Diagnosing Drug Shortages

By

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Abstract

Wealthy countries are increasingly experiencing shortages of a wide range of generic drugs. These shortages are creating substantial harms for patients and problems for health systems. Despite recurring shortages and industry investigations, the nature and character of the drug shortage crisis remain the same: shortage drugs provide slim or negative profit margins, generic drug companies are reluctant to invest in quality improvements, and manufacturers are finding more reason to exit shortage drug markets. This thesis catalogues and explores these and other causes of the problem.

The proposals that have been made to address the problem at best merely mitigate it, and only target the systemic manufacturing and regulatory issues that immediately precede a shortage. The targeted issues are only symptoms, and not the root causes of drug shortages. In order to properly address the drug shortage crisis and minimize these symptoms, solutions must acknowledge the underlying economic mechanisms that make the crisis a reality. This thesis argues that, specifically, tackling drug shortages requires that one examine the economic pressures exerted on drug manufacturers by the Medicare Modernization Act’s Average-Sales-Price (ASP) reimbursement system, and the practices and behaviours of group purchasing organizations. To understand these pressures and effects on manufacturers is to uncover some of the root economic causes of the drug shortage crisis that give rise to the manufacturing issues immediately preceding drug shortages.
Acknowledgements

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
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<td>AHA</td>
<td>American Hospital Association</td>
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<td>ASP</td>
<td>Average-Sales-Price</td>
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<td>ASPE</td>
<td>Office of the Assistant Secretary for Planning and Evaluation</td>
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<td>ASHP</td>
<td>American Society of Health-System Pharmacists</td>
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<td>cGMP</td>
<td>Current Good Manufacturing Practices</td>
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<td>CMS</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
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<tr>
<td>DEA</td>
<td>Drug Enforcement Administration</td>
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<tr>
<td>DHHS</td>
<td>Department of Health &amp; Human Services</td>
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<tr>
<td>DSH</td>
<td>Disproportionate Share Hospital</td>
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<td>DSS</td>
<td>Drug Shortage Staff</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FD&amp;C</td>
<td>Federal Food, Drug, and Cosmetic Act</td>
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<td>FDASIA</td>
<td>Food and Drug Administration Safety and Innovation Act</td>
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<tr>
<td>GAO</td>
<td>Government Accountability Office</td>
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<tr>
<td>GPO</td>
<td>Group Purchasing Organization</td>
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<tr>
<td>HCPCS</td>
<td>Healthcare Common Procedure Coding System</td>
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<tr>
<td>HSCA</td>
<td>Healthcare Supply Chain Association</td>
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<tr>
<td>ISMP</td>
<td>Institute for Safe Medication Practices</td>
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<tr>
<td>MMA</td>
<td>Medicare Modernization Act</td>
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<tr>
<td>NDC</td>
<td>National Drug Code</td>
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<tr>
<td>UMHS</td>
<td>University of Michigan Health System</td>
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<td>UUDIS</td>
<td>University of Utah Drug Information Service</td>
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Chapter 1. Introduction

The drug shortage crisis is a growing problem across the globe. It affects everything from several routine childhood vaccines, anti-infective agents, and cancer medicines to central nervous system agents, cardiovascular drugs, and anaesthetics.

Over the six years since the recognition of drug shortages as a serious international problem, the number and classes of drugs affected by shortages have increased, along with the duration of shortages and the number of manufacturers involved.¹

Despite numerous recurring shortages and industry investigations, the nature and character of drug shortages remain the same. Shortage drugs are not profitable, manufacturers have little incentive to remain in low-profit markets, and companies are reluctant to invest in quality-related manufacturing. Much of the recent literature on drug shortages place little emphasis on the underlying economics of the healthcare industry, instead emphasizing drug and manufacturing quality² or communication issues³ as the root cause of drug shortages over the economic mechanisms that make drug and manufacturing quality a prevailing issue.

Focusing on the United States, this thesis will primarily analyze the overall causes and solutions to drug shortages. Chapter 2 outlines the ethical implications of the drug shortage crisis, identifying how shortages prevent clinicians from fulfilling their moral obligations to patients. Chapter 3 thoroughly traces the aetiology of drug shortages from the oft scapegoated systemic manufacturing issues, and proceeding downward through the communication and regulatory

issues that exacerbate and complicate drug shortages, to the underlying economic mechanisms rooted in faulty government policy and legislation that make the ‘surface’ manufacturing issues a reality. Specifically, Part D offers an economic analysis of the underlying causes of shortages that exert immense financial and economic pressure on drug manufacturers, and make systemic issues more likely to occur. Chapter 4 reviews the current approaches to addressing drug shortages, and offers some criticism of the FDA’s strategic plan for addressing shortages. Lastly, chapter 5 examines some potential solutions to drug shortages, ultimately suggesting significant alterations to the Medicare Modernization Act’s average sales price (ASP) based reimbursement system, and proposing investigative action into group purchasing organization practices only after changes to the Medicare reimbursement system have been made. I conclude the work by emphasizing the necessity of addressing the key economic factors that make drug shortages possible as the root causes of the surface systemic issues if we are to effectively prevent drug shortages, instead of solely mitigating impacts as shortages recur.
Chapter 2. The short on drug shortages

In a drug shortage, local actors rarely know when supplies of a drug may become available.¹ The typical response is that health care systems will order more than the usual quantity of product. Survey data from the American Hospital Association in 2011 indicates that 85 percent of hospitals participate in excessive ordering in response to a drug shortage.² This purchasing behaviour balloons the demand of the requested drugs that are, in a sense, already ‘on backorder’. Large backorders generally equate to longer shortage durations of the backordered drugs, which may lead to an imprecision in subsequent orders from health care systems that are the last systems affected by a shortage. The likely result is excessive ordering from various health care systems in different magnitudes of ‘excessive’, which means that some health care systems may end up with an absurdly excessive supply, whereas other hospitals may still have little or no access to the affected drug.³ Thus shortages are also problems in stockpiling and hoarding drugs at the institutional level, in response to uncertainty about a drug’s future availability, and the absence of this vital information. The American Society of Health-System Pharmacists (ASHP) notes that stockpiling drugs can be quite costly to institutions, especially if the drug shortage is averted or overestimated, in which case the stockpiler will be left with excess supply of a drug at a cost that will not be absorbed, resulting in a financial loss and clear demonstration of misspending.⁴ In an alternative case, where a drug shortage is neither averted nor overestimated, hoarding and stockpiling drugs only exacerbates the drug shortage for other

³ GAO Drug Shortages, p. 18.
health care systems, which ought to collectively service society as a whole. An FDA officer, however, reports that the United States Federal Food, Drug, and Cosmetic Act (FD&C) does not prohibit the hoarding or stockpiling of shortage drugs. Hoarding and stockpiling is not an excitingly topical issue in the realm of drug shortage discussions. For instance, in the United States, what little discussion of stockpiling there has been has only resulted in an agreement that hoarding and stockpiling shortage drugs is a serious issue, but not one that is or will be considered an actionable offense by the Department of Justice (DoJ). Hoarding and stockpiling shortage drugs is only ‘reasonably’ considered a response to drug shortages (despite the temptation to attribute hoarding and stockpiling to competition aggression), specifically when the severity and/or duration of a drug shortage is indeterminable. Sticking to this motive, a calculated treatment or response to the hoarding and stockpiling of shortage drugs is not feasible.

**Impact on Patients**

Tracking and managing the drug shortage is difficult for clinicians because of the lack of actionable information available, and the lack of tools and resources that are useful for clinicians to efficiently and effectively carry out these tasks. Tracking and quantifying the effects of drug shortages on patients reaches another difficulty entirely because of the lack of documented and recorded data. That drug shortages harm patients and affect patient safety is known. However, health systems are not required to document or record this information, making any

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8 See Fox et al supra note 7.
9 GAO Drug Shortages, p. 70.
10 Ibid.,
kind of precision and specificity regarding these harms unavailable.\textsuperscript{13} At most, such information relies on a voluntary-report methodology, where the guidelines and parameters that directs and specify the information to be provided does not yield consistent, categorical data. The best general and imprecise data specific to the United States is an aggregate source available from the Institute for Safe Medication Practices (ISMP).\textsuperscript{14} Outside of the United States, data concerning the impact of drug shortages on patients is virtually unavailable. Whatever broad and general reports that do exist report patient harms that are, in most cases, no different from the harms that patients experience in the United States.

The two general divisions of patient harm associated with drug shortages are 1) increased risk of medication errors, and 2) increased risk of adverse patient outcomes.\textsuperscript{15} In the 2010 ISMP survey, 35 percent of respondents reported that their facility experienced an error that carried the potential for patient harm in the past year.\textsuperscript{16} The survey claims that one in four errors reached patients, and that one in five of these errors led to adverse patient outcomes.\textsuperscript{17} Respondents expressed a worry that because the current forum for reporting errors and adverse patient outcomes in the United States is voluntary, the actual frequency of errors and adverse outcomes is actually much higher.\textsuperscript{18} The voluntary reporting method still remains in place 2015, and drug shortage experts are still pushing for new methods for reporting medication errors and adverse outcomes out of a need to accurately gauge patient harms that result from drug shortages.\textsuperscript{19}

\textsuperscript{13} Fox & Sweet et al, p. 362; McLaughlin, p. 784; ISMP Drug Shortage Survey.
\textsuperscript{14} Ibid.,
\textsuperscript{15} Ibid.,
\textsuperscript{16} Fox & Sweet et al, p. 362.
\textsuperscript{17} See ISMP Drug Shortage Survey.
\textsuperscript{18} Ibid.,
\textsuperscript{19} McLaughlin, p. 783.
When a drug is completely unavailable, health systems must delegate physicians and nurses to researching, ordering, and prescribing costly alternatives. Alternative therapeutics present three significant patient health and safety concerns. First, the time spent by nurses and physicians researching and selecting alternative drugs is time spent away from their primary duties of care. Second, medication errors may occur when a clinician is forced to prescribe or administer unfamiliar alternative agents.\(^\text{20}\) For example, in the hydromorphone shortage, organizations switched from 2 mg/mL ampul or syringe to a 1 mg/mL ampul or syringe to limit the risk of overdose. The 1 mg/mL dosage became unavailable, and so organizations switched to 1 mg/mL Carpuject pre-filled syringes. When Carpuject became unavailable, the 1 mg/mL also reached short supply, which made the 2 mg/mL ampules the only product available in some hospitals. Preparing a 1 mg/mL syringe from the 2 mg/mL ampules posed a challenge, and so the organizations reverted back to the 2 mg/mL concentration, where the risk of error and adverse effects increased further because the clinicians had become accustomed to the 1 mg/mL dose, and were potentially unaware of the difference in potency.\(^\text{21}\) Errors can also occur when ordering alternative therapeutics by purchasing a look-alike or sound-alike medicine because hospitals will typically purchase specific brands in order to avoid such mix-up errors, but this option becomes increasingly unavoidable during drug shortages.\(^\text{22}\) For example, in one case, a health worker had transfused 50 ml of potassium chloride instead of 50 ml of sodium bicarbonate.\(^\text{23}\) Both medications were kept in 10 ml ampules with a red label on each, and both were purchased from the same pharmaceutical company and kept side-by-side on the same rack. The error caused the patient to develop brachycardia followed by cardiac standstill. The

\(^{20}\) McLaughlin, p. 784.


\(^{22}\) Ventola, p. 751.

problem is not rooted in drug shortages, but the case exemplifies the sort of danger that occurs when a drug shortage pressures clinicians to order look-alike and sound-alike medications.

