INJECTABLE CHEMOTHERAPY DRUGS ON SHORT SUPPLY: RELEVANCE OF CHANGES IN SUPPLIERS AND PRICING IN PREDICTING SHORTAGES

by

Douha Fouad Bannan

A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

in

Pharmacotherapy Outcomes Research and Health Policy

Department of Pharmacotherapy

The University of Utah

May 2013

STATEMENT OF THESIS APPROVAL

The thesis of **Douha Fouad Bannan**

has been approved by the following supervisory committee members:

Nancy Nickman	, Chair	**10/29/2012** Date Approved
Joseph Biskupiak	, Member	**10/29/2012** Date Approved
Erin Fox	, Member	**10/29/2012** Date Approved

and by **Diana I. Brixner** , Chair of

the Department of **Pharmacotherapy**

and by Donna M. White, Interim Dean of The Graduate School.

ABSTRACT

Drug shortage is a situation that affects the supply of medications, and in turn, affects hospitals, providers, and patients. When drugs are in short supply, patients may face treatment delays, may be unable to find essential drugs, or may face side effects from alternative agents, if alternatives are available. The problem of drug shortage is getting worse because the United States Food and Drug Administration, hospitals, and providers cannot anticipate future shortages. Left with no advanced strategies to face the problem of drug shortages, patient care can be negatively affected. This thesis was intended to answer three questions: 1) do the fluctuations in the number of suppliers prior to drug shortages has any effect on shortages of oncology drugs, 2) are there identifiable trends in number of suppliers and reasons for shortages that can be used to predict future shortages of oncology drugs, and 3) can variation in drug prices relative to shortages based on the number of suppliers in the market at any given time be used as a predictor of shortages?

The 41 injectable oncology drugs listed on The American Society of Health-System Pharmacists, the University of Utah Drug Information Service, and Novation web site as in shortage between 2002 and 2010 served as the drugs of interest for this study. After excluding drugs that were available only as brand names as of 2011 (n=12 drugs), and drugs that have been in short supply after 2010 (n=5), information on the remaining

generic oncology drugs (n=24 drugs) was collected based on characteristics such as drug name, dosage form, route of administration, strength, quantity, price, manufacturer code, supplier name, and number of suppliers. Only 17 products (18 dosage forms) were available for full analysis due to on-going shortages that extended beyond the data collection period.

Study findings suggested that the volatility of some drug shortages is not in the number of suppliers prior to shortages; rather it is in the absence of the key manufacturer that is associated with the discontinuation of the brand name. The discontinuation of the brand names of the drugs was associated with a longer shortages period compared to shortages due manufacturing problems or delays. In reality, however five generic injectable manufacturers held the majority of the oncology packages and vials sold in the US market. Efforts should be directed at approving generic products from manufacturers committed to providing stability in the marketplace. Suppliers should have facilities and resources available for continued production.

This work is dedicated to my beloved parents, Fouad Bannan and Siham Almarzouki, and my dearest husband, Ali Jifri, for their unconditional love, and support throughout my life. It is also dedicated to my siblings, Ahmed, Amro, and Mohammed Bannan who have supported and encouraged me throughout the process.

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGMENTS

First and foremost, I would like to express my sincere gratitude to Allah Almighty for his continuous blessings. I would like to express my appreciation to my advisors, Nancy Nickman, Erin Fox, and Joseph Biskupiak, for their support. I would like to express my special appreciation and thanks to the chair of my committee Nancy Nickman, who encouraged me and helped me throughout the process. I would also like to give my thanks and praise to my parents, husband, and siblings for their love, support, dream, and sacrifice throughout my life. May Allah accept my work as good deeds and make it useful to mankind.

INTRODUCTION

The Food and Drug Administration (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 at the user level."[1] Drug shortages have an effect on the pharmacy department, healthcare providers, and patient care. When there is a drug shortage, the preparation and dispensing of medication by the pharmacy department is affected.[2] In turn, patient care may also be affected because of potential delay of needed therapy as in the case of chemotherapy where a patient is on a specific chemotherapy regimen and one or more agents may be unavailable.

Drug shortages are not new to the US healthcare system. A few shortages occurred during the mid 1990s, but national tracking began in 2001 when the Drug Product Shortages Management Resource Center was launched.[3] The resource center represents collaboration between The American Society of Health-System Pharmacists (ASHP), Novation, and the University of Utah Drug Information Service (UUDIS). The UUDIS investigates reports of potential shortages. If shortages exist, the UUDIS will post this information on the ASHP Drug Product Shortages Management Resource Center and Novation website.

From 2006 to present the number of drugs on short supply has tripled and through August 2011, 198 drug shortages had been reported[3,4] Nationally, 77 percent of the

shortages in 2010 were sterile injectable drugs.[5] Injectable drugs are more vulnerable to shortage because with their low- profit margin and complexity of the manufacturing process. Only a few companies may be interested in making generic injectable drugs. If a shortage occurs in these cases, it typically lasts months. Also, the majority of scarce drugs are generic, a situation almost never seen with brand name drugs. Therefore, generic drugs may not be economically attractive. Companies may have little incentive to keep up with production.[4,6]

Reimbursement for injectable generic drugs is fixed by Medicare legislation at cost plus 6 percent above the average sale price.[7] This fixed reimbursement scheme may discourage generic drug production, which ultimately limits manufacturers' and providers' profitability. This may also discourage providers, especially oncologists, from prescribing generic drugs that already sell at a low profit margin.[7]

Given a potential multitude of reasons why an injectable medication may end up on a shortage list, this thesis will examine oncology shortage data from 2002 to 2010 to identify a possible correlation between brand products leaving the market and drug shortages. This may be used to better predict shortages in advance and would allow better planning and potentially reduce impact on patient care outcomes.

REVIEW OF LITERATURE

Causes of Drug Shortages

Drug shortages are multifactorial in nature. A combination of factors can contribute to the shortage of a single drug and vice versa. Reasons behind a drug shortage may not always be known, because manufacturers are not required to disclose the reason. According to data from the UUDIS in 2010, 47 percent of drug shortages were due to unknown reasons, 28 percent due to manufacturing issues and 14 percent due to supply-demand imbalances.[5]

Manufacturing Problems

Manufacturing processes of many drugs are complex, especially injectable drugs. Quality problems can occur at any step of production and may vary in intensity. Examples are a wrong expiration date on a package, microbial contamination of contents, impurities or crystallization due to stability changes. In 2010, 54 percent of the shortages of injectable drugs were due to quality issues according to the FDA.[8] Another problem with injectable drugs is that many drugs are available in the form of lyophilized powder that needs to be reconstituted. Lack of lyophilized capability may also precipitate drug shortages. Due to the anticipated growth in demand for lyophilized powders, companies

such as Vetter and Baxter planned to expand lyophilization capacity to keep up with future demand. For example, Vetter proposed increasing their lyophilization capacity to expand their annual production up to 24 million lyophilized units per year.[9,10]

Good Manufacturing Practices (GMPs) are regulations enforced by the FDA to ensure that products meet quality standards throughout the manufacturing process and that final products are pure, safe, and effective. Pharmaceutical manufacturers who violate GMP regulations will be subjected to FDA form 483s, then warning letters, followed by consent decrees if multiple warnings do not result in change. If still not in compliance, manufacturers face product discontinuation, seize product, and finally plant closure by FDA.[11]

