economics Private and Public Choice*. 14th ed. Mason: Cengage Learning; 2013.
11. Kantarjian HM. When the drug you need to cure a cancer is nowhere to be found. *The Washington Post*. April 18, 2011. https://www.washingtonpost.com/national/health/when-the-drug-you-need-to-cure-a-cancer-is-nowhere-to-be-found/2011/04/11/AFH802zD_story.html. Accessed july 3, 2015.
12. Kaitin KL. The landscape for Pharmaceutical Innovation: Drivers of Cost-Effective Clinical Research. *Pharm Outsourcing*. August 2011.
13. DeRuiter J, Holston PL. Drug Patent Expirations and the "Patent Cliff". *US Pharmacist*. June 2012;37(6).
14. Haninger K, Jessup A, Koehler K. *Economic Analysis of the Causes of Drug shortages*: United States Government; 2011. ASPE issue Brier.
15. IMS INSTITUTE for HEALTHCARE INFORMATICS. *Drug Shortages: A closer look at products, suppliers and volume volatility*: IMS INSTITUTE for HEALTHCARE INFORMATICS; 2011. Drug Shortages: A closer look.
16. Selyukh A. Study finds U.S. drug shortage problem concentrated. *Reuters*. November 14,

2011. http://www.reuters.com/article/2011/11/14/us-drugs-shortages-imshealth-idUSTRE7AD1CJ20111114. Accessed August 20, 2015.

17. Hill JM, Reilly C. Can the United States Ensure an Adequate Supply of Critical Medicatios? *Publication of the Food and Drug Law Institute*. August 2011;1(16).
18. Shelley S. The quality improvement drive to address shortages. *Pharmaceutical Commerce*. January 28, 2015. http://www.pharmaceuticalcommerce.com/index.php?pg=manufacturing_and_packaging&articleid=27458&keyword=drug%20shortages-manufacturing%20quality%20problems. Accessed August 21, 2015.
19. Lee SB. The Drug Sjhrotage Crisis: When Generic Manufacturers" Just Say No". *Oregon Law Review*. 2014;93:355.
20. Gottlieb S. *Drug Shortages: Why they happen and what they mean*. Washington, DC: American Enerprise Institude; 2011. Statement before the Senate Finance Committee.
21. Fox ER, Sweet BV, Jensen V. Drug Shortages: A Complex Health Care Crisis. *Mayo Clinic Proceedings*. March 2014;89(3):361-373.
22. Orlovich DS, Kelly RJ. Drug Shortages in the U.S. - A Balanced Perspective. *Journal of the Anesthesia Patient Safety Foundation*. February 2015.
23. US Food & Drug Administration. *DRUG SHORTAGES AND THE FDA RESPONSE*: US Food & Drug Administration; 2014.
24. FDA. Inquiry regarding overseas generic sterile injectable drug manufactering
25. Woodcock J, Wosinska M. Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages. *Clinical Pharmacology and Therapeutics*. Febuary 2013;93(2).
26. Barei F, Le Pen C, Simoens S. The Generic Pharmaceutical Industry: moving beyond incremental innovation towards re-innovation. *Generics and Biosimilars Initiative Journal*. 2013;2(1).
27. Chabner BA. Drug Shortages A Crititcal Challenge for the Generric-Drug Market. *The New England Journal of Medicaine*. December 2011;365:2147-2149.
28. Assistant Secretary For Planning and Evaluation. *Economic Analysis of the Causes of Drug Shortages*: Office of Science and Data Policy; 2011.
29. The Economist. Going large: A wave of new medicines known as biologics will be good for drugmakers, but may not be so good for health budgets. *The Economist*. January 2015.
30. Food and Drug Administration. What Are "Biologics" Questions and Answers. *FDA.gov*. August 15, 2015. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm. Accessed February 2, 2016.
31. FDA. Information on Biosimilars. *FDA.com*. February 22, 2016. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/. Accessed March 17, 2016.
32. Blackstone EA, Fuhr JP. The Economics of Biosimilars. *Am Health Drug Benefits*. Septembe/October 2013;6(8):469–478.
33. Food and Drug Administration. Biosimilars. *FDA.gov*. August 15, 2015. Available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm. Accessed February 2, 2016.