In other instances, an alternative therapeutic that is considered the ‘the next best thing’ may provide significantly less effective treatment than the preferred but unavailable drug for treating a certain condition.\(^\text{24}\) In the case of chemotherapy, a less effective chemotherapy regimen may result in higher relapse rates or reduced survival.\(^\text{25}\) In a less severe example, a patient with ADHD who is prescribed 36 mg of Concerta may find the drug unavailable, and consequently order a generic version of methylphenidate. Despite being bioequivalent, users report differences in overall effectiveness between the drugs, where an individual reportedly performs better on one version of the drug than the other.\(^\text{26}\) Alternatively, a physician might substitute a prescription for Concerta (methylphenidate) with one for Adderall (amphetamine). Both medications are used primarily in the treatment of ADHD, and both are central-nervous system stimulants. Both stimulants promote the release of stored dopamine from presynaptic vesicles while blocking the reabsorption of dopamine into presynaptic nerve endings.\(^\text{27}\) However, Adderall has an additional function in that it also provides the brain with synthetic supplies of dopamine and norepinephrine. Thus, these medications are considerably different. In this case, while the clinician may be familiar with both of these popular medications, the patient’s brain and body may not. One stimulant may cause heart palpitations, irritability, and end with a noticeable ‘crashing effect’, such that this stimulant is ruled out as an effective therapeutic for this individual. The other stimulant may only cause minor appetite suppression, and be a much more tolerable medication that does not disrupt the daily life of the patient. The point that


\(^{25}\) Fox & Sweet et al, p. 366.


alternative therapeutics are not always easily or effectively interchangeable is quite clear, and certainly in cases other than ADHD medication the clinician may not be aware of how an individual handles similar medications of comparable doses. In other cases, alternative therapeutics may not even be sought out, resulting in a delay of treatment.\textsuperscript{28} Instances where this delay is of crucial significance are anti-microbial agents in the use of treatment against infectious diseases.\textsuperscript{29} In the case of antimicrobials, the necessity for timely treatment should be self-evident.

**Impact on Health Systems**

Drug shortages, and the hoarding and stockpiling of shortage drugs, have direct financial implications for health care systems. A 2010 survey of 1800 clinicians, conducted by the Institute for Safe Medication Practices (ISMP), noted that health care systems experience a significant financial impact due to increased commodity of shortage drugs, increased labour costs, and an inability to minimize time spent managing and allocating resources.\textsuperscript{30} Clinicians at the University of Michigan Health System (UMHS) and the AHSP, in another 2010 study, found that pharmacists and pharmacy technicians spent nine and eight hours per week, respectively, managing drug shortages. Physicians and nurses spent less than one hour per week on this task, mostly on identifying drug alternatives and communicating information about the shortage to their colleagues.\textsuperscript{31} Such tasks take health care workers away from directly tending to patients and their clinical duties, and the annual labour cost associated with managing the drug shortage was estimated to be $216 million for all US health systems.\textsuperscript{32} It is important to note that this

\begin{itemize}
\item \textsuperscript{28} McLaughlin, p. 784.
\item \textsuperscript{29} Griffith et al, p. 746.
\item \textsuperscript{30} ISMP Drug Shortage Survey.
\item \textsuperscript{32} Kakeeh et al.,
\end{itemize}
figure was determined in 2010, and the drug shortage numbers have since doubled.\textsuperscript{33} Much of the labour associated with managing and dealing with drug shortages is due to a lack of actionable information concerning drug shortages, and to a lack of resources available to help health workers manage drug shortages.\textsuperscript{34} The most favourable solution, barring the absence of drug shortages, would see to it that clinicians are not spending time away from their health care duties to manage and research drug shortages. This may require hiring dedicated, knowledgeable staff to take over these responsibilities, but this is problematic when the only qualified personnel are the clinicians themselves. The next best alternative, then, is to provide the information and resources necessary for these clinicians to minimize the time spent on drug shortage duties. However, this is also problematic because the required information is reportedly indeterminable, which means that the current tools and programs used to manage the drug shortage are not entirely useful to clinicians in managing drug shortages.\textsuperscript{35} As it stands, tracking shortages, maximizing inventory, managing inventory use, and researching and acquiring the best alternative agents while maintaining financial efficiency is just not altogether possible.\textsuperscript{36}

A second facet of this issue is increased commodity costs, which significantly increases health system expenses.\textsuperscript{37} In a 2010 survey of 311 pharmacists and related experts from 228 hospitals, Premier Healthcare Alliance estimated that increased commodity costs associated with drug shortages cost health systems an additional $200 million annually, which is to be taken in addition to the estimated $216 million in annual labour costs associated with drug

\textsuperscript{33} See GAO Drug Quotas, p. 18; GAO Drug Shortages, p. 11; 2014 Drug Shortages Summit.
\textsuperscript{34} Ibid; Ventola, p. 750; Kakeeh, p. 1814.
\textsuperscript{35} See GAO Drug Quotas.
\textsuperscript{36} Griffith et al, p. 748.
\textsuperscript{37} Ventola, p. 743; See GAO Drug Shortages, p. 70.
shortages experienced by health systems.\textsuperscript{38} From the survey, 98 percent of respondents reported that a shortage resulted in a mean increase of 11 percent in cost of shortage drugs, usually because the drugs were purchased off contract.\textsuperscript{39} Increased commodity costs are attributed to the creation of nontraditional distributors, otherwise known as gray-market or alternative-market suppliers, in response to drug shortages.\textsuperscript{40}

When a drug shortage is imminent, or already underway, gray-market suppliers purchase excessive or entire quantities of the (prospective) shortage drug, and then offer the drug at a significantly marked up price to all health systems and health care service providers that are unable to acquire product from traditional suppliers.\textsuperscript{41} Gray-market suppliers are not illegal, but their practices certainly challenge the moral integrity of the health practitioners who utilize them. Price mark-up aside, gray-market suppliers do not guarantee proper storage and handling of drugs.\textsuperscript{42} The AHSP warns that ordering from gray-market suppliers carries the risk of purchasing counterfeit product, and that many of these suppliers to not offer returns or refunds.\textsuperscript{43} Additionally, gray-market suppliers cannot guarantee adequate quantities of shortage drugs, and reportedly only carry enough product to treat one to two patients.\textsuperscript{44} In the previously cited ISMP survey, 52 percent of respondents reported that they ordered from gray-market suppliers, either because of extreme circumstances, or because of pressure and frustration from physicians.\textsuperscript{45}


\textsuperscript{39} Coleen Cherici et al.,
\textsuperscript{40} Fox & Sweet et al, p. 365.
\textsuperscript{41} Ibid.,
\textsuperscript{42} Ibid.,
\textsuperscript{43} See GAO Drug Quotas.
\textsuperscript{44} Ibid.,
\textsuperscript{45} ISMP Drug Shortages Survey.
There is a lack of sufficient and reliable information about the financial impact of drug shortages that include data from 2013-2015, and part of this can be attributed to the lack of useful resources available for tracking and managing drug shortages, but this should not take away from any estimations of the financial impact of drug shortages using the 2010 figures.

**Conclusion**

The traditional moral obligation of medicine is to provide maximum net medical benefit with minimal harm, i.e., beneficence with non-maleficence.46 Beneficence is action that is taken for the benefit of others. Non-maleficence means ‘to do no harm’, and is accompanied by the imperative to refrain from providing ineffective or malicious treatment to patients.47 By these two principles, drug shortages challenge the traditional moral obligation of medicine.48 Patients may experience a delay or cancellation of treatment in cases where a shortage drug is one such that there is an available alternative. A cancellation may be deemed an outright failure and incapacity to provide patient care. In this sense, treatment delays and cancellations caused by drug shortages result in a clinical failure to uphold the traditional moral obligation of medicine.

Other cases to consider are antimicrobial shortages. Shortages of irreplaceable antimicrobial agents are associated with treatment delay, the research and selection of alternative therapeutics, and treatment cancellation.49 What differentiates this case with the former is that the demand for antimicrobial agents is rising while the market supply remains stagnant.50 Knowledge of an imminent shortage of antimicrobial agents necessitates timely preventative action and proactive management of antimicrobial agents in order to minimize potential harm to

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47 Ibid.,
49 Griffith et al, p. 748.
50 Ibid.,
potentially affected patients. To do otherwise would conflict with the traditional moral obligation of medicine. A failure to even attempt at preventing or proactively managing an imminent antimicrobial shortage, is, in a sense, to maximize the potential harm that can be done to the potentially affected patients—the direct opposite of ethical care.

In the context of infectious diseases, another obvious threat posed by drug shortages is to public health, where a shortage of antimicrobial agents, i.e., routine childhood vaccines, poses a significant threat to the greater public.

With this in mind, drug shortages certainly harm a health system’s ability to provide ethical health care by requiring health systems to allocate and commit significant resources to managing and handling drug shortages. Be it in labour costs, hoarding and stockpiling, resorting to gray-market suppliers, purchasing costly alternative therapeutics, or delaying clinical research and research funding, health systems (and I use the term to include hospitals) always run into paying significant expenses as a result of drug shortages. Rationing shortage drugs, and running into expense-related problems present clear challenges to the delivery of ethical health care, and these problems inevitably fall onto the patient.

Health organizations have an ethical obligation to prepare for drug shortages; and health organizations should have an ethical obligation to provide useful, functioning guidelines, resources, tools, and methodologies for preventing, managing, and communicating decisions concerning drug shortages. This ethical obligation should extend to promoting and ensuring equity in all health systems, i.e., equal distribution, availability, and access to quality medicine and treatment to patients in need. Patient cost and expense is a lengthy topic in itself, but the point remains that patient cost and expense is a concern of every health organization with respect to the moral obligation of health organizations to provide access to ethical health care.
Chapter 3. Cataloguing the Causes

This chapter thoroughly traces the aetiology of drug shortages by cataloguing the systemic issues according to the immediacy of the category to drug shortages themselves. As such, the catalogue starts with manufacturing issues, which immediately precede a drug shortage, and progresses downward through the layers of underlying issues toward the root economic mechanisms that make all of the previous categories of issues, and thus drug shortages, possible.

3.1 Systemic Issues

Systemic issues are those economic and regulatory processes that make drug shortages more likely. For example, shortages of generic injectable medicines in the US are seen to stem from a combination of complex manufacturing processes vulnerable to quality control implications, reliance on few generic manufacturers with very little manufacturing redundancy and flexibility, i.e., no variations in production of generics, and low price fixings for generic drugs bordering on competition law violation, as well as increased pressure on manufacturers to reduce production costs, reduce inventory of generics, outsource production to maintain some minimal profit margin, or altogether halt production of generics for a variety of reasons, two of which include favouring more profitable drugs or negating low-profit expenditures, or a combination of both.

A. Manufacturing

Systemic manufacturing issues are those issues that make drug shortages more likely to occur due to difficulties and complications of manufacturing a drug or sending drug products to the distribution channel.\textsuperscript{51} Systemic issues at the manufacturing level are not necessarily the sole responsibility of the manufacturer. Certain factors throughout the supply chain may cause

\textsuperscript{51} Lipworth, p. 558.
production difficulties for manufacturers, and thereby increase the likelihood of a shortage; and regulatory enforcement action may complicate the supply of drugs by manufacturers. For this reason, systemic manufacturing issues include supply chain issues and some regulatory complications.

Systemic manufacturing issues include: antiquated manufacturing equipment, manufacturing processes vulnerable to quality control implications, loss of experienced production and compliance personnel, manufacturer production decisions that may cause drug shortages, unexpected increase in demand, FDA enforcement actions that result in hindered or halted production of drugs, reliance on few generic manufacturers with very little manufacturing redundancy and flexibility, cGMP (current good manufacturing practices) related issues with subcontractors who supply products to multiple pharmaceutical manufacturers, voluntary recalls, unavailability of raw and bulk material, natural disasters affecting manufacturing facilities, shortage of manufacturers, and general manufacturing decline.