Between 2006 and 2010, five major types of GMP violations accounted for 75 to 85 percent of all FDA form 483s. In 2010 alone, there were 646 FDA form 483s.[12] One of the most common violations is inadequate quality control and manufacturing validation. For example, in November 2011, Hospira received a new form 483 because its Texas plant had issues with quality control and training.[13] As of 2011, Hospira was still not complying with GMP regulations at its North Carolina plant.[13] Another common violation is lack of written documents of production and process control standard operating procedures. For example, in June 2011, Novel Laboratories, Inc., received a form 483 because written procedures for the cleaning and maintenance of equipment used in the processing or packing of a drug product were not established.[14]

Finally, when a sole manufacturer does not comply with the GMPs, they are then forced to delay production, which can precipitate drug shortages. Also, manufacturers

have their own quality standards, and being unable to meet their own standards may result in voluntary recalls and shortages.[2,5]

Drug Recall

Voluntary recalls can be a result of safety concerns such as harmful or defective product, noncompliance with regulations, or technical deficiencies such as deficiencies in labeling of drugs.[2] This is especially problematic when one manufacturer dominates the supply. Voluntary recalls are usually temporary, affect specific lots, and are not subject to FDA legal actions. An example of a voluntary recall is that of Procrit ® (epoetin alfa) in late 2010.[15] Procrit® is a growth factor used to treat anemia in patients with chronic kidney disease, anemia caused by zidovudine in HIV-infected patients and chemotherapy-induced anemia. The recall of the drug was due to the presence of lamellae, glass flakes, and protein clusters in glass vials of Procrit®. The recall of Procrit® led to a shortage not only of Procrit®, but also Aranesp® (darbepoetin alfa) the only other approved drug for chemotherapy-induced anemia. Because when one drug is recalled, the availability of the alternative may be affected. Also, stockpiling of the alternative may take place, resulting in shortages.[16]

Product Discontinuation

If the production of certain drugs, especially injectables, is complex and not economically attractive, some companies may decide to discontinue production. Another reason for drug discontinuation is low demand or safety issues that may force manufacturers to discontinue production either temporarily or permanently. An example

of permanent discontinuation of a drug due to safety concerns is the withdrawal of Vioxx® (rofecoxib) in 2004.[17] Vioxx®, a cyclooxygenase type 2 inhibitor used to reduce pain and inflammation, was found to be associated with an increased risk of myocardial infarction and stroke among those who used it for more than 18 months. Safety concerns resulted in voluntary withdrawal and production discontinuation of the drug from the US and worldwide market.[17] Another recent example of permanent discontinuation of a drug due to safety issues is the withdrawal of Xigris® (drotrecogin alfa) in October of 2011. Xigris® is used in adult patients with severe sepsis and sepsis shock to reduce the risk of mortality. It was withdrawn due to lack of efficacy and its failure to show survival benefits. Yet, neither the discontinuation of Vioxx or Xigris due to safety issues resulted in drug shortages.[18]

Patent expiration and release of generic products can also have an impact on drug availability. Companies are granted exclusive rights to market new drugs for a specific time period as a way to recover the costs of research and development. When patent protection expires, other companies are allowed to compete and develop generic drugs. Generic drugs are usually cheaper to develop compared to brand-name drugs, because manufacturers of generic drugs do not have to go through the same processes as with the development of new drugs. Also, there are no research and development costs associated with the manufacturing of generic drugs. At the same time, generic drugs sell at cheaper prices compared to brand-name drugs. For that reason, it may be more economical for companies to discontinue drugs with low profit margins in order to concentrate on new drugs that could be more profitable.[19]

Industry consolidation may also result in less competition and less investment in new drugs. A recent analysis of data on approximately 1,200 new drugs introduced and approved since 1950 showed that during the past 60 years, the number of new drug approvals was correlated with the number of pharmaceutical companies.[20] Generic injectable drugs also have fewer manufacturers compared to other drugs. According to the IMS Institute for Healthcare Informatics (IMS IHI), two-thirds of all generic injectable drugs in short supply have three or fewer suppliers. Also, data from IMS showed that in 2010, 80 percent of the packages and vials sold in the US market were held by the top five generic injectable manufacturers (Hospira Incorporated, Teva Pharmaceuticals, Boehringer Ingelheim (Bedford Labs), Fresenius Kabi (APP), and Novartis (Sandoz)), and that the top three manufacturers accounted for 71 percent of injectable drugs sold in the US market.[21]

Finally, mergers may result in product discontinuation or delay product availability if the companies that have merged decided to move production lines to new facilities or narrow the focus of product lines.[2] For example, in October 29, 2010, Baxter International Inc. divested its US generic injectables business to West-Ward Pharmaceuticals. Since then, West-Ward had discontinued production of some products such as metoclopramide (used to control nausea and vomiting).[22]

Based on President Obama's 2011 executive order to reduce prescription drug shortages, the FDA released a new interim rule in December of 2011. The new interim rule included a more specific definition of the term "discontinuation" to include not only permanent discontinuation of medically necessary drugs, but also temporary discontinuation as well. In the new interim rule, the FDA defined product discontinuation

as “any interruption of manufacturing of a drug product” more specifically “that could lead to a potential disruption in supply of the drug product, whether the interruption is intended to be temporary or permanent.”[23] According to this new rule, permanent discontinuation should be reported six months in advance, and temporary discontinuation should also be reported only if disruption in supply is anticipated.

Product discontinuation is especially of concern because manufacturers are not obligated to report discontinuation of drugs to the FDA unless 1) it is considered a “medically necessary drug” and 2) if they are the sole manufacturer. FDA defines medically necessary as any drug that is “used to prevent or treat a serious or life-threatening disease or medical condition, for which there is no other available source with sufficient supply of that drug or alterative drug available.”[24] Also, based on the FDA Interim Final rule, sole manufacturer was defined as ‘‘an applicant that is the only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities.’’[23]

Despite the presidential order and the Interim Final Rule, the FDA has no authority or influence on manufacturing capacity, and does not have the authority to impose penalties on manufacturing companies that do not report product discontinuation. Therefore, only a few companies have incentives to report product discontinuation even if they are the sole manufacturer. An example of sole manufacturer abrupt discontinuation of a drug without notifying the FDA is the discontinuation of ethiodized oil by Guerbet LL. Ethiodized oil is the only lipophilic nonionic iodinated contrast medium available in the US. Ethiodized oil is commonly used in chemoembolization

procedures for the treatment of primary and secondary hepatic malignancies. It is also labeled for use in patients undergoing lymphography, hysterosalpingography, and off-label to detect hepatic metastases or for computed tomography of the liver and spleen. This example is considered a critical drug shortage by the Society of Interventional Radiology.[25-28]

Supply-Demand Imbalances

Ideally, when demand for a certain drug is equal to the supply, we are in a balanced situation. In many cases, demand can exceed supply such as in disease outbreaks, new unlabeled uses of drugs, or when a new therapeutic guideline is released, all leading to supply issues.[2] The transition from one product formulation to another may also disrupt the supply of drugs and result in temporary shortages. For example, the change from a beef protein to plant protein source may delay drug production.

Another theory to consider was stated by the Office of the Assistant Secretary for Planning and Evaluation (ASPE), US Department of Health and Human Services in a published analysis showing that supply and demand rules may not always work with medications because even with high prices, demand might remain the same.[29] Given that, supply and demand rules may not apply as a cause of drug shortages.