34. Hospira. Pfizer Completes Acquisition of Hospira. *Hospira.com*. September 3, 2015. Available at: http://www.hospira.com/en/about_hospira/newsroom/press_releases/pfizer_acquisition_press_release. Accessed February 2, 2016.
35. Ramachandra S. Lessons for the United States: Biosimilar Market Development Worldwide. *FTC.gov*. February 4, 2014. Available at: https://www.ftc.gov/system/files/documents/public_events/Follow-On%20Biologics%20Workshop%3A%20Impact%20of%20Recent%20Legislative%20and%20Regulatory%20Naming%20Proposals%20on%20Competition/ramachandra.pdf. Accessed February 2, 2016.
36. Hirschler B, Shields M. Novartis launches first U.S. 'biosimilar' drug at 15 percent discount. *Reuters.com*. September 3, 2015. Available at: http://www.reuters.com/article/us-novartis-drug-idUSKCN0R30C220150903. Accessed February 2, 2016.
37. Fischer E. The Patent cliff:rise of the generics. *Pharmaceutical-technology.com*. October 5, 2011. Available at: http://www.pharmaceutical-technology.com/features/featurethe-patent-cliff-rise-of-the-generics/. Accessed August 21, 2015.
38. Schweitzer SO. How the US Food and Drug Administration Can Solve the Prescription Drug Shortage Proble. *American Journal of Public Health*. May 2013;103(5).
39. Kotler P, Keller KL. *Marketing Management*. Vol 1. 14E ed. Upper Saddle River: Prentice Hall.
40. Throckmorton ,DC. *FDA Response to Drug Shortages*: US Food & Drug Administration; 2014.
41. Graham JR. *A Concentrated Market*: Mackinac Center for Public Policy; 2012. 978-0-9833004-9-6.
42. Palmer E. Hospira again shipping ketorolac but U.S. faces many drug shortages. *FiercePharmaManufacturing.com*. June 2, 2015. Available at: http://www.fiercepharmamanufacturing.com/story/hospira-again-shipping-ketorolac-us-faces-many-drug-shortages/2015-06-02. Accessed Setember 20, 2015.
43. Pfizer. Pfizer Completes Acquisition of Hospira. *Pfizer.com*. September 3, 2015. Available at: http://www.pfizer.com/news/press-release/press-release-detail/pfizer_completes_acquisition_of_hospira. Accessed February 2, 2016.
44. Pierson R, Berkrot B. Pfizer to buy Allergan in $160 billion deal. *Reuters.com*. November 24, 2015. Available at: http://www.reuters.com/article/us-allergan-m-a-pfizer-idUSKBN0TB0UT20151124. Accessed February 2, 2016.
45. Koons C, Cortez. Bloomberg business. *Pfizer and Allergan to Combine With Joint Value of $160 Billion*. November 22, 2015. Available at: http://www.bloomberg.com/news/articles/2015-11-22/pfizer-allergan-said-to-be-close-to-150-billion-merger. Accessed February 17, 2016.
46. Oldfield E. Median Price Chang for Generic Drugs is 0%. *Pharmacy Times*. October 2014.

47. Silverman E. How Much? Some Generic Drug Prices Are Skyrocketing: Analysis. *The wall Street Journal*. August 2014.
48. Colliver. Prices soar for some generic drugs. *SFGATE*. January 2014.
49. Pollack A. Drug Goes From $13.50 a Tablet to $750, Overnight. *The New York Times*. September 2015.
50. Pollack A, Creswell J. Martin Shkreli, the Mercurial Man Behind the Drug Price Increase That Went Viral. *New York Times*. September 2015.
51. Health Policy Briefs. Health Policy Briefs. *Health Affairs*. September 24, 2014. Available at: http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=124. Accessed August 21, 2015.
52. U.S. Food and Drug Administration. Facts About the Current Good Manufacturing Practices (CGMPs). *U.S. Food and Drug Administration*. January 1, 2015. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm. Accessed August 24, 2015.
53. Steger J. Pharmaceutical Regulatory Compliance Congress. *Pharmaceutical Regulatory Compliance Congress ppt*. July 10, 2013. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwicxL3sl9rLAhVLLSYKHSmGARgQFggcMAA&url=http%3A%2F%2Fwww.fdli.org%2Fdocs%2Fmembers-only%2Fsteger-session-3-slides.pptx%3Fsfvrsn%3D0&usg=AFQjCNGV-8FUZYmJy5BHqpugcWu3RB-P-w&bvm=bv.117604692,d.eWE. Accessed August 25, 2015.
54. Szalavitz M. Health.Time.com. *Time.com*. September 17, 2012. Available at: http://healthland.time.com/2012/09/17/pharma-behaving-badly-top-10-drug-company-settlements/slide/amgen/. Accessed August 28, 2015.
55. Office of Public Affairs. Justice News. *The United States Department of Justice*. March 10, 2015. http://www.justice.gov/opa/pr/mcneil-ppc-inc-pleads-guilty-connection-adulterated-infants-and-childrens-over-counter-liquid. Accessed August 25, 215.
56. Fox ER. Manufacturing Quality Drives Drug Shortages. *Pharmacy Purchasing & Products*. March 2014. http://www.pppmag.com/article/1460/March_2014/Manufacturing_Quality_Drives_Drug_Shortages/. Accessed August 2015.
57. Meyer. The Anatomy of the Drug Shortages. *Anesthesia Patient Safety Foundation*. 2012;27(1):7.
58. Food and Drug Administration. Text Version: Drug Shortages Infographic. *U.S. Food and Drug Administration Protecting and Promoting Your Health*. April 10, 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm441585.htm. Accessed October 20, 2015.
59. Fox ER, Birt A, James KB, Kokko H, Salverson S, Soflin DI. ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems. *American Journal Health-System Pharm*. 2009;66:1399-406.
60. Sklamberg. FDA Voice- Globalization. *FDA.gov*. March 18, 2015. Available at: http://blogs.fda.gov/fdavoice/index.php/tag/globalization/. Accessed October 13, 2015.