The unavailability of raw and bulk material and components can be especially problematic when one or more manufacturers rely on a single source of material to make a drug product. Should the single source of material discontinue production, meet an unexpected increase in demand, experience facility or distribution issues, then all reliant manufacturers will run into production difficulties and delays claiming an unavailability of raw or bulk material as the root cause. Drug manufacturers are increasingly importing raw materials from other countries, and are therefore reliant on a global supply chain. An estimated 80 percent of the raw materials and

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52 Lipworth, p. 558.
53 Ibid.; GAO Drug Shortages; 2014 Drug Shortages Summit; Ventola, p. 748.
55 U.S Department of Health, p. 4.
components in the pharmaceuticals sold in North America and Europe are manufactured in China and India—two countries that are believed to have more lenient safety and regulatory standards than the western regulatory bodies, and India itself depends on China for over 90 percent of certain key raw materials.\(^{56}\) Reliant drug manufacturers are also subject to the potential availability issues that may also result from factors related to the geographic location of raw materials, including hostilities, political unrest, and trade disputes.\(^{57}\) Sourcing materials from undeveloped locations may result in contaminants that render the source useless for extracting raw material, climatic and environmental factors may alter the overall availability of source plants used for extraction, or damage may be caused to raw material during harvesting, storage, or transportation.\(^{58}\)

A trend in China for raw drug material companies is to register as chemical companies in order to avoid being subject to Chinese drug regulatory bodies, which has led to extreme consequences.\(^{59}\) The 2008 heparin crisis is one such example, where a contaminated batch of heparin was sold to Baxter International by a Chinese raw material supplier.\(^{60}\) Investigators of the case reported that the batch was contaminated with a “heparin-like” contaminant known as oversulfated chondroitin sulfate (OSCS).\(^{61}\) The FDA contended that OSCS was made in China from animal cartilage, and that it was chemically altered to act like heparin, and it was used in

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\(^{58}\) Ibid.,

\(^{59}\) See U.S China Economic and Security Review Commission.


the process to lower the cost of producing heparin.\textsuperscript{62} Over 12 other Chinese companies have been found by the FDA to have produced contaminated heparin since 2006, with samples containing OSCS having shown up in 12 countries.\textsuperscript{63} The FDA cites over 200 deaths and thousands of adverse cases in the US since Baxter’s initial recall of nine lots in 2008, with voluntary recalls being issued by three other heparin supplies thereafter.\textsuperscript{64}

Voluntary recalls can have a significant impact on overall supply of a given drug product, especially if the recalled drug has dominion over the market supply. Voluntary recalls commonly result from general manufacturing problems or a lack of adherence to current good manufacturing practice regulations.\textsuperscript{65} Voluntary recalls usually affect specific lots and are conducted because of a lack of assurance that the recalled product is safe and for non-safety related reasons, such as technical deficiencies in the drug’s labeling.\textsuperscript{66} Keeping the drug product available is desirable, but in serious cases this may not be possible. Defects may include drug products containing no active ingredient, injectable products containing rubber gasket material or metal shavings, and products for intravenous injection containing particulate matter, bacteria, or mold.\textsuperscript{67}

Manufacturing decline and scarcity are also significant factors that make drug shortages more likely. The globalization of the pharmaceutical industry means that medicines are often manufactured at a handful of sites worldwide. Add to this the issue that production schedules must be planned months in advance, along with the move to ‘just-in-time’ manufacturing to

\textsuperscript{63} Ibid.,
\textsuperscript{64} Ibid.,
\textsuperscript{65} McLaughlin, p. 783; Ventola, p. 742.
\textsuperscript{66} Ibid.,
\textsuperscript{67} GAO Drug Shortages, p. 21.
reduce the cost of stockholding means that there is little flexibility in the system when problems actually arise.  

This issue is more severe when one considers that many manufacturers have limited manufacturing capacity. In many facilities, multiple products are produced on the same equipment, meaning an increase in production of one product results in a decrease or delay of production of another. This is especially true for manufacturers of generics. Only a small number of manufacturers produce the majority of generic sterile drug product volume, and these manufacturers may produce multiple drug products on a single line. If any problem occurs, a plant may not have the capacity to shift a significant number of products to different production lines or facilities. Moving products to different production lines may only take place after the manufacturer secures regulatory approval of the new line, and complications and delays may arise if the regulatory body is experiencing capacity issues and resource constraints.

Shortage prevention strategies for generics are difficult to plan and implement because of market demand uncertainties—a generic manufacturer cannot foresee the generic market years in advance, nor can it reliably determine if it will remain in any market in the future. Furthermore, many facilities operate with aging equipment at a capacity that reduces the frequency of preventative maintenance, causing the equipment to wear out more rapidly. Initiatives to replace and upgrade equipment take time during which the production capacity of upgrade-in-progress

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70 Barry, p. 282.


72 U.S Department of Health, p. 5.

73 Ibid.,
facilities are off-line. Upgrading equipment, building facilities and adding or updating production lines, and increasing capacity, can take several years complete, increasing capacity issues and making drug shortages more likely to occur.

B. Regulation

cGMP enforcement actions and recalls certainly contribute to drug shortages, but recalls and strict GMP enforcement are measures that aim to ensure quality of care and limit negative patient outcomes. Nevertheless, strict regulation and enforcement, and the drug shortages that may occur or be exacerbated as a result, give rise to ethical dilemmas in addition to apparent deficiencies in capacity and authority.

The 2012 Ameridose Recall is an example of an abundance of caution exacerbating six drug shortages. In October 2012, Ameridose voluntarily agreed with the Massachusetts Board of Registration and Pharmacy to temporarily cease all pharmacy and manufacturing operations due to concerns with sterility assurance during a fungal meningitis outbreak. The FDA recommended that Ameridose voluntarily recall all non-expired drugs based on preliminary results of a then-in-progress inspection. The FDA announced that no product made by Ameridose had been found to be associated with the meningitis outbreak, and that the recall is not based on reports of patients with infections associated with any Ameridose products. Rather, the FDA recommended the recall out of an abundance of caution, and also recommended that health professionals did not need to follow up with patients who received Ameridose products. However, all unused Ameridose products were to be returned to the firm.

The FDA identified six Ameridose injectables on the FDA critical shortage list: sodium

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75 See FDA Ameridose Recall supra note 74.
76 Ibid.,
77 Ibid.,
bicarbonate, succinylcholine, atropine sulfate, bupivacaine hydrochloride, lidocaine hydrochloride, and furosemide. The FDA’s response to the exacerbated shortages was to contact manufacturers of the six drugs, and request that they ramp up production if they were willing and able to do so, explore companies that were willing and able to import foreign drugs, and offer appropriate assistance to manufacturers to ensure safe and high quality drugs. This is not a problem of overzealous enforcement, but an emphasis on the systemic manufacturing issue of manufacturer scarcity.

With the globalization of the pharmaceutical industry, new threats to drug safety and quality have grown. North America has a surprising dependency on global markets to supply drugs, with over 40 percent of finished drugs made overseas, from over 150 countries, including those with less stringent regulatory practices. In response, the FDA has also stepped up its frequency of inspecting foreign facilities. In 2008, the FDA almost doubled its number of inspections in China from the previous fiscal year, moving from 19 inspections to 36. In 2009, the FDA conducted 52 inspections out of 920 establishments, meaning 811—or 88 percent—of China’s drug manufacturers may never have been inspected. In fiscal year 2009, the FDA conducted 424 foreign inspections in total compared to 333 and 324 in fiscal years 2007 and 2008, respectively. The total number of foreign establishments in the FDA’s inventory, as of 2009, is 3765. As of 2014, the FDA conducted 1,379 foreign inspections, with a foreign establishment inventory of 3615—a decrease in 150 facilities from 2009. The FDA considers

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78 See FDA Ameridose Recall supra note 74.
79 Ibid.,
81 Ibid.,
82 GAO High Risk Update, p. 272.
84 Ibid.,
85 See GAO Drug Safety.
the number of foreign inspections to be unsatisfactory, claiming that the rapid pace and magnitude of globalization has complicated FDA’s efforts to ensure the quality and safety of drug products finished overseas.86

Foreign inspections are quite costly, and the FDA cites resources as a concern, stating that it may not have the capacity to implement the U.S Government Accountability Office (GAO) recommendation of taking a risk-based approach to inspecting both foreign and domestic facilities.87 The risk-based approach would ensure that FDA resources are used effectively and efficiently to address the most significant health risks.88 The approach would also calculate risk of potential harm associated with loss of pharmaceutical quality.89 This means that the approach evaluates the probability and severity that a drug will fail to meet the safety and quality needs of patients and their surrogates, with quality meaning both clinical performance and product availability.90 The end goal of the risk-based model is the ability to identify and prioritize those facilities that pose the greatest health risk. The FDA estimates that it may not be able to fully implement the risk-based approach to inspection until fiscal year 2017.91 Furthermore, the FDA’s published strategic priorities for 2014-2018 features a desire to expand regulatory presence and partnerships overseas to build a more secure global protection against harmful products, but the FDA’s Office of International Programs (which oversee the FDA’s foreign offices) has yet to establish any performance goals or measures that can be used to monitor long-term efficacy of the overseas offices and present any indication of improvement in the regulation and oversight of imported medical products.92 It is worth mentioning that the FDA is

87 Ibid.; GAO Drug Safety, p. 10.
88 GAO High Risk Update, p. 273.
89 Ibid.,
90 Ibid.,
91 Ibid.,
92 Ibid., p. 272.
still struggling with capacity constraints due to an inability to staff its foreign offices. The FDA has not addressed a recommendation made by the GAO in 2010 to develop a workforce plan to ensure the recruitment and retention of experienced staff.

The FDA’s response to globalization and the foreseeable increase in the number of inspections could lead to an increase in the number of closures of facilities in noncompliance with the FDA’s regulations, which could lead to additional or exacerbated drug shortages.

According to the FDA’s 2013 Strategic Report for Preventing and Mitigating Drug Shortages, most drug shortages are preceded by a production disruption. The report further claims that problems in product or facility quality are the primary factor leading to production disruptions, with 66 percent of production disruptions in 2012 resulting from quality concerns (Figure 1).

Figure 1. FDA Chart on Drug Shortages by Primary Reason for Disruption in Supply in 2012

Source: FDA Strategic Plan for Preventing and Mitigating Drug Shortages, October 2013.

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93 GAO High Risk Update, p. 272.
94 Ibid.,
95 FDA Strategic Plan p. 13.
96 Ibid.,
97 Ibid.,
The FDA repeatedly claims that it is committed to working with industry manufacturers to resolve or avoid quality issues, and where justified, exercise regulatory flexibility to prevent or mitigate drug shortages. Quality control and preventing or mitigating drug shortages are two separate priorities serving the FDA’s commitment to preventing patient harms. Observing economic theories of regulation, while the FDA’s policies may yield the benefit of drug safety and quality, these policies also produce corresponding negative externalities. In the case of the Ameridose Recall, quality control measures and enforcement actions exacerbated critical drug shortages, resulting in patient harms and negative care outcomes. Regardless of whether or not this is a violation of the FDA’s commitment to preventing patient harms, it is worthwhile to consider that regulating a drug supply has corresponding costs. The balancing act involved here engages significant ethical considerations, and ought to be examined with respect to the underlying mechanisms causing drug shortages to ensure that the relative trade-offs made are both economically and ethically justifiable.