Limited manufacturers' capacity may also worsen the situation. Because multiple products may be produced in the same manufacturing line, increasing production of one drug as a result of high demand may automatically result in decrease production of another drug, again resulting in a shortage.[30]

Raw Material Shortages

Raw materials shortages can result from environmental conditions such as climate, conflicts that may affect trade policies, natural disasters such as floods, fires, hurricanes and tornadoes, or damage during harvest, storage, and transportation. Since 80 percent of raw materials come from outside the US, [2] changes in trade policies or problems during production and transportation such as contamination may easily affect the whole US healthcare system. For example, heparin is produced by two companies; Baxter International and APP Pharmaceuticals. In 2008, FDA discovered that heparin produced by Baxter was contaminated by Chinese suppliers. Since the only other company that produces heparin was APP, FDA turned to APP for assistance. The dilemma however was that the source of APP's product was also China.[31]

Raw material unavailability may also be due to manufacturers' relocation of their facilities, such as the case of kanamycin sulfate injection shortage. As of September 2011, kanamycin sulfate injection had been on short supply since February 2009 because the manufacturer, APP, had been unable to obtain raw materials from the supplier, USP, who was relocating its facilities. Shortages due to raw material unavailability can be challenging if the primary source of the raw materials has difficulties with production.[2,32,33]

The "Gray Market"

The majority of health systems, hospitals, pharmacies, and physician practices obtain their drug supplies from traditional distributors such as wholesale distributors or direct from the manufacturers. Gray market distributors are nontraditional and are non-

authorized from the manufacturers. Gray market vendors can be a source of frustration during a shortage, because they buy excessive quantities of certain drugs and then resell them at high markups.

Between July and August of 2011, the Institute for Safe Medication Practices (ISMP) conducted a survey on gray market usage and drug shortages.[34] In the survey, pharmacists and purchasing agents at 549 hospitals across the nation were asked about their experiences with drug shortages. Results showed that 56 percent of respondents reported they have been contacted on a daily basis by up to 10 different gray market vendors. Additionally, 35 percent of community hospitals reported price markups that were 10 times or more than the regular price.[34] For example, the survey found that the markup for Cytarabine, an antineoplastic agent used to treat acute nonlymphocytic leukemia, acute lymphocytic leukemia and in the prophylaxis and treatment of meningeal leukemia, was as high as 3,980 percent.[35] To know whether gray market distributors are contributing to the problem or not, it is important to determine how distributors find out about shortages and from where they buy the drugs in short supply.

End-User Stockpiling

Finally, end-users may exacerbate the problem of drug shortages if they start stockpiling as an attempt to protect themselves from any possible shortage. Stockpiling occurs when end-users place orders that are far more than their normal requirement, resulting in instability of the drug supply chain.[36] In June 2011, the American Hospital Association (AHA) surveyed community hospital chief executive officers from 820 hospitals in 50 states to assess the impact of drug shortages on hospitals and patients.

Survey results indicated that 85 percent of hospitals had purchased excess drug inventory in order to make sure they are ready in case of shortages.[37]

Publicly Available Information on Drug Shortages

Information about drug shortages can be obtained from different sources. FDA, ASHP, Centers for Diseases Control and Prevention (CDC), and manufacturing companies themselves are all publicly available information sources. The FDA and ASHP websites are the most comprehensive sources, although they provide slightly different information. The ASHP website tracks all prescription drugs that are in short supply, including manufacturers' names, reasons for the shortage, estimated resupply dates, and implications for patient care. FDA website, on the other hand, mainly focuses on drugs believed to be "medically necessary."[2] CDC's primary focus is on vaccine shortages, and obtaining vaccine information from drug companies is sometimes challenging.

As previously described, companies are not obligated to report manufacturing problems or product discontinuation to the FDA. Therefore, abrupt shortages can occur with no advance strategy to help hospitals, pharmacies, providers, or patients cope with either the problem or planning for drug shortages.

Broadening Public Interest in Drug Shortages

In July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) were signed into law. This bill, mandated that the FDA track all drugs that are prone to shortages, 2) all drug companies to notify the FDA about manufacturing problems or drug discontinuation six months in advance of when the actual shortage is

projected to begin, and 3) manufacturers report product discontinuation either it is temporary or permanently.[38]

Other public recognition of the problem of drug shortages comes from Rep. Elijah E. Cummings' investigation into drug shortages and gray market practices. On October 5, 2011, Rep. Cummings, the ranking Democrat on the House Oversight and Government Reform Committee, sent a request to five distributors (Allied Medical Supply Inc., Superior Medical Supply Inc., Premium Health Services Inc., PRN Pharmaceuticals, and Reliance Wholesale, Inc.) to provide detailed information on sources of drugs in short supply that they are buying and selling to hospitals. He also asked for an accounting of their profits from selling them. One of the letters was sent to Allied Medical Supply, Inc., to get answers on the company's sales and sources of cytarabine. The usual price of cytarabine was $12 per vials, but Allied Medical Supply was selling it for approximately $990.[26] Having to pay more than 80 times the typical sale price for a certain drug may also lead to direct or indirect costs such as paying more for the drug in short supply or added labor to manage and find alternatives.[39]

As previously described, President Obama released an executive order in 2011 in an effort to reduce prescription drug shortages. The order directed the FDA to take the steps necessary to reduce and prevent shortages of lifesaving medications, to expedite regulatory review as much as possible, and to communicate with the Department of Justice (DOJ) any finding related to drugs being sold at very high markups.[40] The previously mentioned efforts show that the problem of drug shortages is on government radar and that policymakers, politicians, and the public are paying attention to the problem.

Impact of Drug Shortages

Drug shortages may raise some safety concerns such as adverse effects on patients or medication errors, especially when using medications purchased from unknown sources. When familiar drugs are in short supply, physicians have to choose alternative medications if available, and clinicians' unfamiliarity with alternative medications may risk patients' safety. For example, an assessment done between January 1, 2001, and June 30, 2002 in the University of Utah Hospitals and Clinics (UUHC) showed that clinicians' unfamiliarity with alternative medications in term of dosage requirement was the most common source of safety problems.[41]

Medication Errors

A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication, product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."[42] On the other hand, near-miss errors or a close call is defined as "an event, situation, or error that took place but was captured before reaching the patient." [43]The 2011 ISMP survey showed that due to drug shortages, one in four of the 1,800 healthcare practitioners they surveyed experienced medication errors, whereas, nearly one in three experienced near-miss errors.[43]

Most of the errors mentioned in the ISMP survey were reportedly due to shortages of high-alert medications. High-alert medications typically have a low margin of safety and a high risk of causing harm when misused. Examples of high-alert medications are heparin, morphine, and propofol. The ISMP survey also mentioned that errors were common due to shortages of cancer drugs such as etoposide. Etoposide is used in combination with other chemotherapeutic agents to treat many cancers such as small cell lung cancer, refractory testicular tumors, lymphomas, leukemias, and brain tumors. When IV etoposide was unavailable, providers switched to oral etoposide. Because not many providers knew that oral dose of etoposide needed to be double the IV dose, near-miss errors occurred. Also, when leucovorin, used in combination with 5-fluorouracil in patients with advanced colorectal cancer, was in short supply, some patients were instead prescribed capecitabine, used to treat breast and colorectal cancer, which resulted in serious gastrointestinal toxicity. Other patients were prescribed wrong doses of levoleucovorin, the levo isomeric form of racemic leucovorin, of which the impact on quality of life or overall survival was undetermined.[44]

Adverse Outcomes

The 2011 AHA survey showed that 35 percent of hospitals reported that patients experienced adverse outcomes as a result of drug shortages. In other words, one in five patients treated experienced adverse outcomes. This could be an underestimation of the magnitude of the problem because only 820 hospitals were included in the survey. Nationwide, there are about 5100 urban, critical, and rural hospitals.[37]

Clinical Impact

Finally, drug shortages can result in suboptimal treatment, delay of treatment, or no treatment at all. The 2011 AHA survey showed that due to drug shortages, 82 percent of the 820 participants reportedly delayed patients' treatment, and 69 percent reportedly provided patients with less effective drugs.[37]