61. GAO. Protecting Public Health through Enhanced Oversight of Medical Products. *gao.gov*. February 11, 2015. Available at: http://www.gao.gov/highrisk/protecting_public_health/why_did_study#t=1. Accessed January 30, 2016.
62. Sullivan T. Prescription Drug Shortages: Crisis Abating - Still Need for Pricing Reform. *Policy and Medicine*. December 19, 2012. Available at: http://www.policymed.com/2012/12/prescription-drug-shortages-crisis-abating-still-need-for-pricing-reform.html. Accessed September 9, 2015.
63. PDM Healthcare. PDM Healthcare. *History of GPO's*. 2015. Available at: http://www.pdmhealthcare-gpo.com/HistoryOfGPOs.aspx.
64. Health Care Supply Chain Association. 2025 M Street NW, Suite 800 Washington, DC 200 36 Phone (202) 367-1162 Fax (202) 367-2162 Web www.SupplyChainAssociation.org Email info@SupplyChainAssociation.org A PRIMER ON GROUP PURCHASING ORGANIZATIONS Questions and Answers. *www.SupplyChainAssociation.org*. Available at: http://c.ymcdn.com/sites/www.supplychainassociation.org/resource/resmgr/research/gpo_primer.pdf. Accessed September 8, 2015.
65. Jayanthi A. Becker's Review. *Becker's Healthcare*. july 18, 2014. Available at: http://www.beckershospitalreview.com/hospital-management-administration/50-things-to-know-about-the-country-s-largest-gpos.html. Accessed September 9, 2015.
66. Roger BD, Durrance CP. Group Purchasing Organizations, Monopsony, and Antitrust Policy. *Managerial and Decison Economics*. 2013.
67. United States Govenment Accountability Office. *Group Purchasing Organizations: Funding Structure Has Potential Implications for Medicare Cost*: United States Government; 2014. Report to Congress.
68. Sethi SP. *Group Purchasing Organizations: An Undisclosed Scandal in the U.S.* 1st ed. New York: Palgrave Macmillan.
69. Pizzi R. Healthcare GPO revenue to hit $2B in 2010. *Healthcare Finance*. January 5, 2010. Available at: http://www.healthcarefinancenews.com/news/healthcare-gpo-revenue-hit-2b-2010. Accessed September 9, 2015.
70. Healthcare Purchasing News. GPO FACTS & FIGURES. *CLINICAL INTELLIGENCE FOR SUPPLY CHAIN LEADERSHIP*. October 2012. Available at: http://www.hpnonline.com/resources/GPOs.html. Accessed September 9, 2015.
71. Nelson R. medscape. *medscape.com*. January 24, 2013. Available at: http://www.medscape.com/viewarticle/778146. Accessed March 4, 2015.
72. Blair RD, Piette C. Group Purchasing Organizations, Monopsony, and Antitrust Policy. *Managerial and Decision Economics*. October 2014;35(7):433-443.
73. Kurian. *The AMA Dictionary of Business and Management*. New York: Publishing Division of the American Management Association; 2013.
74. Lindsay MA. Antitrust and Group Purchasing. *Antitrust*. 2009;23(3).
75. Sethi SP. *Group Purchasing Organizations: An Evaluation of Their Effectiveness in Providing Services to Hospitals and Thier Patients*: International Center for Corporate

Accountability; 2006.