On 15 June 2012, the U.S Committee on Oversight and Government Reform (COGR) released a report claiming that the FDA’s enforcement and compliance activities have created critical and unnecessary drug shortages that date back to 2010. In 2009, shortly following the heparin crisis, U.S President Barack Obama appointed Dr. Margaret Hamburg as FDA Commissioner. In her 6 August 2009 speech, Hamburg announced that the FDA will significantly increase its surveillance programs for pharmaceuticals, and that the agency will be taking several steps towards this commitment. The steps are as follows: 1) the FDA will set post-inspection deadlines, 2) the FDA will responsibly speed the issuance of letters, 3) the FDA will seek to

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98 FDA Strategic Plan p. 13.
101 Ibid.
collaborate with regulatory partners to increase risk control and enforcement strategies, 4) the FDA will prioritize enforcement follow-up, 5) the FDA will be prepared to act swiftly and aggressively to protect the public, and 6) the FDA is developing a formal warning letter “close-out” process to indicate that the issues presented in the warning letters have been successfully addressed. To support these six initiatives, Hamburg also revealed that the FDA “received significant funding increases for the current and next fiscal year that will be devoted to additional inspection and compliance activities.”

The overall goal of this plan is to protect the public from undue harm relating to drugs and medical devices by aggressively tackling quality concerns and failures. By 2010, the total number of warning letters issued by the FDA across all overseen industry areas increased by 42 percent--from 474 letters to 673 letters. By 2011, this number increased by an additional 156 percent--1,720 letters. The substantial changes in these figures demonstrate the impact of the FDA’s new and aggressive regulatory strategy on the total number of warning letters. The FDA’s new surveillance plan for pharmaceuticals emphasizes a dedicated effort and allocation of resources towards the overall priority of ensuring safe, high quality drugs to patients.

Absent from the FDA plan, however, is any foresight or acknowledgement of the possibility that aggressive enforcement and compliance activities may lead to undue patient harms by way of mass simultaneous shutdowns of drug production lines. In 2010, 31 percent of all generics and 36 percent of all generic injectable drugs were produced by two or fewer suppliers, and 90 percent of generic injectable oncology drugs were produced by three or fewer suppliers. A

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102 See Hamburg FDA Speech supra note 100.
103 Ibid.,
104 COGR 2012 Report, p. 16.
105 Ibid., p. 16.
production disruption at any manufacturing facility requires competitors to increase production to meet the increased demand, which may not always be possible if the facility cannot produce at excess capacity. This may certainly be the case if a facility is already under pressure to offset the increased demand of another drug. For drugs with less than a handful of suppliers, even a temporary production disruption may result in or exacerbate a drug shortage.

As a result of the FDA’s new policies, four out of five of America’s largest suppliers of generic injectables underwent simultaneous remediation efforts, and agreed to suspend manufacturing operations to address the issues raised in the FDA warning letters.\(^{107}\) Prior to the remediation efforts, the facilities of the four companies--Sandoz, Teva, Hospira, and Bedford--were producing close to one billion units of generic injectable products per year.\(^ {108}\) As of 2012, that number has shrunk to approximately 700 million units of generic injectable products per year--a 30 percent decrease in production capacity forcing drug manufacturers to decide which drugs to produce over others, and whether to suspend production temporarily or permanently.\(^ {109}\) By 21 February 2012, 128 (58 percent) of the 219 shortage drugs were being manufactured by one or more of the facilities undergoing FDA remediation efforts.\(^ {110}\)

Despite the number of FDA issued warning letters and responses, the Congressional committee reported that they were unable to find evidence that any of the drugs produced at the facilities undergoing remediation had harmed anyone.\(^ {111}\) The report cites one comment from an unnamed recipient of an FDA warning letter, claiming that the letter did not denote any specific concern for safety, purity, or quality of the products manufactured at the facility undergoing remediation, however the company voluntarily undertook remediations under the general

\(^{107}\) COGR 2012 Report, p. 16.

\(^{108}\) Ibid.,

\(^{109}\) Ibid.,

\(^{110}\) Ibid.,

\(^{111}\) Ibid., p. 18.
sentiment of satisfying FDA requirements. The report further claims that the FDA’s field inspectors are detached from the FDA branch that works on review and compliance functions; and that the field inspectors do not consider it a part of their role to evaluate the implications of aggressive enforcement actions, even if these implications lead to or exacerbate a drug shortage.\footnote{112 COGR 2012 Report, p. 18.}

An FDA response to the Congressional committee’s report, signed by Jeanne Ireland, the FDA’s assistant commissioner for legislation, claims that the warning letters issued to drug manufacturers involved critical defects and safety risks requiring urgent attention, and serious enough to halt production. The FDA’s response runs contrary to the Congressional committee’s allegations, reporting the following potential defects and safety risks: endotoxin contamination of Teva’s propofol injection emulsion product; presence of metal particles in sterile drugs, aseptic conditions, and under-filled drugs at Ben Venue Labs (Bedford Laboratories); metal particles in several injectable drugs and overfills of vials of liquid morphine up to twice the indicated quantity by Hospira; and crystals forming in injectable drugs at Sandoz, as well as over 1000 complaints of foreign, stray, and broken tablets in opiate products made by parent company Novartis, indicating potential contamination.\footnote{Ibid.} Additionally, the letter argues that the FDA’s inspections do not cause facilities to have manufacturing or quality problems, stating these problems to be the root causes of drug shortages.\footnote{Ibid.} The letter further claims that facility closures were voluntary and in the context of serious, unresolved safety concerns.\footnote{Ibid.}

\footnote{112 COGR 2012 Report, p. 18.}  
\footnote{113 Ibid.}  
\footnote{114 Letter from Jeanne Ireland, Assistant Commissioner for Legislation, U.S. Food & Drug Admin., to Rep. Elijah E. Cummings, Ranking Member of the Committee on Oversight & Gov’t Reform, U.S. House of Representatives (July 23, 2012), [hereinafter FDA Letter to COGR].}  
\footnote{115 Ibid.}  
\footnote{116 Ibid.}
It is quite possible that strict regulations may lead to the identification of safety issues and quality concerns that are only considered severe from the perspective of one regulatory body, meaning a regulatory body is capable of creating quality and manufacturing problems by way of identification according to strict policies and criteria. This may evidently be the case in the FDA warning letters observed by the Congressional committee for its investigation. The issued letters did not specify safety or quality concerns, but rather the failure of the facilities to satisfy to aggressively enforced FDA standards. Even considering that many of the recipients of FDA warning letters had been producing drugs for decades without any reports of negative outcomes, the ‘critical defects and safety risks requiring urgent attention’ may have been identified on the basis of a risk averse approach to inspections.\textsuperscript{117} Furthermore, while the FDA argues that facility closures and remediations were voluntary, it is often the case that facilities must take actions that impede production in order to address cited issues and upgrade operations to satisfy FDA standards.\textsuperscript{118} The warning letters following the new FDA policies explicitly threaten enforcement action, which compels drug manufacturers to take immediate action regardless of the potential implications:

\textit{You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility, until the above violations are corrected.}\textsuperscript{119}

What is absent from the FDA’s response to the Congressional report is a justification for allowing simultaneous remediation efforts, especially when overlapping facility closures involves four of the five largest suppliers of generic injectables. What is more concerning is that the FDA

\textsuperscript{117} COGR 2012 Report, p. 18.  
\textsuperscript{118} FDA Letter to COGR.  
\textsuperscript{119} Ibid., p. 16.
letter argues that the root causes of drug shortages “lie outside the purview of the FDA,” and that the agency is committed to helping to avoid drug shortages. The FDA claims that the number of drug shortages began to rise steadily in 2005, well before the FDA increased its surveillance program for pharmaceuticals. This means that the FDA must have had some awareness that the number of drug shortages had increased dramatically from 2009 to 2010, but the FDA warning letters issued to Teva on 11 December 2009 and to Hospira on 12 April 2010 failed to make any reference to drug shortages. The warning letters to Sandoz on 18 November 2011, and to APP on 22 February 2012, did express an urgent awareness of the crisis. The FDA’s role in contributing to drug shortages, and its portrayal of the root causes of drug shortages, calls into question the FDA’s ability to balance its commitments to resolving safety and quality concerns while preventing and mitigating drug shortages.

Further complicating the issue with regulation and even the oversight of regulatory bodies are instances in which the validity of the defects and safety risks noted in warning letters are suspect. Drugs produced at many of the facilities that underwent remediation had been produced for decades without change or alteration to the manufacturing process, and without any evidence or report of undue harm to patients. In 2011, the FDA conducted three separate inspections of Sandoz Canada’s plant in Boucherville, Quebec, and on 18 November 2011 issued a warning letter citing that the Boucherville facility’s procedures may potentially lead to a contamination. The warning letter cited violations including insufficient media studies tests due to inconsistencies between the number of units filled and the number of units being incubated or evaluated, and initiating inspections when such discrepancies arise. It should also

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120 FDA Letter to COGR.
121 See FDA Letter to COGR.
123 Ibid., p. 18.
be noted that Sandoz Canada also proposed corrective actions following the investigation of an initial discrepancy, including improvements to documentation processes and the re-training of personnel.\textsuperscript{125} The letter also cites contamination concerns due to considered inadequate investigations of some of Sandoz Canada’s sterile injectables that were released for distribution in the United States, resulting in a field letter on 05 November 2011.\textsuperscript{126} While none of Sandoz Canada’s products were recalled, the warning letter primarily criticized the Quebec facility for falling short of agency standards, and failing to quickly alert the FDA of potential problems.\textsuperscript{127} A separate Health Canada investigation completed later that month did not identify any issues or concerns, which raises questions concerning differences in approach and scope of inspections between Health Canada and the FDA.\textsuperscript{128} In response to the letter, Sandoz Canada suspended the production of some non-essential medicines (mostly antibiotics, painkillers, and anaesthetics)—with a temporary suspension to all production in February—in order to ramp up efforts to upgrade operations to meet U.S. safety standards, leading to critical drug shortages and cancelled surgeries across Canada.\textsuperscript{129}

C. Communication

Communication issues largely involve regulatory issues, but go beyond the authority of the regulatory bodies. Communication issues include wholesale and distribution difficulties, contract negotiation, inventory management, reporting and notification, and information transparency and dissemination.

\textsuperscript{125} FDA Warning letter from Steven Lynn. \\
\textsuperscript{126} Ibid. \\
\textsuperscript{127} Ibid. \\
\textsuperscript{129} Ibid. \\
If competitors are not given advanced notice of a manufacturer exiting the market, the remaining manufacturers may have to respond quickly to keep up with demand.\textsuperscript{130} However, this runs into common manufacturing issues with production lines and antiquated equipment, especially if the manufacturer is already operating at a high capacity, and even more so if it is as producer of generics that makes multiple drug products on a single production line.

For antitrust reasons, a manufacturer that decides to leave the market cannot call a competitor to give advanced notice and a go ahead to increase production.\textsuperscript{131} The manufacturer must first report to the FDA in any instance of permanent or temporary product discontinuance. It is the sole responsibility of the FDA to notify the remaining manufacturers of the shortage drug, identify additional manufacturers that are willing and able to initiate or increase production of the shortage drug, expedite FDA inspections and reviews of various submissions from the manufacturer to alleviate the shortage, and under certain circumstances exercise enforcement discretion for the temporary importing of shortage drugs, and to distribute the shortage product if and only if the safety of the patients can be preserved.\textsuperscript{132} The FDA’s responsibilities during a manufacturing-related shortage make timely communication and the appropriate allocation of drug shortage personnel of utmost importance. To carry out these priorities, the FDA has increased its number of staff dedicated to drug shortages, assigning a drug shortage coordinator to each of its 20 offices, and increasing the amount of staff working on any given drug shortage by an estimated average of 25 additional qualified and expert personnel from the clinical review, chemistry, and compliance divisions, and from others as required on a case-by-case basis.\textsuperscript{133} In a 2014 report, the GAO found the FDA’s efforts to improve drug shortage-related communication and responsiveness to be successful in preventing more potential drug shortages.