Problems with Alternative Agents

When switching from one agent to an alternative agent, many issues may arise. First, the alternative agent may have a lower risk profile and/or superior efficacy that require dosage adjustments. For example, three patients were given IV hydromorphone at the intended dose for morphine, which resulted in the death of two patients and increased length of hospitalization of the third patient.[44]

Second, alternative agents may be of different dosage form. Many errors have been experienced by providers and patients due to dosage form differences between the standard of care medication and alternative agents. When propofol was in short supply, Precedex® (dexmedetomidine) was used instead. The dosing of Precedex® is in mcg/kg/hour, but physicians' unfamiliarity with the new agent resulted in errors due to dosing it in mcg/kg/minute as with propofol. Also, pharmacists may experience problems with dosing as well. When pre-diluted methotrexate was unavailable, a vial of dry powder had to be reconstituted, and some vials were incorrectly diluted, resulting in a less than effective dose of methotrexate being provided to a patient.[44]

Third, problems with alternative agents of questionable quality are especially critical if they were obtained from unknown sources such as the gray market. Drugs sold

in the gray market may be stolen, mislabeled, or stored in unknown conditions. The August 2011 ISMP survey on gray market usage showed that approximately 12 percent of the 549 hospitals they included in the survey reported adverse events and errors from the improper storage and counterfeit drugs sold in the gray market.[34]

Fourth, the supply of effective alternative agents may be affected as well due to increased demand, which may in turn worsen the shortage situation or further delay treatment. Or in worst cases, hospitals may be encouraged to either stockpile or ration care. For example, when morphine was in short supply, increased demand on the alternative, hydromorphone, resulted in both drugs being included in the list of drugs on short supply.[44]

A fifth problem is simply the unavailability of an alternative such as treatment for patients with *pseudomonas* infection who are only sensitive to amikacin. The unavailability of that drug resulted in patients hospitalized due to treatment failures, and in some cases, patients died.[44]

Chemotherapy Drug Shortages

Shortage of chemotherapy drugs is a growing problem that affects providers and threatens patient care. In 2010 alone, there were 23 cancer drugs on shortage, some of which included cytarabine, cisplatin, doxorubicin, leucovorin, etoposide, paclitaxel, vinblastine, and busulfan.[5] According to the AHA survey, in the first six months of 2011, 99.5 percent of U.S hospitals experienced one or more drug shortages. And, 44 percent of hospitals reported more than 21 drug shortages. Of those hospitals experiencing drug

shortages, 66 percent experienced chemotherapy drug shortages, and nearly 47 percent of hospitals had to deal with shortages on a daily basis.[37]

Shortages of chemotherapeutic agents are of great concern, because a significant number of the drugs in short supply are part of the oncology standard of care. Oncology "standard of care" is usually a combination of three to four drugs (chemo cocktail) with different mechanisms of action in order to limit the chances of cancer cells to mutate and become resistant, as may be experienced with single agent. A shortage of one single drug may cause delays in treatment and dosing of drugs, or result in the use of less effective alternatives or alternatives with more side effects. Also, not treating the cancer in a timely manner or with the established standard of chemotherapy combination therapies may increase the likelihood of metastasis of the primary cancer to other parts of the body.

Another concern with chemotherapy drug shortages is people fear that shortages may impact their survival, leading to a feeling of helplessness and anxiety. Also, many patients rely on clinical trials to access treatment, and shortage of the old cancer drugs will force some trials to stop or change protocols, a step that has a negative effect on the quality of care provided and the results of the trial itself.[4,6] Pediatric oncology could also be affected by drug shortages. Many of the therapies used in children with cancer have few or no acceptable alternatives and lack evidence-base for substitutions, making it even harder for children to stand shortages.[6]

Finally, only a few companies manufacture cancer drugs. If one or two companies face a production problem or have to stop the supply of raw materials or specific parts required for the production process, other companies may be unable to meet the demand, and shortages may worsen. For example, cytarabine, a drug used to treat acute myeloid

leukemia with no known substitute, is a product of companies such as Hospira, APP Pharmaceuticals, and Bedford Laboratories. In 2010, Hospira and APP found crystals in some of the vials and had to stop production and shipment of the drug. Bedford Laboratories, on the other hand, faced a huge demand that exceeded its supply capacity.[5] Since then, cytarabine has been in short supply because of Bedford production delays. In November 19, 2011, Ben Venue Laboratories, the manufacturing arm of Bedford Laboratories, voluntarily and temporarily decided to suspended manufacturing and distribution of products manufactured in its Bedford, OH facility.[45] This further delays production and worsens the shortage problem.

With chemotherapy drug shortages, there is also a risk of rationing care, a challenging situation to both providers and patients. According to the AHA survey of hospitals relative to drug shortages, 78 percent of hospitals have rationed care for drugs in short supply; almost three out of four hospitals implemented restrictions on drug use for specific patients.[37] Hospitals can also reserve drugs for desperately needed patients or patients on critical care and exclude new patients. For example, Doxil® (doxorubicin liposomal), a drug used to treat advanced ovarian cancers, was in short supply. Janssen Products, LP the sole supplier of doxorubicin liposomal, rationed this product and assigned it only to specific patients. They posted a letter on its website that included information on the shortage of the drug and advised healthcare providers not to start the drug with new patients without any information on who is to use it and who not.[46]

Drug Shortages and Cost

Drug shortages are also sometimes blamed for driving up healthcare costs.[37] Cost increases due to drug shortages may be direct, indirect, or intangible. “Direct” costs are

related to drug prices. For example, many hospitals have to buy drugs at high markups from the gray market in order to continue providing care for their patients. According to the August 2011 report by Premier Healthcare Alliance, the average markup of drugs sold in the gray market was 650 percent.[47] For that, the cost of drugs from the gray market is 10 to 1,000 times the usual cost. Therefore, the economic burden on hospitals is estimated to be approximately $200 million annually, and healthcare providers are paying 11 percent more for those drugs on shortages.[48]

"Indirect costs" are related to the added labor to find alternatives to drugs on short supply and to manage shortages as well as time spent by providers themselves to manage drug shortages. It is estimated that the annual labor costs associated with managing drug shortages for all health systems nationwide in 2010 were approximately $216 million. And, the median time spent by pharmacists and pharmacy technicians to manage shortages were eight to nine hours per week.[49]

Finally, "Intangible" costs are those related to the anxiety and stress patients and providers have to go through to manage shortages and find alternatives. "Intangible" costs are hard to quantify because the patients and providers affected may have different perspectives and may be affected differently. Chemotherapy drug shortages have not only affected patients' stress and anxiety, but also have an effect on chemotherapeutic drugs costs. Yet, the change in chemotherapeutic agents' costs due to shortages is not well known. Have the shortages of chemotherapeutic agents increased, decreased, or had no effect on the costs and prices of cancer drugs?

The only study that looked at the effect of drug shortages on drug prices was conducted by the Office of the Assistant Secretary for Planning and Evaluation (ASPE),

US Department of Health and Human Services in 2011.[29] The ASPE study examined the factors that led to prescription drug shortages, and then looked at the impact that shortages had on pricing for oncology drugs in particular. In short, Medicare Part B data were evaluated to review the change in volume of services and change in prices of injectable drugs between the period of 2006 and 2008 where no drug shortages were reported and between the period of 2008 and 2011 where drug shortages were reported. The analysis showed that the average price of drugs that experienced shortages in supply decreased in the years before shortages started, resulting in drug shortages. The study was homogenous since it used only Medicare Part B data, and it was performed at the national level using Medicare Part B data. Also, the ASPE study tracked the change in prices only from 2008 to 2011 regardless of the number of suppliers. Therefore, a major unknown is still whether 1) shortages are due, in part, to the number of suppliers for a product, and 2) whether there is some optimal number of suppliers that would be required in order to avoid drug shortages.