76. Kantarjian H. Chemotherapy Drug Shortages in the United States Revisited. *Journal of Oncology Practice*. September 2014;10(5):329-31.
77. AmosWeb Encyclonomic. Oligopoly and Monopolistic Competition. *amosweb.com*. 2015. Available at: http://www.amosweb.com/cgi-bin/awb_nav.pl?s=wpd&c=dsp&k=oligopoly%20and%20monopolistic%20competition. Accessed October 13, 2015.
78. Economics Online. Economics Online - Oligopoly. *economicsonline.co.uk*. 2015. Available at: http://www.economicsonline.co.uk/Business_economics/Oligopoly.html. Accessed October 13, 2015.
79. Burns LR, Joo-Jin Kim J. *The Performance of Group Purchasing Organizations (GPOs) in the Health Care Value Chain: A literature Review*: Wharton University of Pennsylvania; 2014.
80. Weinstein, Weinstein BL. The Role of Group Purchasing Organizations (GPOs) in the U.S. Medical Industry Supply Chain. *Estudios De Economia Aplicada*. 2006;24(3):789-802.
81. Earl P, Zweig PL. Connecting the Dots: How Anticonpetitive Contracting Practices, Kickbacks, and Self-dealing by Hospital Group Purchasing Orgainizations (GPOs) Caused the U.S. Drug Shortage. *careandcost.com*. February 14, 2012. Available at: http://careandcost.com/2012/02/14/connecting-the-dots-how-anticompetitive-contracting-practices-kickbacks-and-self-dealing-by-hospital-group-purchasing-organizations-gpos-caused-the-u-s-drug-shortage/. Accessed October 7, 2015.
82. Walsh M. When a Buyer for Hospitals Has a Stake in Drugs It Buys. *NYTimes.com*. March 26, 2002. Available at: http://www.nytimes.com/2002/03/26/business/when-a-buyer-for-hospitals-has-a-stake-in-drugs-it-buys.html?pagewanted=all. Accessed October 8, 2015.
83. Subcommittee on Antitrust, Business Rights, and Competition BUSINESS RIGHTS, AND COMPETITION. Hospital Group Purchasing: Lowering Cost at the Expense of Patient Health and Medical Innovation? *United States Government Printing Office*. April 30, 2002. Available at: https://www.gpo.gov/fdsys/pkg/CHRG-107shrg85986/html/CHRG-107shrg85986.htm. Accessed August 15, 2015.
84. GAO. *Study Suggests Large Buying Groups Do Not Always Offer Hospitals Lower Prices*: United States Congress; 2002. Testimony.
85. GAO. *Group Purchasing Organizations: Funding Structure Has Potential Implictions for Medicare Costs*: U.S. Congress; 2014. Report to Congress.
86. Wharten University of Pennsyvania. Knowledge @ Wharton. *Hospital Consolidation: Can It Work This Time?* May 11, 2015. Available at: http://knowledge.wharton.upenn.edu/article/hospital-consolidation-can-it-work-this-time/. Accessed November 5, 2015.
87. Cultler DM, Morton FS. Hospital, Market Share, and Consolidation. *Journal of the American Medical Association*. November 2013;310(18).
88. Dafny. Hospital Industry Consolidation — Still More to Come? *The New England Journal of Medicice*. January 2014;370:198-199.
89. Channick SA. The ACA, Provider Mergers, and Hospital pricing: Experimenting with

Smart, Lower-Cost Health Insurance options. *William & Mary Policy Review*. 2015;6(2).

90. Myers C, Lineen. hospital consolidation outlook surviving in a tough economy. *Healthcare Financial Management*. November 2009;63(11).
91. American Hospital Association. Fast Facts on U.S. Hospitals. 2015. Available at: http://www.aha.org/research/rc/stat-studies/fast-facts.shtml. Accessed October 29, 2015.
92. Weltman. THE NATION'S WEALTH ABOVE SENIORS' HEALTH? DRUG SHORTAGES RESULTING FROM MEDICARE PART B LEGISLATION. *Elder Law Journal*. July 2015;23:265-296.
93. Mark M. Challenges Posed by Drug Shortages. *American Society of Healt-System Pharmacists*. December 9, 2002. Available at: https://www.ashp.org/DocLibrary/Policy/DrugShortages/DShort-abbott-drug.aspx. Accessed November 28, 2015.
94. American Hospital Association. *AHA Survey on Drug Shortages*: American Hospital Association; 2011. Survey.
95. Guharoy R, Noviasky J, Haydar Z, Fakih MG, Hartman C. Coumpounding Pharmacy Conundrum: "We Cannot Live Without Them but We Cannot Live With Them". *Chest Journal*. April 2013;143(4).
96. Lee J. Compounding effort: Quality control, costs drive hospitals to mix drugs. *Modern Healthcare*. March 2013;43(9):12-14.
97. CONNECTION BETWEEN DRUG SHORTAGES CMSS. Inside Health Reform. *InsideHealthPolicy.com's*. November 14, 2012. Available at: http://libproxy.umflint.edu:2106/nursing/docview/1151717879/566DF53B5A1A4C67PQ/2?accountid=14584. Accessed Noveber 7, 2015.
98. Food and Drug Administration. Compounding and the FDA: Questions and Answers. *Drugs*. October 6, 2015. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm. Accessed November 3, 2015.
99. Food and Drug Administration. The Special Risks of Pharmacy Compounding. *For Consumers*. October 14, 2014. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107836.htm. Accessed November 3, 2015.
100. American Pharmacists Association. Pharmacist.com. *Frequently Asked Questions About Pharmaceutical Compounding*. November 19, 2012. Available at: http://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding. Accessed November 5, 2015.
101. Outterson K. Regulating Compounding Pharmacies after NECC. *Close:block:scholUnivAuthors Open:block:publicationBlock The New England Journal of Medicine*. November 2012;367(21):1969-72.
102. Modern Healthcare. When tragedy hit, providers were quick to respond. *Modern Healthcare*. December 2012;42(52):29.
103. Meyer T, Martin E, Prielipp R. The Largest Health Care Associated Fungal Outbreak in the U.S. *The Official Journal of the Anesthesia Patient Safety Foundation (APSF)*.