\textsuperscript{130} Ventola, p. 741.
\textsuperscript{131} Ibid.,
\textsuperscript{132} Ibid.,
\textsuperscript{133} GAO High Risk Update, p. 271-272.
shortages than in previous years.\textsuperscript{134} In addition, the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) further improved the FDA’s ability to respond to drug shortages by eliminating part of a rather large communication issue. FDASIA requires manufacturers of drugs that are life-supporting, life-sustaining, or used to prevent or treat debilitating diseases and conditions (including any drug used in emergency medical care or during surgery) to notify the FDA at least 6 months in advance of an expected or anticipated discontinuation or interruption that may lead to a drug shortage. For all other drugs, it is only optional to give an early notification to the FDA of an anticipated drug shortage. If a manufacturer knows that it is going to have a manufacturing problem, it may not give early notification because that information is proprietary. Giving advanced notice would allow purchasers to seek out different suppliers, and for the FDA to timely respond with assistance, but a manufacturer may withhold such information to protect its own market share from competitors. Once a shortage actually occurs, then the manufacturer is required to notify the FDA.

Withholding early notifications of potential shortages not only make drug shortages more likely to occur, but can add to the severity of any resulting shortage. Information that approximates the severity and duration of current and potential drug shortages provides clinicians, pharmacists, and inventory managers with the ability to make informed decisions about how to manage inventory, ration medications, order shortage drugs, and how to allocate personnel for the purposes of researching alternative therapeutics and suppliers. Such information prevents poor ordering and inventory practices, including hoarding and stockpiling due to rumours and thereby inflating demand of a product, causing severe backorders and grossly marked up prices from alternative suppliers.

\textsuperscript{134} GAO Drug Shortages, p. 49.
Health Canada does not yet have any mandatory report system. All notifications to Health Canada about drug shortages are optional and voluntary. Canadian Health Minister Rona Ambrose announced in February 2015 that companies will required to post information about shortages, but no information was provided as to when this would come into effect. The extent of Canada’s ability to deal with drug shortages lies in Health Canada’s recently implemented register that lists manufacturers with a drug identification number, who have formally committed to sending drug shortage notifications.

Another key communication issue is the question of what constitutes a drug shortage. Different bodies have different definitions and criteria for determining a ‘drug shortage’, which makes things all the more challenging for clinicians and manufacturers to respond to or make notification of drug shortages. For example, the FDA defines a drug shortage as a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand; the ASHP and the University of Utah Drug Information Service (UUDIS) define a drug shortage as a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent; and once the UUDIS identifies a drug shortage, it generally does not consider the shortage resolved until the shortage drug is available in all strengths and package sizes from all manufacturers that currently produce the drug. This latter part presents a particular problem. To use the example from the GOA-15-202, UUDIS could be notified of a shortage involving three manufacturers: Manufacturer A has no product available; Manufacturers B and C still do, but have limited supply of certain package sizes. According to a UUDIS official, UUDIS would consider the shortage to be resolved (1) when all of


137 See GAO Drug Quotas.
Manufacturers A, B, and C have all strengths and package sizes back in stock; (2) if Manufacturer A decides to discontinue its product, when Manufacturers B and C both have all strengths and package sizes back in stock; or (3) when UUDIS obtains other information indicating that a shortage has been resolved, such as the FDA telling UUDIS that Manufacturers B and C have increased supply and all market need has been met.\textsuperscript{138} These definitions and criteria make it difficult for clinicians to adequately assess the severity and duration of a shortage, or even understand what is exactly meant by ‘drug shortage’ upon notification. This basic conceptual confusion can significantly impact the precision and appropriateness of preventive or proactive measures, especially measures that include drug rationing.

Moreover, the FDA’s Drug Shortage Staff (DSS) verifies a drug shortage much differently than the ASHP and UUDIS, utilizing historical data of product demand in addition to contacting individual manufacturers and wholesalers about the potential shortage drug in order to determine \textbf{total} supply of a drug, together with the viable alternatives of that drug, and comparing this broad total supply to the demand, even in response to a reported shortage of a specific drug within a kind or classification of drugs.\textsuperscript{139} These differences are quite harmful to the clinicians’ decision making process in preventing and managing drug shortages because the discrepancy between the two criteria for a ‘drug shortage’ prevent the clinician from being adequately or precisely informed. This hinders the clinician’s capacity to make informed decisions in the management of drug shortages, which directly affects the delivery of effective patient care. This only speaks to the severity of the lack of useful resources available for clinicians to track drug shortages and patient harms. This deficiency effectively denies clinicians from acquiring all of the information necessary to make the best informed decisions possible that ensure net medical benefit to patients while minimizing harms caused by drug shortages.

\textsuperscript{138} See GAO Drug Quotas.
\textsuperscript{139} Ibid.,
D. Economics

The health and character of any given drug market plays an important role in shaping critical and strategic business decisions made by manufacturers; and conversely, the business decisions that manufacturers make directly affect the health and character of any drug market in the industry.\textsuperscript{140} In many ways, the unique nature of the healthcare market may be the unifying mechanic behind all causes of drug shortages, and tracing the aetiology of these economic factors may yield the critical understanding necessary to address the overall issue.

Manufacturer scarcity and decline is leaving the industry dependent on fewer manufacturers producing drugs with low production capacity, antiquated equipment, and complex manufacturing processes that are vulnerable to quality and regulatory implications.\textsuperscript{141} Over 80 percent of shortage drugs are generic, and in the U.S., over 80 percent of shortage generics are sterile injectables.\textsuperscript{142} The generic sterile injectable market consists of just seven manufacturers producing the majority of all drugs; and for any given drug in this market only three to four manufacturers are producing product.

1. Low Price Elasticities of Supply and Demand

In most markets, shortages are rare. Price changes keep the quantity of products supplied balanced with the quantity demanded. When product supply decreases, the price increases and consumer demand adjusts accordingly, demonstrating price elasticities of supply and demand. Shortages generally occur when there are low price elasticities of supply and demand. In the healthcare markets, this is very much the case.

\textsuperscript{141} Ibid.; GAO Drug Shortages, p. 16; see IMS Health Supply Study.
\textsuperscript{142} Ibid.,
In the prescription drug market, price elasticities are low for two reasons. First, the majority of prescription drugs are, by definition, medically necessary, suggesting that there are few—if any—alternative therapeutics. The demand for medically necessary drugs does not respond to supply because patients do not control what illnesses and conditions they will suffer, and what medications they will require. Second, consumer demand for prescription drugs are largely unaffected by price because patient health insurance contracts typically pay providers using pre-established payment rates and guarantee the provision of necessary services to consumers.

On the supply side, manufacturers use a just-in-time approach to production in order to keep inventories as low as possible. Production capacity and product output are calculated to perfectly match current demand. There is little reason for manufacturers to produce excess product in a market with low price elasticity of demand. In fact, manufacturers have more economic incentive not to saturate their inventories. Drugs have a limited shelf life and holding product in excess of demand is wasteful.

Finding a source for raw drug materials is a frequent difficulty, and requires both manufacturer and regulatory approvals. Manufacturing equipment is costly, and production processes are complex and must adhere to current good manufacturing practices. Increasing production capacity increases the risk of equipment and product failure. The costs associated with excess production are too high, while the cost of producing too little is low—except for consumers. Manufacturers are unable to cope with shock, and sudden changes in supply and demand can result in drug shortages—especially in a market that is reliant on only a handful of suppliers. This

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143 U.S Health Department, p. 4.
144 Ibid.,
145 GAO Drug Shortages, p. 30.
146 U.S Health Department, p. 4.
is especially true of generic markets. Generic drugs offer slim profit margins, and drug companies see little to no benefit in expanding manufacturing infrastructure.\textsuperscript{147} Gaining FDA approval for a new production facility takes two to three years, while unanticipated increases in demand are expected to be temporary. Expanding manufacturing infrastructure offers drug companies little benefit over balancing the cost of building redundancy into their facilities. Drug companies have little incentive to participate in the generic market, where drugs are virtually absent of any price floor. Within the first two or three years after coming off patent, a cancer drug can lose up to 90 percent of its value in price as manufacturers compete for market share.


In 2003, Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act (also called the Medicare Modernization Act or MMA) that converted drug reimbursement to an average sales price (ASP) based system.\textsuperscript{148} The new system based reimbursement rates on manufacturer’s average sales price and went into effect in 2005.

The MMA intended to reduce overpayments for drugs administered in physician offices and hospital outpatient settings by basing reimbursement formula on a more reliable and readily verified average sales price. Health providers were reimbursed the amount of the acquired drug’s ASP plus an additional 6 percent margin to cover overhead costs for drugs administered in physician settings, or a 6 percent margin for separately payable drugs administered in hospitals.\textsuperscript{149} The new formula, along with other provisions, capped price increases by proprietary drug manufacturers by 6 percent and lower while effectively removing the price floor.

\textsuperscript{147} COGR 2012 Report, p. 17.
\textsuperscript{148} Ibid., p. 4
\textsuperscript{149} Ibid., p. 9.
from generic drugs. The price increase cap, together with the 6-month delay in reimbursement rates caused price increases to be placed on medical providers.\textsuperscript{150}

A drug’s ASP is defined as the volume-weighted average manufacturer sales price net of all price concessions to U.S purchasers, excluding sales that are exempt from Medicaid best price calculations and sales to other federal purchasers.\textsuperscript{151} Manufacturers are required to provide the quarterly sales price and volume of sales for National Drug Code (NDC) covered drugs to the Centers for Medicaid and Medicare Services (CMS) within 30 days of the quarter, and the CMS then calculates a volume-weighted ASP for each HCPCS (“hickpicks”) drug code to be the reimbursement rates for the following quarter.\textsuperscript{152} This means that any ‘current’ reimbursement rate reflects a drug’s ASP from two quarters prior, reflecting a lagged price (see Figure 1).

Figure 2. Timeline for Medicare Part B Reimbursement Rates

\begin{figure}
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\includegraphics[width=\textwidth]{timeline.png}
\caption{Timeline for Medicare Part B Reimbursement Rates}
\end{figure}

Source: ASPE Issue Brief, Medicare Part B Reimbursement of Prescription Drugs, June 2014.\textsuperscript{153}

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\item \textsuperscript{150} COGR 2012 Report, p. 13.
\item \textsuperscript{151} 42 U.S.C § 1395w-3a(c).
\item \textsuperscript{152} U.S Department of Health and Human Services, “Part B Reimbursement of Prescription Drugs” (June 2014) [hereinafter ASPE 2014] \url{http://aspe.hhs.gov/sites/default/files/pdf/106966/ib_mprpd.pdf}.
\item \textsuperscript{153} ASPE 2014, p. 4.
\end{itemize}
In 2006 and 2007, MedPAC published two Congress-mandated reports, which found that the new ASP-based reimbursement system allowed health care providers to be reimbursed above cost for most covered drugs.\textsuperscript{154} Hospitals also realized that they could guarantee reimbursement at or above cost by qualifying for the 340B program, which offered participating hospitals discounts ranging from 30 to 50 percent, and therefore drastically reduced their drug expenses.\textsuperscript{155}

The 340B program is a government program created by Congress in 1992 to provide vulnerable, uninsured indigent patients access to care and requires manufacturers to provide outpatient drugs to qualifying healthcare providers at significantly reduced prices.\textsuperscript{156} The 340B program is invaluable for indigent patients, however from 2005 to 2011, the number of 340B eligible hospitals almost tripled from 591 to 1673.\textsuperscript{157} In 2014, 2,140 (37 percent) hospitals in the US participated in the 340B program. A hospital and all of its affiliate sites count as one hospital, otherwise, in 2014 a total of 14,061 hospitals and affiliated sites participated in 340B program.