The only other study that looked at the relationship between the number of drug suppliers and the volatility of drug shortages was the study done by the IMS IHI in 2011.[21] The study looked at all injectable and oral drugs that had been reported in national shortages as of October 7 2011. One of their findings was that drugs that supplied by three or fewer companies are at the highest risk of being in shortages. The IMS IHI findings help in the way we look at drug shortages from a supply perspective. But at what point are drugs more prone to become listed as part of a shortage? Is it one supplier, two suppliers, or three suppliers? Can we figure out a trend between the number of suppliers and drug shortages to predict if a shortage will occur? And, if a shortage does

occur, is there any relationship to price, i.e., too low a price will encourage producers to withdraw from the market?

Problem Statement

Given the unknown of whether changes in the number of suppliers actually have an impact on drug shortages in the US, three primary questions will be studied. First, whether the number of suppliers prior to shortages has any effect on the shortages of oncology drugs will be analyzed. Second, whether identifiable trends can be used to predict future shortages. Third, based on the number of suppliers in the market at any given time during the time period 2002-2010, variation in drug prices relative to shortages will also be studied.

METHODS

The purpose of this thesis is to assess whether during the time period 2002-2010

1) fluctuations in the number of suppliers prior to drug shortages have any effect on shortages of oncology drugs,
2) identifiable trends in number of suppliers and reasons for shortages can be used to predict future shortages of oncology drugs, and
3) variation in drug prices relative to shortages based on the number of suppliers in the market at any given time can be used as a predictor of shortages

Data Collection Methods

For the purposes of this study, a "drug shortage" will be defined as "an inadequate supply of any injectable oncology drug between 2002 and 2010." The 41 injectable oncology drugs that were listed on the ASHP/UU DIS/Novation web site as in shortage between 2002 and 2010 served as the drugs of interest for this study. After excluding drugs that were only available as brand names as of 2011 (n=12 drugs) and drugs that have been in short supply after 2010 (n=5), information on the remaining generic oncology drugs (n=24 drugs) will be collected based on characteristics defined in Table 1. Drug name, generic and brand if available, dosage form, route of administration, strength, quantity, price, manufacturer code, supplier name, and number of suppliers will

Table 1: Characteristics of injectable oncology drugs

Variable	**Description**	**Source of Variable**
Drug Name	Generic name Brand name	University of Utah Drug Information Service (UUDIS) Food and Drug Administration (FDA) The Red Book
Supplier Name		
Number of Suppliers		
Dosage Form	Solution (SOL) Powder for Solution (PDS)	
Route of Administration	Intravenous (IV) Injection (IJ)	
Strength		
Quantity		
Price	Average Wholesale Price (AWP)	
Manufacturer Code	National Drug Code (NDC)	
Shortage	Yes No	University of Utah Drug Information Service (UUDIS)
Shortage Time Frame	x months in shortage	
Reasons for Shortages	Business Decision (BD) Discontinued (D) Manufacturing delays (MD) Manufacturing Problems (MP) Raw material (RM) Regulatory Problems (RP) Supply/ Demand (S/D) Unknown (UKN)	

be collected from three different sources; UUDIS, FDA, and The Red Book. The Average Wholesale Price from the Red Book is updated on a yearly basis. Shortage information, length of shortages, and reasons for shortages will be collected from the UUDIS. Reasons for shortages are predefined reasons according to UUDIS recordkeeping. The 24 oncology drugs of interest for this study are listed in Table 2. Data collection tables such as Table 3 will be used to categorize and record data for each of the injectable oncology drugs listed in Table 2.

Statistical Analysis

Descriptive statistics will be used to assess the mean change in number of suppliers prior to drug shortages, mean number of suppliers during shortages to predict future shortages, and mean annual change in price based on the annual Average Wholesale Price (AWP) listed in the Red Book. Reasons for shortages will be quantified by drug across the 24 oncology drugs of interest in order to evaluate shortage patterns by company.

Table 2: Injectable generic oncology drugs of interest (2002-2010)

Bleomycin	Idarubicin
Carboplatin	Ifosfamide
Cisplatin	Leucovorin
Cyclophosphamide	Mesna
Cytarabine	Methotrexate
Dacarbazine	Mitomycin
Daunorubicin Hydrochloride	Mitoxantrone
Doxorubicin Hydrochloride	Paclitaxel
Epirubicin Hydrochloride	Pentostatin
Etoposide	Thiotepa
Fludarabine	Vinblastine
Fluorouracil	Vincristine

Table 3: Sample data collection form for Drug x

			2002	2003	2004	2005	2006	2007	2008	2009	2010
Shortage in year (X = yes)											
Length of shortage (days)											
Reason(s) for shortages											
Supplier Name	NDC	Dosage form, route of administration, strength, and quantity	AWP ($)	AWP ($)	AWP ($)	AWP ($)	AWP ($)	AWP ($)	AWP ($)	AWP ($)	AWP ($)
Supplier 1											
Supplier 2											
Supplier 3											
Supplier 4											
Supplier x											
Total number of suppliers											

RESULTS

Supplier Fluctuation Trends as a Shortage Predictor

After data were collected for each of the 24 oncology drugs of interest, the total number of companies in each year as well as the total number of distinctive companies throughout the study period were counted. Table 4 shows the number of companies for each of the 24 injectable generic multisource oncology drugs of interest (2002-2010) and the total number of distinctive companies during the same period.

Table 5 lists descriptive statistics relative to the number of manufacturers for each oncology drug that was in short supply during the studied period. Evaluation shows that the majority of drugs had a median number of less than five producers during any given year. Ten drugs were available from four or more producers, of which only mesna and doxorubicin were still available from the brand name manufacturer (20 percent). Eleven drugs were available from three producers or less, of which only three were still available from brand name manufacturers (27.2 percent). Finally, three products were only available from one producer, two of which were only available as the brand name (66.7 percent). Analysis appears to support the premise that as brand name manufacturers step out of the market and generic producers increase in number, volatility in availability is introduced.

Table 4

Number of companies for the 24 injectable generic oncology drugs of interest (2002-2010)

Drug Name	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Total number of distinctive companies**	**Year brand discontinued**
Bleomycin	3	4	4	5	4	4	4	5	4	6	2007
Carboplatin	1	1	1	5	8	11	9	9	7	12	Brand discontinued prior to shortages
Cisplatin	5	5	5	5	5	4	4	3	3	5	2005
Cyclophosphamide	2	2	2	2	2	2	2	2	2	3	2008
Cytarabine	5	4	3	4	4	4	5	5	5	6	Brand discontinued prior to shortages
Dacarbazine	4	5	5	5	5	5	5	5	5	5	Brand discontinued prior to shortages
Daunorubicin Hydrochloride	2	2	3	3	3	3	3	3	3	3	Available
Doxorubicin Hydrochloride	5	2	4	4	4	4	5	4	4	7	Available
Epirubicin Hydrochloride	1	1	1	1	1	2	9	7	7	9	Available
Etoposide	6	6	5	5	5	4	4	4	4	6	2010
Fludarabine	1	1	2	2	2	2	4	5	6	7	Available
Fluorouracil	4	3	3	3	3	3	4	4	4	7	2003
Idarubicin	1	2	2	2	2	2	4	4	5	6	Available