Spring/Summer 2013;28(1):4-7.

104. Centers for Disease Control and Prevention. Multistate Fungal Meningitis Outbreak Investigation. *CDC.Gov*. March 25, 2013. Available at: http://www.cdc.gov/hai/outbreaks/infographic.html. Accessed November 28, 2015.
105. Institute for Safe Medication Practices. Sterile Compounding Tragedy Is A Symptom Of A Broken System On Many Levels. *Ismp.com*. October 18, 2012. Available at: http://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=34. Accessed November 28, 2015.
106. Young. Outsourced Compounding Can Be Problematic. *American Society of Health-System Pharmacists*. December 1, 2002. Available at: http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=1125. Accessed November 28, 2015.
107. Tyler S. Understanding Drug & Managing Shortages. *American Society of Health-System Pharmacits*. December 9, 2002. Available at: https://www.ashp.org/DocLibrary/Policy/DrugShortages/DShort-abbott-drug.aspx. Accessed November 28, 2015.
108. Kaakeh R, Sweet BV, Reilly C, Bush C, DeLoach S. Impact of drug shortages on U.S. health systems. *American Journal of Health-System Pharmacy*. October 2011;68(19):1811-1819.
109. Navigating Drug Shortages in American Healthcare: A Premier healthcare alliance analysis. *Premierinc.com*. March 2011. Available at: https://legacy.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf. Accessed January 10, 2015.
110. Institute for Safe Medication Practices. Drug shortages: National survey reveals high level of frustration, low level of safety. *ISMO.org*. September 23, 2010. Available at: http://www.ismp.org/newsletters/acutecare/articles/20100923.asp. Accessed December 1, 2015.
111. American Society of Anesthesiologist. Drug shortages. *American Society of Anesthesiologist*. March 2012. Available at: https://www.asahq.org/advocacy/federal-activities/regulatory-activity/drug-shortages#Drug%20Shortages%20Survey. Accessed December 3, 2015.
112. O'Donnell JT, Vogenberg RF. Drug Shortages Pose Problems for P&T Committees in Accountable Care Organizations. *Pharmacy and Therapeutics*. July 2013;38(7):404-406.
113. Mazer-Amirshahi M, Pourmand A, Singer S, Pines JM. Critical Drug Shortages: Implications for Emergency Medicine. *Academic Emergency Medicine*. June 2014;21(6):704-711.
114. Jagsi R, Spence R, Rathmel KW. Ethical Considerations for the Clinical Oncologist in an Era of Oncology Drug Shortages. *Oncologist*. February 2014;9(2):186-192.
115. Johnson LM, Levine D. Allocation of Drugs in Short Supply. *AMA Journal of Ethics*. August 13, 2013. Available at: http://journalofethics.ama-assn.org/2013/08/ecas2-1308.html. Accessed January 3, 2015.
116. Committee on Oversight and Government Reform. *DRUG SHORTAGE CRISIS: LIVES ARE IN THE BALANCE*: House of Representative, US Government; 2011. Serial No. 112–

102.