The GAO noted that in 2008, Part B drug spending at disproportionate share hospitals (DSH) were similar to non-DSH hospitals; and in 2012, after the DSH hospitals joined the 340B program, Part B drug spending at these hospitals became 53 percent higher than non-DSH hospitals.\textsuperscript{158} While spending was higher at these 340B DSH hospitals, the average risk score of patients at 340B DSH hospitals (1.41) differed by only 0.04 in non-340B DSH hospitals (1.45).\textsuperscript{159}


\textsuperscript{155} COGR 2012 Report, p. 19.

\textsuperscript{156} ASPE 2014, p. 4.


\textsuperscript{159} Ibid., p. 26.
The GAO believes that these newer participants were responding to the financial incentives of the program.\textsuperscript{160}

Increasing participation in the 340B program is extracting an increasing dollar volume of discounts from drug manufacturers. Generic drug prices are already low, and are forced even lower by 340B concessions. Since the MMA, drug prices have generally dropped, and reimbursement rates, reflecting a 2-month lagged price, have generally been more than 6 percent above the prevailing ASP rates.\textsuperscript{161} The ASPE conducted an analysis of quarterly ASPs and Medicare Part B reimbursement rates for covered drugs from 2005 to 2013, and found that ASPs for 73 percent of HCPCS codes increased by more than 6 percent from the previous quarter at least once between 2005 and 2013.\textsuperscript{162} However, the CMS July 2015 drug pricing files reveal that 24 out of the top 50 Part B drugs experienced a price change of 2 percent or less, and that 15 of the top 50 drugs decreased in price.\textsuperscript{163} Any increase in drug price was offset by savings generated from the Medicaid Rebate Program. Because of the rebate program, Medicaid’s net costs for brand-name drugs in particular increased at a lower rate than inflation.

Another factor that largely impacts the Part B reimbursement rates received by providers is the large shift to generics. Between 2002 and 2013, the overall market for sterile injectables increased by 39 percent, while the number of units sold by generic manufacturers increased by 59 percent.\textsuperscript{164} Because of the lag on reimbursement rates, newly available generics are matched with the rates of their brand counterparts for two quarters or more.\textsuperscript{165} During this time,

\textsuperscript{160} GAO Medicare Part B, p. 34
\textsuperscript{161} ASPE 2014, p. 4.
\textsuperscript{162} Ibid., p. 5.
\textsuperscript{163} Centers for Medicare and Medicaid Services, “July 2015 ASP Pricing Files,” CMS, last modified September 02, 2015, \url{https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFil.es.html}.
\textsuperscript{164} ASPE 2014, p. 8.
\textsuperscript{165} Ibid.,
providers would have often been receiving reimbursements for acquiring newly available generic drugs at rates based on the price of the proprietary drug, meaning that providers were often reimbursed at rates above the cost of purchase.

The ASP reimbursement system also influences physician prescribing habits by giving economic incentives to prescribe expensive brand-name drugs over previously available generics.\textsuperscript{166} Because Medicaid reimbursements are 106 percent of the ASP for a drug, purchasing expensive branded drugs yield more dollars than inexpensive generics. For example, six percent of the cancer drug Abraxane, which sells for $5824, is greater than the total price of the generic paclitaxel, priced at $312.\textsuperscript{167}

3. Business Decisions and Generic Drug Markets

Drug companies have little incentive to remain in the generic market producing low cost drugs with slim profit margins. Pricing in the generic market is generally a race to the bottom, and when the price of a drug is no longer economically viable for the manufacturer, production may be abandoned in favour of more profitable drug products.\textsuperscript{168}

These policies and market conditions may influence drug manufacturer decisions to sell products to other purchasers. For example, Medicare price caps do not exist in Europe, and generic drugs are sold at higher prices than in the North America. As a result, drug companies seeking more profitable markets may divert shortage drugs away from North American consumers. In 2014, global pharmaceutical market was worth an estimated $980.1 billion. The North American market (USA and Canada) kept its place as the world’s largest market with a

\textsuperscript{166} ASPE 2014, p. 4.  
\textsuperscript{167} Hoffman, p. 7.  
\textsuperscript{168} COGR 2012 Report, p. 13.
44.5 percent market share. The U.S alone holds approximately 40 percent of the global market, and U.S exports account for 12.4 percent of its sales, or $54 billion. Drug manufacturers turning to more profitable overseas markets does not appear to be a serious factor contributing to drug shortages, however the diversion of shortage drugs away from its own domestic market exacerbates the shortages of those drugs.

4. Group Purchasing Organizations

The contracting practices of Group purchasing organizations (GPOs) contribute to drug shortages by exerting a significant amount of downward pressure on drug prices, reducing overall profitability of critical drugs that heavily influencing the production decisions of manufacturers. According to legislature, a GPO is defined as an entity “authorized to act as a purchasing agent for a group of individuals or entities who are furnishing services reimbursed under a Federal health care program.” GPOs negotiate consolidated purchasing contracts with drug companies that provide participating health systems with substantially discounted drug prices and reduced transaction costs. Due to the financial efficiencies granted by GPOs, membership and utilization is widespread in the healthcare industry.

Approximately 96 to 98 percent of US hospitals utilize GPO contracts to purchase drugs, and 73 percent of purchases made by hospitals are done through GPO contracts. The Healthcare Supply Chain Association (HSCA), a trade association representing 14 healthcare GPOs,

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estimates that an average of 2 to 4 GPOs per facility. In 2012, the 5 largest GPOs by purchasing volume control approximately 90 percent of the market, and reportedly negotiated contracts worth a total purchasing volume of $130.7 billion.

GPOs generate operating revenue by collecting “contract administrative fees” on a percentage of each manufacturer's' GPO contract sales. Contract administrative fees are legally capped at three percent, but in some cases, GPO fees have exceeded this limit. In addition to covering operating expenses, a portion of the fees may be distributed to health care provider customers, invested in other companies, or used to fund other services for their customers, such as clinical evaluations, technology assessments, or marketing and insurance services.

Figure 3. General Flow of GPO Administrative Fees.

These fees, otherwise known as ‘kickbacks’ are generally prohibited, however the 1987 Medicare anti-kickback safe harbour exempted GPO system members from criminal

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172 GAO GPO 10-2014, p. 4.
173 Ibid.,
175 Ibid.,
176 GAO GPO 10-2014, p. 5.
177 Ibid., p. 6
prosecution for taking kickbacks from suppliers.\textsuperscript{178} The anti-kickback statute is intended to protect patients and federal healthcare programs, e.g., Medicare, from fraud and abuse by reducing the influence of money on important healthcare decisions.\textsuperscript{179} According to a House of Representatives Committee report, it was believed that GPOs could help reduce healthcare costs by allowing hospitals to obtain volume discounts on drugs, and that a safe harbour should be established to protect GPOs from persecution for collecting such fees.\textsuperscript{180} However, this percentage-of-sales funding structure presents an inherent conflict in which GPOs have incentive not to obtain lower prices on drugs on behalf of their providers because higher prices yield fees.

In order for GPOs to secure low prices, a GPO must exercise some measure of monopsony power, which raises competition concerns.\textsuperscript{181} In addition, many GPO contracts amount to exclusionary contracts often involving exclusivity provisions, bundling arrangements, and extended terms that may limit the sources of supply to their members.\textsuperscript{182} Altogether, GPO practices raise significant policy concerns, and have recently been linked to drug shortages.\textsuperscript{183}

These contract provisions have a tendency to exclude competing manufacturers from drug markets, reduce drug profitability, and play a significant role in manufacturer decisions to stop the production of a drug or leave a drug market entirely.\textsuperscript{184} Sole-source contracts, for example, grant one vendor exclusive rights to sell the drug products specified in the contract.\textsuperscript{185} The GAO reported that three of the five largest GPOs negotiated sole-source contracts for brand-name

\textsuperscript{178} 42 C.F.R. § 1001.952(i).
\textsuperscript{179} GAO GPO 10-2014, p. 6.
\textsuperscript{180} Ibid.
\textsuperscript{181} Roger D. Blair & Christine Piette Durrance, Group Purchasing Organizations, Monopsony, and Antitrust Policy, Managerial and Decision Economics, 2014.
\textsuperscript{182} Ibid.
\textsuperscript{183} GAO GPO 10-2014, p. 6-7.
\textsuperscript{184} Blair, p. 436.
\textsuperscript{185} GAO GPO 08-2010, p. 5.
drugs; and four of the five GPOs negotiated sole-source contracts for generic drugs, including generic injectable drugs. Bundling negotiation contracts also tend to exclude rival manufacturers from the market, bundling contracts group together multiple, related drugs for purchase at a large discount. 

The GAO review revealed that these contracts tend to give only select manufacturers an advantage, while competitors suffer market exclusion. GPO contracts heavily favour large manufacturers with greater economies of scale, and the financial pool required to pay contract fees, which can exceed half of a company’s total revenue for a single drug. This is especially true of GPO contracts that offer minimum volume purchase requirements that go beyond the capacity of smaller generic manufacturers, effectively blocking these smaller manufacturers from competing or securing these contracts. Securing a contract provides the drug manufacturer with incentives that limit market competition, essentially guaranteeing sale of product to GPO member hospitals, although at a severely discounted price due to the amount of competition to secure GPO contracts. Manufacturers that cannot produce a drug at large enough volumes to counteract the discounted price will eventually stop producing the product or leave the market; and manufacturers that do not secure a contract often halt production entirely due to the lack of buyers. Each outcome effectively shrinks the available market supply, and possibly the number of active suppliers in the market. Drug markets with limited suppliers are

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190 GAO GPO 07-2003.
more vulnerable to drug shortages, and given the nature of GPO contracts, these shrunken drug markets are unlikely to experience any resurgence in suppliers.

In drug markets, GPOs present a guaranteed source of demand. In order to reduce wasteful stock holding, drug manufacturers aggressively compete for GPO contracts by putting drug prices in a downward spiral. These drugs are usually generics, and offer slim profit margins to manufacturers. In some cases, manufacturers may contract a drug price equal to or below the cost to produce. These drugs are considered “loss leaders” that allow manufacturers to secure contracts to sell more profitable drugs. Manufacturers may avoid matching the price of loss leaders with rising production costs in order to remain competitive for larger contracts covering anywhere from several to hundreds of other drugs. More frequently, a manufacturer will simply suspend the production of a loss leader entirely.

Any examination of a list of shortage drugs shows that there is a strong correlation between drug price and availability with most of the drugs in shortage being loss leaders and low-profit generics. The two main issues are economic in nature, and primarily rooted in GPO practices and the MMA reimbursement system. The effects of GPO practices and the MMA reimbursement system exert tremendous pressure on drug manufacturers to continually cut production costs in order to supply low cost drugs. As a result, drug manufacturers are forced to utilize antiquated manufacturing equipment and processes that are vulnerable to quality-related enforcement action; and in some cases discontinue the production of low profit drugs.