Table 4 continued

Ifosfamide	1	2	2	2	3	3	4	4	3	4	Available
Leucovorin	6	3	2	4	3	2	2	2	2	6	Unknown
Mesna	2	3	3	5	5	5	5	5	4	5	Available
Methotrexate	6	3	3	3	3	3	4	4	5	8	Unknown
Mitomycin	5	4	4	4	4	4	2	2	3	6	2007
Mitoxantrone	1	1	1	1	1	5	7	7	7	7	2011
Paclitaxel	4	5	5	6	6	5	7	8	6	10	2009
Pentostatin	1	1	1	1	1	1	2	2	2	3	Available
Thiotepa	3	3	3	2	2	2	2	2	2	3	2004
Vinblastine	3	3	2	2	2	2	2	2	2	3	Brand discontinued prior to shortages
Vincristine	3	3	2	2	2	2	2	2	2	3	Brand discontinued prior to shortages

Table 5: Mean and median number of suppliers for the 24 injectable generic oncology drugs of interest (2002-2010)

Drug Name	**Mean**	**Median**	**Range**
Carboplatin	5.7	7	1-11
Paclitaxel	5.7	6	4-8
Cisplatin	4.3	5	3-5
Dacarbazine	4.8	5	4-5
Etoposide	4.7	5	4-6
Mesna*	4.1	5	2-5
Bleomycin	4.1	4	3-5
Cytarabine	4.3	4	3-5
Doxorubicin Hydrochloride*	4.0	4	2-5
Mitomycin	3.5	4	2-5
Daunorubicin Hydrochloride*	2.7	3	2-3
Fluorouracil	3.4	3	3-4
Ifosfamide*	2.6	3	1-4
Methotrexate	3.7	3	3-6
Cyclophosphamide	2.0	2	2
Fludarabine*	2.7	2	1-6
Idarubicin*	2.6	2	1-5
Leucovorin	2.8	2	2-6
Thiotepa	2.2	2	2-3
Vinblastine	2.2	2	2-3
Vincristine	2.2	2	2-3
Epirubicin Hydrochloride*	3.3	1	1-9
Mitoxantrone	3.4	1	1-7
Pentostatin*	1.3	1	1-2

* Brand name available as of December 2010

Table 6 shows the trend in number of suppliers and reasons for shortages of the 24 original study drugs of interest (2001-2010), ongoing shortages of injectable generic oncology drugs that started prior to December 2010, as well as the shortages of those drugs that started after December 2010 (the studied period). Study drugs have been ordered from most to least total number of months of shortage from 2002 to 2010. The majority of shortages of injectable generic oncology drugs of interest (2002-2010) were due to unknown reasons (14/24, 58.3 percent), while the majority of ongoing shortages of injectable generic oncology drugs that started prior to December 2010 and continued past the December 2010 deadline for this study were due to manufacturing problems, (9/15, 60 percent). These products were dropped from the full analysis.

Only 17 products (18 dosage forms as both cisplatin injection and powder qualified for the study) were available for full analysis. Of the 17 drugs remaining for analysis, 5/17 (29.4 percent) continued with brand name manufacturers as producers. For cisplatin, fluorouracil, and paclitaxel (3/17, 17.6 percent); brand name products were discontinued the same year the shortage started (see Table 4). The brand version of three drugs (bleomycin, cyclophosphamide, and methotrexate) was discontinued after the first shortage began. Finally, the brand name of five drugs (29.4 percent) was discontinued at an unknown time prior to shortages.

Table 6

Trends in number of suppliers and reasons for shortage

Name of drug	**Shortage period* (months)**			**Reason(s) for shortage**	**Number of suppliers prior to first year of shortage**
	Year Range	**Months (N)**	**Total Months**		
Shortages of injectable generic oncology drugs of interest (2002-2010)					
Fluorouracil	2003-2004	4	59	Supply/Demand	4
	2004-2009	55		Unknown	3
Methotrexate	2004-2008	55	55	Regulatory Problems	3
Vinblastine	2002	-	36	Unknown	Unknown
	2005-2006	4		Manufacturing	2
	2008-2010	32		Unknown	2
Mitomycin	2008-2010	28	28	Manufacturing	4
Epirubicin Hydrochloride*	2007-2008	17	17	Unknown	1
Cisplatin					
Injection	2005-2006	6	17	Manufacturing	3
	2008-2009	8		Unknown	4
Powder	2005	3		Supply/Demand	5
Doxorubicin Hydrochloride*	2001-2002	8	13	Manufacturing	Unknown
	2008-2009	5		Unknown	4
Leucovorin	2008-2009	12	12	Manufacturing	2
Bleomycin	2005-2006	2	9	Unknown	4
	2007	7		Unknown	4
Vincristine	2005-2006	9	9	Manufacturing	2
Daunorubicin Hydrochloride*	2010	8	8	Manufacturing	3

Table 6 continued

Paclitaxel	2009	1	5	Unknown	7
	2010	4		Unknown	8
Cyclophosphamide	2004	1	5	Unknown	2
	2005-2006	1		Unknown	2
	2008	3		Discontinued	2
Thiotepa	2008-2009	3	3	Manufacturing	2
Ifosfamide*	2005-2006	3	3	Manufacturing	2
Dacarbazine	2005-2006	2	2	Supply/Demand	5
Pentostatin*	2010	2	2	Unknown	2
Ongoing shortages of injectable generic oncology drugs (Shortages Prior to December 2010)**					
Cytarabine	May 2008-April 2012	48	48	Supply/Demand	4
Etoposide	Dec. 2008-April 2012	41	41	Unknown	4
Mitoxantrone	Nov.2009-April 2012	30	30	Unknown	7
Cisplatin inj.	Feb. 2010-April 2012	27	27	Unknown	3
Carboplatin	May 2010-April 2012	24	24	Manufacturing	9
Doxorubicin Hydrochloride	May 2010-April 2012	24	24	Manufacturing	4
Fludarabine	May 2010-April 2012	24	24	Manufacturing	5
Fluorouracil	July 2010-April 2012	24	24	Unknown	4
Leucovorin	May 2010-April 2012	24	24	Manufacturing	2
Mesna	May 2010-April 2012	24	24	Manufacturing	5
Vincristine	May 2010-April 2012	24	24	Manufacturing	2
Dacarbazine	June 2010- April 2012	23	23	Manufacturing	5
Idarubicin	June 2010-April 2012	23	23	Manufacturing	4
Methotrexate	Nov. 2010-April 2012	18	18	Unknown	4
Epirubicin Hydrochloride	2010-2011	15	15	Manufacturing	7

Table 6 continued

Ongoing shortages of injectable generic oncology drugs (Shortages After December 2010)**					
Irinotecan	Feb. 2011-April 2012	15	15	Unknown	10
Thiotepa	Feb. 2011-April 2012	15	15	Unknown	2
Daunorubicin Hydrochloride	March 2011-April 2012	14	14	Manufacturing	3
Vinorelbine	March 2011-April 2012	14	14	Unknown	6
Mitomycin	April 2011-April 2012	13	13	Unknown	3
Paclitaxel	May 2011-April 2012	12	12	Unknown	6
Pentostatin	2011	2	7	Unknown	2
	Dec. 2011-April 2012	5		Manufacturing	2
Floxuridine	Nov. 2011-April 2012	6	6	Manufacturing	3
Ifosfamide Lyophilized powder	Nov. 2011-April 2012	6	6	Manufacturing	3
Ifosfamide Solution for injection	Nov. 2011-April 2012	6	6	Manufacturing	3
Cyclophosphamide	2011	2	2	Manufacturing	2

* Brand name available as of December 2010

** Active shortages were unresolved as of April 30, 2012 due to the time period of data collection (March-April 2012), but time was calculated based on a data collection end date of April 2012

Use of Supplier Trends as a Shortage Predictor

To clearly demonstrate the volatility of the key manufacturers, Table 7 summarizes the number of drugs that experienced shortages (2002-2010), and the average total months of shortages for drugs that still have a brand manufacturer, and drugs that no longer have a brand manufacturer (2002-2010). At the end of the observation period, five drugs out of the 17 drugs of interest still have the brand manufacturers in the market with an average of 8.6 ± 6.4 S.D months of shortages. On the other hand, the brand manufacturers discontinued 12 drugs (13 dosage form; as both cisplatin powder and injection were discontinued). Those 12 drugs had an average of 18.5 ± 19.8 S.D months of shortages. The volatility in the group where the brand was discontinued was higher than the group where the brand was still available.