117. Fink S. Drug Shortages Forcing Hard Decisions on Rationing Treatments. *nytimes.com*. January 29, 2016. Available at: http://www.nytimes.com/2016/01/29/us/drug-shortages-forcing-hard-decisions-on-rationing-treatments.html?_r=0. Accessed March 18, 2016.
118. Hoffmaster B, Hooker C. Tragic Choices and Moral Compromise: The Ethics of Allocating Kidneys for Transplantation. *Milbank Quarterly*. September 2013;91(3):528-557.
119. U.S. Food and Drug Administration. History. *About FDA*. March 23, 2015. Available at: http://www.fda.gov/AboutFDA/WhatWeDo/History/. Accessed January 4, 2016.
120. U.S. Food and Drug Administration. FDA Organization Overview. *About FDA*. November 2, 2015. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm393155.htm. Accessed January 4, 2016.
121. U.S. Food and Drug Administration. Members of the Drug Shortages Task Force. *FDA-Drugs*. December 10, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm358208.htm. Accessed January 4, 2015.
122. Kweder SL. *Prescription Drug Shortages: Examining a Public Health Concern and Potential Solutions*. Washington, D.C: U.S. Government; 2011. Testomony.
123. GAO. *DRUG SHORTAGES Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*. Washington, DC: United States Government Accountability Office; 2014. Report to Congressional Addressees.
124. University of Utah Health Care. National drug shortages at all-time high, threatening patient care. *University of Utah Health Care*. 2015. Available at: http://healthcare.utah.edu/publicaffairs/news/current/02-27-2014_National_drug_shortages.php. Accessed January 4, 2016.
125. Committee on Oversight and Government Reform. *FDA's Contribution to the Drug Shortage Crisis*. Washington D.C.: Committee on Oversight and Government Reform; 2012. Staff Report.
126. Roy A. How Margaret Hamburg's FDA Causes Cancer Drug Shortages. *Forbes.com*. June 15, 2012. Available at: http://www.forbes.com/sites/theapothecary/2012/06/15/how-margaret-hamburgs-fda-causes-cancer-drug-shortages/#2715e4857a0b3e30b87014ca. Accessed January 10, 2015.
127. House Committe and Oversight and Government Reform. Oversight Report: Meaningless Red Tape Causing Medication Shortages. *oversight.house.gov*. June 15, 2012. Available at: https://oversight.house.gov/release/oversight-report-meaningless-red-tape-causing-medication-shortages/. Accessed January 17, 2015.
128. FDA. Enforcement Activity. *Inspections, Compliance, Enforcement, and Criminal Investigations*. May 18, 2015. Available at: http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm. Accessed January 7, 2016.
129. FDA. Teva Parenterals Medicines, Inc.. *Inspections, Compliance, Enforcement, and Criminal Investigations*. December 11, 2009. Available at:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm209222.htm. Accessed January 10, 2016.

130. Rye B. *Medicare Price Controls Worsen Drug Shortages, Boost Gray Market*: Bloomberg Government Study; 2012.
131. Gaffney A. FDA Fires Back at Legislative Critics, Blames Manufacturers for Drug Shortages. *Regulatory Affairs Professionals Society*. July 25, 2012. Available at: http://www.raps.org/focus-online/news/news-article-view/article/1967/. Accessed January 7, 2016.
132. Weiss D. FDA Rejects Blame for Drug Shortages. *Pharmacytimes.com*. Augus 7, 2012. Available at: http://www.pharmacytimes.com/news/fda-rejects-blame-for-drug-shortages. Accessed January 7, 2016.
133. Gaffney A. Regulatory Affairs Professionals Society. *FDA Fires Back at Legislative Critics, Blames Manufacturers for Drug Shortages - See more at: http://www.raps.org/focus-online/news/news-article-view/article/1967/#sthash.6fxdSdqE.dpuf*. July 25, 2012. Available at: http://www.raps.org/focus-online/news/news-article-view/article/1967/. Accessed February 22, 2016.
134. Food and Drug Administration. *Strategic Plan for Preventing and Mitigating Drug Shortages*: U.S. Government; 2013.
135. FDA. Prescription Drug Shortages: Examining a Public Health Concern and Potential Solutions. *FDA.gov*. December 15, 2011. Available at: http://www.fda.gov/NewsEvents/Testimony/ucm282956.htm. Accessed January 10, 2015.
136. The U.S. Federal Trade Commission and the Antitrust Division. *COMPETITION ISSUES IN THE DISTRIBUTION OF PHARMACEUTICALS*: The U.S. Federal Trade Commission; 2014.
137. Dey S. If I follow US standards, I will have to shut almost all drug facilities: G N Singh. *Business-Standard.ocm*. January 30, 2014. Available at: http://www.business-standard.com/article/economy-policy/if-i-follow-us-standards-i-will-have-to-shut-almost-all-drug-facilities-g-n-singh-114013000034_1.html.
138. Clarke T. FDA chief says U.S. not targeting Indian drug companies in crackdown. *rueters.com*. February 21, 2014. Available at: http://www.reuters.com/article/fda-india-drug-safety-idUSL2N0LQ25P20140221. Accessed January 18, 2015.
139. The White House. Executive Order 13588 -- Reducing Prescription Drug Shortages. *Whitehouse.gove*. October 31, 2011. Available at: https://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-13588-reducing-prescription-drug-shortages. Accessed January 10, 2015.
140. Emanuel EJ. Shortchanging Cancer Patients. *The New York Times*. August 2011.
141. Krasomil A. Measuring the impact of the Medicare Prescripton Drug, Improvement, and Modernization Act of 2003 on Shortages of Sterile Injectable Oncology Drugs. *Dukespace.lib.duke.edu*. April 20, 2012;:Prepared for: The Office of Senator Robert P. Casey, Jr. Available at: http://dukespace.lib.duke.edu/dspace/bitstream/handle/10161/5236/evan_krasomil_MP.pdf?sequence=3. Accessed January 14, 2015.