191 See Blair supra note 181.
193 Ibid.,
194 Ibid.,
GPO practices and the MMA reimbursement system have grossly warped the health and function of drug markets, creating an economic reality of loss leaders, generic drugs offering slim profit margins, vast market uncertainties, and limited sources of supply. Generic manufacturers can hardly thrive in today’s drug markets, let alone afford to invest in quality-related improvements. As a result, manufacturers are vulnerable to the entirety of systemic manufacturing issues that exacerbate or immediately precede drug shortages.
Chapter 4. Reviewing the solutions

1. Executive Order 13588 - Reducing Prescription Drug Shortages

In response to the increasing number of drug shortages, on 31 October 2011, U.S President Barack Obama issued Executive Order 13588. The Executive Order directs the FDA to take appropriate steps to aid in the prevention and mitigation of current and future production disruptions in facilities producing lifesaving drugs. Key sections of the Executive Order include broader reporting of manufacturing discontinuances, which requires manufacturers to provide adequate advance notice of any product discontinuations that may lead to permanent or temporary shortages of life supporting or life sustaining medicines, or drugs that prevent debilitating disease; expedited regulatory review processes, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, and carrying out this expedited process whenever necessary to prevent or mitigate existing or potential drug shortages, and instructing that the FDA consider the severity of the drug shortages, potential impact, and the importance of the affected drug to public health; and reviewing market participant behaviours in which the FDA is instructed to observe and report to the Department of Justice (DOJ) any findings that drug shortages have led to stockpiling and reselling drugs at marked up prices, allowing the DoJ to make informed decisions as to whether these activities are consistent with applicable law.

The most notable take away from the executive order is that drug companies are required to give advanced notice of a potential shortage. This certainly addresses an aspect of the communication issues between key stakeholders, which may certainly be considered beneficial.

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196 Ibid.,
However, every benefit has an associated cost. With respect to giving advanced notice of potential drug shortages, the associated cost is the potential for sources of demand to abuse this information and treat the advanced notice as a green light to hoard or stockpile.

2. Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)

The Food and Drug Administration Safety and Innovation Act gave the FDA much needed authorities to help prevent and mitigate drug shortages, amending the existing drug shortage notification requirements of the Food, Drug & Cosmetic Act (FD&C) and adding new provisions. For example, Section 1001 requires manufacturers of all covered prescription drugs-approved or unapproved-to notify the FDA of any discontinuation. Prior to FDASIA, only sole manufacturers of approved drugs were required to notify the FDA of a shortage. With the passing of FDASIA, all manufacturers are required to notify the FDA of both temporary and permanent product discontinuations or disruptions that may lead to a shortage in the United States, and supply the reason for the discontinuation or disruption in the notification. FDASIA also grants the FDA the authority to require early notification of discontinuances or interruptions in the manufacturing of biologics, and drugs used in emergency medical care or surgery.

Manufacturers are also required to provide the FDA with a six months advance notice of any permanent discontinuations, and report any potential product interruptions that may lead to any change in production that affects the manufacturer's ability to meet expected demand.

Title X of FDASIA: 1) expands supply disruption and notification requirements, 2) direct specific actions for the FDA in the prevention and mitigation of shortages, 3) establishes a system for

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tracking and distributing drug shortage data, and 4) orders a task force to investigate the causes of drug shortages and create strategic plans that address the shortages.200

One of the responsibilities of the drug shortage task force is to develop and implement an effective strategy plan for addressing drug shortages. Part of that plan is the examination of a Qualified Manufacturing Partner Program that allows for program participants to have the capability and capacity to supply drug products that are currently or potentially in shortage, and do so within a short and rapid timeline.201 In addition, the strategy initiative must identify and propose incentives to participate in the Qualified Manufacturing Partner Program.202 Finally, the task force must investigate, identify, and conclusively determine the causes of drug shortages, and tailor the strategic plan to address these causes.203

The FDA is also required to send a non-compliance letter to firms that fail to notify the agency in accordance with section 506C, as amended by FDASIA.204 Section 506C also provides the FDA with the authority to expedite reviews of drug applications and supplemental applications and to expedite inspections that may help prevent a shortage.205

FDASIA adds new responsibilities to the FDA for improving drug shortage information to the public, in addition industry stakeholders, including the creation of a process for disseminating drug shortage information, keeping a list of shortage drugs, and improving communication between the FDA and DEA regarding shortages of controlled substances.

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203 Ibid., § 1008, 126 Stat. at 1107.
204 See Section 506C.
205 Ibid.
More importantly, FDASIA requires that the FDA consider the potential impact that a warning letter may have on drug supply before taking any enforcement action—including the potential impact on research and clinical trials. This requirement goes beyond addressing the implications of the FDA’s overzealous enforcement activities that led to mass simultaneous facility closures between 2010 and 2012.

3. FDA Strategic Plan for Preventing and Mitigating Drug Shortages

The plan, issued in October 2013, is the strategic plan counterpart to the Title X provision of the FDASIA directing the FDA to establish a drug shortage task force to develop and submit a strategy plan to Congress to aid in the FDA’s steps for preventing and mitigating drug shortages.

The plan outlines certain details on the origins of drug shortages, an account of the FDA’s processes and procedures for helping to prevent or mitigate drug shortages, and the FDA’s strategy for strengthening those processes and procedures. The plan also recommends actions for stakeholders to help prevent drug shortages.

The plan identifies two central goals to address drug shortages: 1) Strengthening the FDA’s mitigation response to current or potential drug shortages, and 2) developing long-term prevention strategies by focusing on the root causes of shortages.206

Tasks for the first goal include developing and streamlining FDA internal processes. The FDA will have to revise and standardize its internal procedures and communications, and maximize the efficiency of the FDA’s response to a drug shortage notification.207 The FDA will also seek to

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206 FDA Strategic Plan, p. 17-21.
207 Ibid., p. 18.
improve its drug shortage database and tracking capabilities in order to better assess the progress on preventing and mitigating drug shortages.\textsuperscript{208} The third task is to finalize the proposed rule requiring manufacturers to notify the FDA of a product discontinuation or disruption, clarify the roles and responsibilities of manufacturers, and encourage best practices to avoid or mitigate shortages caused by manufacturing issues.\textsuperscript{209} The final task is to enhance public communication about drug shortages by 1) developing accessible mobile applications offering individuals the capacity to access drug shortage information as conveniently as possible, 2) implementing a list of shortage drugs by therapeutic category, and 3) improve the usability of the FDA website by adding effective sort and search functions and capabilities.\textsuperscript{210}

For the second goal, the FDA will identify and propose incentives to promote and improve drug and manufacturing quality; refine a risk-based approach to identifying drug and manufacturing quality issues in order to more effectively prevent supply disruptions; collaborate with key stakeholders to further expand knowledge regarding drug shortages, and examine the benefits and feasibility of a Qualified Manufacturing Partner Program; and finally, continue to develop strategies for addressing drug shortages.\textsuperscript{211}

With the FDASIA requirements formalizing the role of the FDA in preventing and mitigating drug shortages, stakeholders outside of the FDA should assess and acknowledge the considerations available to help mitigate and prevent drug shortages. The FDASIA addressed many of the issues and activities on the part of the FDA that led to unnecessary drug shortages from 2009-2012. A comprehensive strategy plan requires that the FDA collaborate with external

\begin{footnotesize}
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  \item \textsuperscript{208} FDA Strategic Plan, p. 18.
  \item \textsuperscript{209} Ibid., p. 19.
  \item \textsuperscript{210} Ibid., p. 20.
  \item \textsuperscript{211} Ibid., p. 20-21.
\end{itemize}
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stakeholders, and discuss the roles and potential contributions of stakeholders to the drug shortage crisis, and the efforts to prevent and mitigate shortages.

Overall, the Strategic plan is more akin to a straw man proposal created for the purpose of discussing its disadvantages in preparation for a newer, and better draft. The FDA continues to argue that quality-related drug and manufacturing issues are the root cause of drug shortages.\textsuperscript{212} This is a gross mischaracterization of the underlying mechanisms behind drug shortages.

The plan fails to identify and examine the length of interrelated factors that contribute to drug shortages, and instead oversimplifies the causes of drug shortages by taking the overall drug market at face value. The FDA repeatedly names ‘quality issues’ as the leading cause of drug shortages, but fails to examine the underlying economic mechanisms responsible for creating the conditions under which drug manufacturers make important business decisions that ultimately lead to trade-offs in product and manufacturing quality. This is demonstrated in the proposed actions for external stakeholders, which are visibly unsympathetic and insensitive to drug manufacturers.

The FDA's suggestion that external stakeholders find ways to incentivize manufacturers to promote and improve product and manufacturing quality is an extremely basic proposal. Drug manufactures have great long-term incentive to promote and improve product and manufacturing quality in the way of reduced risk of production disruptions, product recalls, and regulatory action. The proposal to incentivize quality improvements goes right through the more meaningful question that asks, “why aren’t manufacturers improving drug and manufacturing quality?” Examining this question dissolves the third proposal that manufacturers could consider

\textsuperscript{212} FDA Strategic Plan, 11, 20-23.
opportunities for building redundant manufacturing capacity, holding space capacity, or increasing inventory levels--because it is more economically beneficial not to, and further exploration will reveal why this is the case. Understanding the unhealthy characteristics of the drug markets is key to devising an appropriate strategy for addressing the causes of drug shortages.

This failure to thoroughly examine the causal climate behind the factors that immediately precede drug shortages undermines key sections of the FDA’s strategic plan. The FDA’s overall strategies focus on advanced notification and availability of information regarding drug shortages, promoting and improving product and manufacturing quality, and improving internal and external communication are useful and valuable measures, but they will not prevent shortages. These measures aim at addressing the symptoms of drug shortages, and not the underlying causes as the FDA claims. One of the key purposes of the plan is to outline a strategy for preventing drug shortages in addition to mitigating the impact of shortages. Addressing the symptoms supports the mitigation efforts, which only fulfils a part of the Strategic Plan for Preventing and Mitigating Drug Shortages. Preventing drug shortages requires measures that address the economics that make drug shortages possible, and towards this endeavour the FDA is limited.

\[213 \text{ FDA Strategic Plan, 4-5.}\]
Chapter 5. Revising old approaches

1. Manufacturing: finding the right incentives

The Strategic Plan for Preventing and Mitigating Drug Shortages identifies a number of important considerations for industry stakeholders. Offering incentives would provide drug manufacturers with viable opportunities to make otherwise unfeasible business decisions given the unique nature of drug markets. Offering incentives to improve product and manufacturing quality would contribute to preventing drug shortages, but the incentives must be beneficial enough to merit abandoning current approaches. For example, if economic constraints are preventing manufacturers from implementing the necessary changes to improve manufacturing quality, then an incentive to do so must provide enough economic benefit to offset the losses suffered during the time it takes to implement those changes. For initial upgrades and implementations, noneconomic incentives do not present viable business opportunities for manufacturers to suspend or reduce production capacity in order to upgrade equipment and modernize facilities.214

For buyers of generics, the main consideration in making purchases is price.215 Purchasers want low cost drugs, and manufacturers do not have the bargaining power to establish a favourable price floor, especially for generics. Moreover, a general observation is that buyers do not take manufacturer quality disruptions into consideration when purchasing drugs.216 For this reason, manufacturers must prioritize cost reductions over quality. With these considerations, a single stakeholder option is for a to provide tax credits, or increased exclusivity for produced shortage drugs, to manufacturers that take sufficient steps to improve manufacturing quality.