Use of Price Variation as a Shortage Predictor

Prices of the original 24 drugs of interest were collected from The Red Book (2002-2010). The decision then was not to proceed with collecting or analyzing data related to drug prices for the following reasons. First, the Red Book used to collect the data related to the AWP and the number of companies manufacturing the drugs was published at the beginning of each year. This has some implications such as; it does not represent the actual number of manufacturers in the market. Companies may enter or leave the market during the year without being documented in the Red Book. Second, the Red Book is not sensitive to changes in prices; it only publishes a benchmark price. However, in reality, hospitals, providers, and end users negotiate drug prices with

Table 7: Volatility of 17 drugs of interest (2002-2010)

Name of drug	Total Shortage period (months)	Reasons for Shortages
Volatility of five drugs that still have brand name manufacturer		
Epirubicin Hydrochloride	17	Unknown
Doxorubicin Hydrochloride	13	Manufacturing
Daunorubicin Hydrochloride	8	Manufacturing
Ifosfamide	3	Manufacturing
Pentostatin	2	Unknown
Average ± S.D	**8.6 ± 6.4**	
Volatility of 12 drugs that were discontinued by the brand manufacturer		
Fluorouracil	59	Unknown + Supply/Demand
Methotrexate	55	Regulatory Problems
Vinblastine	36	Unknown + Manufacturing
Mitomycin	28	Manufacturing
Cisplatin injection	14	Unknown + Manufacturing
Leucovorin	12	Manufacturing
Bleomycin	9	Unknown
Vincristine	9	Manufacturing
Cyclophosphamide	5	Unknown + Discontinued
Paclitaxel	5	Unknown
Cisplatin powder	3	Supply/Demand
Thiotepa	3	Manufacturing
Dacarbazine	2	Supply/Demand
Average ± S.D	**18.5 ± 19.8**	

manufacturers. Therefore, no analysis was completed on AWP prices of drugs on shortage 2002-2010.

DISCUSSION

Of the original 24 shortage drugs identified for more in-depth analysis, only 17 drugs (18 dosage forms) remained as listed in Table 8.

Supplier Fluctuation Trends as a Shortage Predictor

Study findings suggested that the volatility of drug shortages is not in the number of suppliers prior to shortages, as some drugs had few suppliers (2, 3, or 4 suppliers) and others had so many suppliers (7, 9, or 10 suppliers). Rather the absence of the key manufacturer is associated with the discontinuation of the brand name, as shown in the case of cisplatin, fluorouracil, and paclitaxel. So, the volatility is not in the number of manufacturers, but the key manufacturers themselves. This finding, which is specific to oncology drugs, is contrary to what was found in the IMS IHI study in 2011 where they

Table 8: The 17 injectable generic oncology drugs of interest that were analyzed (2002-2010)

Bleomycin	Leucovorin
Cisplatin	Methotrexate
Cyclophosphamide	Mitomycin
Dacarbazine	Paclitaxel
Daunorubicin Hydrochloride	Pentostatin
Doxorubicin Hydrochloride	Thiotepa
Epirubicin Hydrochloride	Vinblastine
Flurouracil	Vincristine
Ifosfamide	

showed that drugs that are supplied by three or fewer companies are at the highest risk of being in shortages regardless of the presence or absence of the brand manufacturer.[50]

Another interpretation is that as we showed earlier, 80 percent of the oncology packages and vials sold in the US market were held by the top five generic injectable manufacturers.[21] For that, efforts should be directed at approving generic products from manufacturers committed to providing stability in the marketplace, toward generic companies to make quality a priority, toward suppliers to have facilities and resources available for continued production.

Use of Supplier Trends as a Shortage Predictor

Another important interpretation from the results of this study is that the discontinuation of the brand names of the drugs was associated with a longer shortages period compared to shortages due manufacturing problems or delays as shown in Table 7. This is not matching to what was found by the GAO study in 2011.[50] The GAO study showed that the average shortage lasted more than nine months, whereas in this study, the average shortages lasted 8.6 ± 6.4 and 18.5 ± 19.8 for drugs that brand name were still available and for drugs that the brand name manufacturers were discontinued. In reality, brand manufacturers may leave the market at any time after the patent expires and there is no way to force them to stay in the market.

One of the limitations for this study is that it ended up with a small sample size (n=17) out of the original 24 drugs that were described in Chapter 3 (Table 2). Therefore, results and discussion were mainly focused on the remaining 17 drugs. Of the drugs that were excluded, some were excluded because the drug only had one manufacturer in the

studied period, such as oxaliplatin and dactinomycin. Others were excluded because not enough information on the shortages was available, because they experienced shortages after the cutoff date (December 2010) such as floxuridine and irinotecan, or the shortages started prior to December 2010, but were still active as of April 2012. Another limitation for this study is the dynamic marketplace. Information related to drug shortages changes quickly; there is always new information; drugs entered the shortage lists, others leave, new efforts, acts, law and so on. I had to choose a cutoff point where I am not going to update my paper anymore.

Drug shortages are a topic of great interest to hospitals, pharmacists, providers, policy makers, and regulations bodies such as the FDA and the ASHP. Opportunities for future research are great. Future research on a bigger sample size and for a longer period of time may reveal more significant findings and predict trends that were not so clear or noticeable in this study.

REFERENCES

1. Manual of policies and procedures Center for Drug Evaluation and Research. U.S Food and Drug Administration Website. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf. Accesse November 7, 2011.

2. Fox ER, Birt A, James KB, Kokko H, Salverson S, Soflin DL. ASHP guidelines on managing drug product shortages in hospitals and health systems. *American journal of health-system pharmacy*. 2009;66(15):1399-1406.

3. Fox ER, Tyler LS. Managing drug shortages: Seven years' experience at one health system. *American journal of health-system pharmacy*. 2003;60(3):245-253.

4. Kaiser J. Shortages of cancer drugs put patients, trials at risk. *Science*. 2011;332(6029):523.

5. Drug shortages summit summary report. American Society of Health-System Pharmacists Web Site. http://www.ashp.org/drugshortages/summitreport. 2010. Accessed November 8, 2011.

6. Ault A. Chemotherapy drug shortages present challenges for oncologists and their patients. *Community Oncology*. 2011;8(1):48.

7. Medicare Part B drug regulations. Centers for Medicare and Medicaid Services Web Site. http://www.cms.gov/mcrPartBDrugAvgSalesPrice/03_regulations.asp. Accessed December 6, 2011.

8. Cox E. US drug shortages. U.S Food and Drug Administration Web Site. http://www.fda.gov/Drugs/NewsEvents/ucm265968.htm. 2011. Accessed November 7, 2011.