142. Gatesman ML, Smith, TJ. The Shortage of Essential Chemotherapy Drugs in the United States. *N Engl J Med*. November 2011;365:1653-1655.

143. Twombly. Medicare Cost Containment Strategy Targets Several Oncology Drugs. *JNCI J Natl Cancer Inst*. August 2004;96(17):1268-1270.

144. United States General Accounting Office. *Payments for Covered Outpatient Drugs Exceed Providers' Cost*. Washington, DC: United States Government; 2001. Report to Congressional Committees.

145. Graham JR. The Shortage of Generic Sterile Injectable Drugs: Diagnosis and Solutions. *Mackinac Center for Public Policy*. June 14, 2012. Available at: https://www.mackinac.org/17073. Accessed January 14, 2015.

146. Federgruen A. The Drug Shortage Debacle—And How to Fix It. *WSJ.com*. March 1, 2012. Available at: http://www.wsj.com/articles/SB10001424052970203986604577253242913478400. Accessed January 15, 2015.

147. Cobb P. *Testimony on: Drug Shortages: Why They Happen and What They Mean*. Washington, DC: United States Senate Committee on Finance; 2011.

148. McCartney M. Daily drug shortages place avoidable pressure on primary care. *BMJ*. May 2015;350:2514.

149. Torjesen I. Drug shortages: it's time for Europe to act. *The Pharmaceutical Journal*. January 2015;294(7847).

150. Pauwels K, Simoens S, Casteels M, Huys I. Insights into European Drug Shortages: A Survey of Hospital Pharmacists. *PLoS One*. March 2015;10(3).

151. McLaughlin M, Kotis D, Thomson K, et al. Effects on Patient Care Caused by Drug Shortages: A Survey. *J Manag Care Pharm*. November/December 2013;19(9):783-88.

152. Schoen D. The Drug Shortage Crisis in America. *Forbes*. February 2012.

153. Koba M. Drug Shortage in the U.S. May Pose Deadly Problem for Patients. *Time*. January 2015.

154. Silverman E. The Number of Drug Shortages – And Patient Frustration – Keeps Growing. *WSJ.com*. June 1, 2015. Available at: http://blogs.wsj.com/pharmalot/2015/06/01/the-number-of-drug-shortages-and-patient-frustration-keeps-growing/. Accessed March 18, 2016.

155. The Health Strategies Consultancy LLC. *Follow the Pill: Understanding the U.S. Commercial Pharmaceutical Supply Chain*: Prepared for The Kaiser Family Foundation; 2005.

156. Cherici C, McGinnis P, Russell, W. Buyer beware: Drug shortages and the gray market. *Premier*. August 2011. Available at: https://legacy.premierinc.com/about/news/11-aug/Gray-Market/Gray-Market-Analysis-08152011.pdf. Accessed January 22, 2015.

157. Merriam-Webster dictionary. Gray market. *Merriam-Webster*. nd. Available at: http://www.merriam-webster.com/dictionary/gray%20market. Accessed October 10, 2015.

158. House Committee on Oversight and Government Reform. *Shining Light on the "Gray Market"*. Washington D.C.: The United States congress; 2012. Staff Report.

159. Food and Drug Administration. CPG Sec. 160.900 Prescription Drug Marketing Act --

Pedigree Requirements under 21 CFR Part 203. *Inspections, Compliance, Enforcement, and Criminal Investigations*. March 20, 2015. Available at: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073857.htm. Accessed January 26, 2016.