215 FDA Strategic Plan, p. 22.
216 Ibid.,
Noneconomic incentives, such as ‘quality stamps of approval’, reduced FDA oversight, or greatly expedited inspection processes, may not front load enough economic benefit to entice manufacturers to make the initial improvements to manufacturing quality, such as replacing antiquated equipment and modernizing facilities. These noneconomic incentives are more suitable for supporting and maintaining long-term quality manufacturing in companies that have already completed quality-related upgrades, and have returned to sustainable production levels. Noneconomic incentives cannot reliably encourage manufacturers enough to incur the costs of upgrading and modernizing equipment, facilities and processes, which includes personnel and consultation costs, and in addition to the loss of revenue from taking production lines offline and the minimal projected overtime costs to make up for lost production capacity. This is especially the case for generic manufacturers producing drugs with slim profit margins.

Current generic markets do not provide manufacturers with sustainable, long term options for prioritizing quality over cost. In these markets, companies assign greater risk to investing in quality-related upgrades over measures for cutting costs. In 2013, generic injectables manufacturer Ben Venue permanently shut down its operations after investing over $350 million in quality-related upgrades, stating that the company could not return to long-term sustainable production.\textsuperscript{217} The two fronts in this case are short-term impact, and long-term sustainability. Therefore, companies need financial incentives to address the short-term risks and concerns associated with investing in quality-related upgrades \textit{in addition} to incentives that help manufacturers achieve long-term sustainable production levels after they’ve invested in and completed adequate quality-related upgrades.

\textsuperscript{217} “Bedford-based Ben Venue to shut down operations permanently; 1,100 employees affected,” \textit{CLEVELAND.COM}, last modified October 04, 2013, \url{http://www.cleveland.com/healthfit/index.ssf/2013/10/bedford-based_ben_venue_to_shu.html}. 
Direct government funding for quality-related improvements may be a viable option. Offering government support to drug manufacturers that can demonstrate need would offer some support for the short-term impacts of implementing quality-related changes by offsetting all or some of the costs to upgrade, in addition to the potential loss in revenue. Additional incentives (from any source) aimed at long term sustainability, such as reducing regulatory oversight, or expediting drug review applications, would provide manufacturers with even more reason to make the initial investments in quality.

One alternative that may be worth discussing is for group purchasing organizations to provide funding for quality improvements in addition to long-term exclusivity contracts for shortage drugs. This sort of dual-pronged incentive addresses some of the short and long-term considerations of drug manufacturers. Exclusivity is already an incentive for suppliers to produce a certain drug, and the funding from the purchasing organization would go part of the way to preventing quality-related supply disruptions from a long-term source. Group purchasing organizations would see little benefit in providing this incentive to a single supplier involved in a saturated drug market. However, focusing the incentive on shortage drugs that are unattractive to produce may temporarily activate market entry or increase the viability of producing the drug. There also remains the slim possibility that such an incentive would reset a dead or dying market suffering from quality-related supply issues, but the more plausible outcome is a situation in which the 'revived' market consists of only one producer for any significant period of time; and group purchasing organizations may not have the ability to incentivize a meaningful number of drug producers in this way that is conducive to a healthy market.

Incentives may be useful for improving manufacturing quality, but other issues related to drug shortages that are caused by low price elasticities or negative or unsustainable profits cannot be addressed solely by offering incentives. For example, offering tax breaks to companies for
producing shortage drugs in an attempt to attract newcomers to a certain drug market and stimulate competition may fail to address the real problem. This is especially the case for drug markets that are characterized as anticompetitive due to GPO involvement. In such a case, the goal of a tax break is to attract newcomers and increase the number of suppliers of a certain drug. However, the tax break does not address the underlying cause for the market’s anticompetitive character. Similarly, offering tax breaks or government funding for building additional capacity and increasing redundancy would be unsuccessful incentive programs in the overall drug market. Even if drug companies were incentivized to build additional infrastructure, it would not make any financial sense to leave the facility idle as a backup capacity in the case of a shortage. The decision-to-implementation period for increasing production takes approximately three to five years. Temporary drug shortages may be resolved within this timeframe, which presents a difficulty in directing such incentives towards the production of shortage drugs.

2. Improving Regulatory Communication

Problems in the supply chain beyond the manufacturer can be indicative of future drug shortages on a regional level; and supply problems at the manufacturer level indicate future drug shortages on a national level. Both are problematic, and all organizations involved in the healthcare industry—including the pharmaceutical industry—have some kind of ethical obligation associated with the delivery of ethical health care to patients. This includes the development and implementation of guidelines, resources, and tools that allow those involved to properly prevent, manage, and communicate decisions concerning drug shortages in such a way that benefits the patient in the delivery of care with minimal harm.

In Canada, a significant fault is the lack of useful tools for accurately tracking drug shortages and collecting precise data about the specifics of the harms experienced by patients as a result
of drug shortages. The online database intended to track drug shortages in Canada fails to provide complete and actionable information about drug shortages, i.e., information that allows clinicians to make informed decisions in the prevention and management of drug shortages. This failure is recognized in Canadian Health Minister Rona Ambrose’s announcement that companies be required to post information about shortages; and in Health Canada’s newly implemented register that lists manufacturers with Drug Identification Numbers who have committed to send notification of shortages.\(^\text{218}\)

Stockpiling is a symptom of a larger problem expressed by the legal complacency on the matter of stockpiling shortage drugs. The problem exists partially due to the lack of drug shortage related tools and resources available to clinicians. Such information is actionable information, and therefore valuable information, because it allows clinicians to make informed decisions that will directly impact their ability to deliver ethical care. Actionable information may be any data that can be used to determine the most effective way to manage and allocate resources, ration medications, order shortage drugs from traditional or nontraditional distributors, or prescribe alternative therapeutics. Such informed actions prevent unethical and irresponsible behaviour that artificially inflates demands and exacerbates drug shortages.

3. Economics

The above approaches only aim at mitigating the current crisis. Streamlining communication and identifying incentives for manufacturers to produce drugs only address the symptoms of the root causes of the crisis. Many shortage drugs are loss leaders or low-profit generics. In order to meaningfully prevent drug shortages, solutions must address the economic factors that make loss leaders and low-cost generics a reality in the first place.

Drug shortage prevention starts by addressing the faulty government policies and legislation that enabled group purchasing organizations and the Medicare Modernization Act to distort the economics of drug markets. There is ample documentation of GPO anticompetitive contracting practices, self-dealing, and kickbacks presented in Senate Antitrust subcommittee hearings, GAO reports, and lawsuit dockets over the past decade; and significant data connecting GPO practices and the MMA reimbursement system with the low profitability of shortage drugs.\textsuperscript{219}

3.1 The Medicare Modernization Act Reimbursement System

The Medicare Modernization Act, intended to reduce overpayments for drugs administered for drugs, has also made a significant contribution to the drug shortage crisis. The ASP-based reimbursement system capped price increases at 6 percent while setting a flat price for each category of drug. Instead of reflecting the price of each individual drug, the ASP reflects the blended average of all the drugs in the category.\textsuperscript{220} This means that drugs with a high production cost have the same ASP as the low cost-of-production drugs in the category. Thus the average sales price will always be pushed downward by the lowest cost product.

The ASP system places a significant economic burden on generic manufacturers. Drug companies sacrifice significant profit margins in order to secure sources of demand. Many manufacturers produce certain generic drugs as loss leaders in order to secure large contracts, significantly reducing the overall profitability of these drugs for competing generic manufacturers. Loss leaders effectively remove the price floor for that drug, causing rival


\textsuperscript{220} Gottlieb, p. 6.
manufacturers to compete for scap profits or exit the market for that drug entirely due to the increasing cost of production.

Restructuring the price controls under Part B to more accurately reflect the acquisition costs of purchased drugs would go part of the way to impeding the negative economic effects of the Act. Alternatively, resetting the ASP of a drug when its price reaches a certain threshold conducive to drug shortages may minimize the utilization of loss leaders and preserve the overall supply.

3.2 Group Purchasing Organizations

Under certain conditions, GPOs raise serious competition issues that is worthy of antitrust investigation. Evaluating these issues must pay attention to particular circumstances because traditional economic considerations do not apply to drug markets in every case. Drug markets in which GPOs have consolidated buyer demand and acquired monopsony power do not exhibit the usual monopsonist behaviour by which profits are maximized by restricting purchases. In drug markets, GPOs want to command the same purchasing volumes at lower prices because hospitals do not want to reduce their use of drugs, nor do hospitals want to purchase in short of patient demands. Doing so would result in negative patient outcomes and malpractice claims. Healthcare GPOs want to maintain or enhance purchasing volumes, and one strategy to do so is the use of ‘all-or-nothing’ offers to drug suppliers.\(^{221}\) An all-or-nothing offer is essentially an offer to purchase a product at a lower price, or purchase nothing at all. This strategy only works in drug markets with two or more suppliers, so that if one refuses an all-or-nothing offer, the GPO goes to the other. Due to the just-in-time approaches to manufacturing used by drug companies, rejecting an offer in absent of another is economically unviable. Therefore, in such markets, GPOs are not at any real risk of failing to secure a product in supply.

\(^{221}\) Blair, p. 434.
The information provided heavily emphasizes abusive GPO practices that stifle competition, create unfavourable economic realities, and even inflate healthcare prices. GPOs have effectively strayed from their initial purpose, and current practices, policies, and structural safe harbours have lead to serious outcomes that have contributed to the decrease in the number of drug manufacturers in critical drug markets. However, this information is only evidence of the apparent effects of GPO practices, and not the actual reality of the effects.

It is clear that GPO practices, in addition to the MMA reimbursement system, jointly exert significant economic pressure on manufacturers. Until changes are made to the MMA, and the impact of those changes can be measured, suggesting any significant alterations to GPOs is simply too much, too soon.

To date, a thorough and conclusive investigation of GPO practices and behaviours has yet to be conducted. The DHHS Office of Inspector General (OIG) has the authority to compel production of the necessary information for such an investigation, but has failed to do so for the past eleven years, when Congress requested an investigation of the impact of GPO practices on manufacturers’ ability to invest in quality-related improvements and facility upgrades. A thorough investigation is necessary to determine the appropriate measures.


Chapter 6. Conclusion

In order to address drug shortages and minimize patient risks and negative outcomes, solutions must consider the underlying economic mechanisms that are responsible for the crisis. The Medicare Modernization Act and group purchasing organizations present just two obstacles that exert significant economic pressures on manufacturers. Allowing manufacturers to secure sufficient profit margins through the sustainable production of critical shortage drugs is a necessity for sustaining a healthy drug market in which drug shortages are at an absolute minimum.

The FDA has a long way to go toward accurately characterizing the causes of the drug shortage crisis. Systemic manufacturing issues are typically the most immediate issues preceding a shortage. In the grand scheme of the crisis, systemic manufacturing issues are only symptoms of underlying problems. Underneath the manufacturing issues are communication issues, under which lie regulatory problems, and lying even deeper are the economic mechanisms and faulty policies that are the root causes of drug shortages.

The FDA has shifted from causing unnecessary drug shortages by way of overzealous enforcement activities leading to mass, simultaneous closures of competing facilities to establishing a series of necessary tools and resources for managing, tracking, and dealing with drug shortages. The FDA has the capacity to implement measures for mitigating the severity of shortages, and should make efforts to identify any possible financial or economic incentives that may be offered to manufacturers.
Addressing the root causes calls for legislative action to eliminate the negative impact of the MMA’s reimbursement system, and GPO pay-to-play schemes that exploit vendor kickbacks. The way forward is quite clear, beginning with restructuring the ASP based reimbursement system to accurately reflect the price of drugs. The second course of action is a thorough investigation of the impact of GPO practices on drug manufacturers after any changes to the MMA and the related ASP based reimbursement system, specifically the ability to secure sustainable profit margins off of generic drugs, and invest in quality improvement with little to no risk of failing to return to sustainable production levels. Without addressing these root issues, any talk of addressing drug shortages can only aim for mitigation, not effective prevention.
Bibliography