9. Baxter ramps up halle plant lyophilisation capacity, again. http://www.outsourcing-pharma.com/Contract-Manufacturing/Baxter-ramps-up-Halle-plant-lyophilisation-capacity-again?utm_source=RSS_text_news&utm_medium=RSS%2Bfeed&utm_campaign=RSS%2BText%2BNews. 2011. Accessed January 20, 2012.

10. Vetter invests in ddditional lyophilization capacity. Fierce Pharma Web Site. http://www.fiercepharma.com/press_releases/vetter-invests-additional-lyophilization-capacity. 2011. Accessed January 20, 2012.

11. Drug applications and Current Good Manufacturing Practice (CGMP) regulations. U.S Food and Drug Administration Web Site. http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm090016.htm. Accessed December 6, 2011.

12. Gorvine M. GMP violations are a consistent but well-shuffled deck, FDA data show. *The Pink Sheet*. 2011;73(23). http://www.elsevierbi.com/publications/the-pink-sheet/73/23/gmp-violations-are-a-consistent-but-wellshuffled-deck-fda-data-show Accessed January 2, 2012.

13. Drug GMP report. FDA News Web Site. http://fdanews.com/newsletter/article?issueId=15238&articleId=141529. 2011. Accessed November 8, 2011.

14. 483 reports. FDA News Web Site. http://fdanews.com/483-report/detail?productId=38215. 2011. Accessed November 24, 2011.

15. Epogen and Procrit (epoetin alfa): Recall-Particulate matter in vials. U.S Food and Drug Administration Web Site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm227225.htm. 2010. Accessed December 6, 2011.

16. Tyler TG. Infrastructure issues in the US drug supply: Where did the drug go? *Journal of Hematology Oncology Pharmacy*. 2011;1(1):10-15.

17. Thompson CA. MI risk prompts rofecoxib withdrawal. *American journal of health-system pharmacy*. 2004;61(21):2234-2238.

18. Xigris [drotrecogin alfa (activated)]: Market Withdrawal - Failure to Show Survival Benefit. U.S Food and Drug Administration Web Site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm277143.htm. Accessed January 10, 2012.

19. Generic Drugs: Questions and answers. U.S Food and Drug Administration eb Site.http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm. Accessed January 2, 2012.

20. Munos B. Lessons from 60 years of pharmaceutical innovation. *Nature reviews*. 2009;8(12):959-968.

21. Drug shortages: A closer look at products, suppliers and volume volatility. IMS Institute for Healthcare Informatics Web Site.

http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Static%20Files/IIHI_Drug_Shortage_Media_ExecSumm.pdf. 2011. Accessed January 23, 2012.

22. Drug shortages: Current drugs. American Society of Health-System Pharmacists Web Site. http://www.ashp.org/menu/PracticePolicy/ResourceCenters/DrugShortages/CurrentShortages.aspx. Accessed December 7, 2011.

23. FDA interim final rule: Changes to notification requirements. *Federal Register*. 2011;76(243). http://www.gpo.gov/fdsys/pkg/FR-2011-12-19/pdf/2011-32354.pdf Accessed February 3, 2012.

24. Drug shortage: Transcript. U.S Food and Drug Administration Web Site. http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm235352.htm. 2010. Accessed October 17, 2011.

25. Drug Facts and Comparison (eFact). Wolters Kluwer Health, Inc; 2010.

26. Lexi-Comp (Medical Abbreviations) [computer program]. Lexi-Comp; 2010.

27. Drug ezaluation: Ethiodized oil. In: Hutchison TA, Shahan DR, Anderson ML, eds. Thomson Healthcare; 2010.

28. Brown DB, Geschwind JF, Soulen MC, Millward SF, Sacks D. Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. *Journal of vascular and interventional radiology*. 2006;17(2 Pt 1):217-223.

29. Haninger K, Jessup A, Koehler K. Economic analysis of the causes of drug shortages. *ASPE Issue Brief*. 2011. http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf Accessed February 1, 2012.

30. Jensen V, Kimzey LM, Goldberger MJ. FDA's role in responding to drug shortages. *American journal of health-system pharmacy*. 2002;59(15):1423-1425.

31. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. *The New England journal of medicine*. 2008;359(25):2674-2684.

32. APP letter. http://editor.apppharma.com/PIUs/Kanamycin_Ltr_2_24_09_ltrhd.pdf Accessed January 2, 2012.

33. Amikacin injection. American Society of Health-System Pharmacists Web Site. http://www.ashp.org/DrugShortages/Current/Bulletin.aspx?id=501. Accessed October 24, 2011.

34. ISMP survey on drug shortage "gray market" shows widespread impact on hospitals. http://www.ismp.org/pressroom/PR20110825.pdf. 2011. Accessed October 18, 2011.

35. Cherici C, McGinnis P, Russell W. Buyer beware: Drug shortages and the gray market. http://www.premierinc.com/about/news/11-aug/Gray-Market/Gray-Market-Analysis-08152011.pdf. 2011. Accessed October 17, 2011.

36. Cherici C, Frazier J, Feldman M, et al. Navigating drug shortages in American healthcare: A Premier healthcare alliance analysis. Premier Web Site. http://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf. 2011. Accessed October 19, 2011.

37. AHA survey on drug shortages. American Hospital Association Web Site. www.aha.org/content/11/drugshortagesurvey.pdf 2011. Accessed December 2, 2011.

38. Food and Drug Administration Safety and Innovation Act (FDASIA). U.S Food and Drug Administration Web Site. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/default.htm 2012. Accessed October 11, 2012.

39. Cummings investigates "drug speculation" and "gray market" sales of drugs in critically short supply. U.S House of Representatives Web Site. http://democrats.oversight.house.gov/index.php?option=com_content&task=view&id=5449&Itemid=104. 2011. Accessed January 4, 2012.

40. Executive order: Reducing prescription drug shortages. The White House Web Site. http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages. 2011. Accessed November 26, 2011.

41. MacDonald ED, Fox ER, Tyler LS. Drug Shortages: Process for evaluating impact on patient safety. *Hospital Pharmacy*. 2011;46(12):1-10.

42. The National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/ Accessed November 4, 2011.

43. ISMP survey helps define near miss and close call. Institute for Safe Medication Practices Web Site. http://www.ismp.org/newsletters/acutecare/articles/20090924.asp. 2009. Accessed November 23, 2011.

44. Drug shortages: National survey reveals high level of frustration, low level of safety. Institute for Safe Medication Practices Web Site. http://www.ismp.org/newsletters/acutecare/articles/20100923.asp. 2010. Accessed November 24, 2011.

45. Ben Venue Laboratories, Inc. temporarily suspends manufacturing and distribution of drug products. Fierce Pharma Web Site. http://www.fiercepharma.com/press-releases/ben-venue-laboratories-inc-temporarily-suspends-manufacturing-and-distribut. 2011. Accessed December 20, 2011.

46. Important update regarding the availability of Doxil® (doxorubicin HCl liposome injection). Association of Community Cancer Centers Web Site. http://www.accc-cancer.org/advocacy/pdf/2011-Janssen-doxil-letter.pdf. 2011. Accessed January 3, 2012.

47. Dooren JC. Congressman investigates high drug markups. *The Wall Street Journal*. 2011. http://online.wsj.com/article/SB10001424052970203388804576613551837210410.html Accessed November 8, 2011.

48. Eastman P. Oncology drug shortages worsening, threatening patient care. *Oncology Times*. 2011;33(15):14-15.

49. Kaakeh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. *American journal of health-system pharmacy*. 2011;68(19):1811-1819.

50. GAO. FDA's ability to respond should be strengthened. U.S Government Accountability Office Web Site. http://www.gao.gov/assets/590/587000.pdf. 2011. Accessed January 2, 2012.