160. Majority Committee Staff. The Committee on Energy and Commerce. *docs.house.gov*. February 25, 2014. Available at: http://docs.house.gov/meetings/IF/IF02/20140227/101804/HHRG-113-IF02-20140227-SD002.pdf. Accessed January 25, 2015.
161. Food and Drug Adminstration. Counterfeit Drug Task Force Report October 2003 - Backround: Vunerabilities in the U.S. Drug Distribution System. *Drug Safety and Availability*. October 2003. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm174479.htm. Accessed January 24, 2015.
162. Blackstone EA, Fuhr JP, Pociask S. The Health and Economic Effects of Counterfeit Drugs. *Am Health Drug Benefits*. June 2014;7(4):216-224.
163. Food and Drug Administration. FDA Initiative to Combat Counterfeit Drugs. *Drug Safety and Availability*. September 10, 2009. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm180899.htm. Accessed January 25, 2015.
164. Valdez ML. Challenges and Opportunities of Globalization. *FDA.gov*. September 18, 2014. Available at: http://www.fda.gov/NewsEvents/Speeches/ucm415612.htm. Accessed February 28, 2016.
165. National Community Pharmacists AssociationNational Community Pharmacists Association. *"Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages"*: United States House of Representatives Committee on Energy and Commerce; 2012. Hearing.
166. Fox E. *Current Trends In Drug Shortages*: National Pharmacy Forum; 2013. Presentation.
167. Deloitte. *2015 Global life sciences outlook Adapting in an era of transformation* 2014. Deloitt.market analysis of generics.
168. Rattinger GB, Jain R, Ju J, Mullins DC. Principles of Economics Crucial to Pharmacy Students' Understanding of the Prescription Drug Market. *American Journal of Pharmaceutical Education*. June 2008;72(3):61.
169. Zwolinski M. The Ethic of Price Gouging. *St. John University.edu*. November 10, 2014. Available at: http://website-box.net/site/facpub.stjohns.edu. Accessed January 15, 2016.
170. GAO. Drug Saftey FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed. *GOA.gov*. September 2010. Available at: http://www.gao.gov/products/GAO-10-961. Accessed February 28, 2016.
171. Feldstein PJ. *Health Care Economics*. Vol 1. 7th ed. Clifton Park: Delmar; 2012.
172. Polite BN, Ward JC, Cox JV, Morton RF, Hennessy J, Page RD. Payment for Oncolytics in the United States: A History of Buy and Bill and Proposals for Reform. *Journal of Oncology Practice*. November 2014;10(6):357-362.
173. Goodbaum B. The Race is On: Chain of Custody in the Pharmaceutical Supply Chain. *inboundlogistics.com*. April 2015. Available at:

http://www.inboundlogistics.com/cms/article/the-race-is-on-chain-of-custody-in-the-pharmaceutical-supply-chain/. Accessed January 31, 2016.

174. HEARING BEFORE THE SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES. *THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES.* Washington D.C.: United States Government; 2008. Hearing.
175. Trieste Mv. Ensuring a Robust Raw-Materials Supply Chain. *BioPharm International.* july 2014;27(7).
176. Challener CA. Supply Chain Security Tops Concerns for Biopharma Raw Materials. *Pharmaceutical Technology Sourcing and Management.* September 2014;10(9).
177. Federal Trade Commission. Examining Health care Competition. Paper presented at: Hosted by the Federal Trade Commission and U.S. Department of Justice, Antitrust Division , 2015; Washington DC.
178. American Society of Health-System Pharmacist. *Best Practices for Hospital and Health-System Pharmacy 2013-2014*: American Society of Health-System Pharmacist; 2013.
179. Stiff , Johnson , Tour K. Scarcity and Hoarding: Economic and Social Explanations and Marketing Implications. *Association for Consumer Research.* 1971. Available at: http://www.acrwebsite.org/volumes/5764/volumes/v02/NA-02. Accessed November 28, 2015.
180. Fleming H. Stop stockpiling! *Drug Topics.* February 1999;143(4):65.
181. Association of State and Territorial Health Officials. Coping with and Mitigating the Effects of Shortages of Emergency Medications. *EMS.gov.* December 2012. Available at: http://www.ems.gov/pdf/2013/ASTHO_Shortages_of_Emergency_Meds.pdf. Accessed November 30, 2015.
182. National Conference of State Legislatures. OVERSIGHT OF THE U.S. DRUG SUPPLY. *National Conference of State Legislatures.* October 1, 2014. Available at: http://www.ncsl.org/research/health/regulation-and-oversight-of-the-u-s-drug-supply-h-r-3204-the-drug-quality-and-security-act.aspx. Accessed November 30, 2015.
183. Duham DF, Sheffet J. Gray Markets and the Legal Status of Parellel Importation. *Journal of Marketing.* July 1988;52(3):75.
184. Allen TJ. Grey Market Drugs: Profiting from Poorly Managed U.S. Health Care. *Corpwatch.org.* January 22, 2012. Available at: http://www.corpwatch.org/article.php?id=15666. Accessed January 28, 2016.
185. Woodward C. Prices gone wild: Grey market 'scalpers' scoring windfall in American drug market. *CMAJ.* February 2012;184(2):119-120.
186. Feldstein PJ. *Health and Economic Policy Perspective Issues.* Vol 1. 5th ed. Chicago: Aupha; 2011.
187. Cohen LP. Many Medicines Are Potent Years Past Expiration Dates. *Wall Street Journal.* March 2000.