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The Recurring Problem of Drug Shortages—How Do We Overcome It?

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Generic medications have been an integral part of the US healthcare system, given that they allow patients greater access to affordable treatments. Generic therapies constitute 89% of written prescriptions and yet, they make up only 26% of the total drug costs in the United States [1]. Despite their significant role in healthcare, shortages of generic medications have plagued hospitals across the country over the past few years. The American Society of Health-System Pharmacists states that, as of November 18, 2018, 199 generic medications face shortages, a problem which has caused a shockwave of consequences throughout the healthcare sector [2].

Before generic versions of a medication are permitted to be manufactured, the patent-holding company which developed the medication has the exclusive right to sell their drug under a brand name for 20 years [3]. Once the patent expires, other companies can submit an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA) requesting legal permission to manufacture a bioequivalent, generic version of the drug. While an ANDA requires the demonstration of bioequivalence between the generic and the brand name drug, it does not require the submission of clinical data indicating safety or efficacy of the generic version [4]. This is because the safety and efficacy of the drug was previously established during the approval of the parent drug. As a result, generic medications are able to be sold at a much lower cost, since the manufacturer has a reduced need to advertise and/or recuperate expensive clinical trial investment costs.

To have a stable generic drug market, competition is vital. Unfortunately, the current generic drug market has experienced minimal competition due to several factors. Corporate consolidation has driven out smaller competitors who could potentially help increase the supply of generics [5]. The companies which remain in the market lack profit incentives to produce older drugs or delve into smaller drug markets [5]. On the regulatory side, the FDA has been strained in allocating resources necessary to approve generic drug applications in a timely manner while, at the same time, higher manufacturing and quality standards have forced companies out of drug markets [5]. This lack of competition is a major contributor to drug shortages, as less total product is made and the market demand cannot be met. Furthermore, a lack of competition causes the existent product supply to become more vulnerable to market shocks and manufacturing challenges. For example, Baxter, a prominent saline solution and saline bag provider, had their manufacturing facilities in hurricane-hit Puerto Rico, which worsened the already existing saline shortage [6]. As such, a lack of competition propagates an unstable supply of product, leading to unexpected and potentially dangerous shortages in key generic drugs.

These shortages have resulted in a multitude of issues for providers as well as for patients. The inability for hospitals to purchase medications due to a low supply and inflated prices has led to ethical concerns regarding prioritization of therapy, specifically, which patients will receive the short-in-supply treatment and which patients will not [7]. In addition to the ethical dilemmas that shortages force providers to address, shortages have also directly impacted patient outcomes. In 2011, a disruption of three production lines resulted in a shortage of norepinephrine, a vasoconstrictor important in treating septic shock. During this period of undersupply, a 4% higher likelihood of death due to septic shock resulted, translating into the death of hundreds of patients across the United States [8]. The researchers attribute these deaths to the shortage of preferred generic norepinephrine, which forced doctors to use alternative treatments which were potentially less effective. For example, during the shortage of norepinephrine, many doctors utilized another common vasoconstrictor, phenylephrine, to treat septic shock; however, the efficacy of phenylephrine in lieu of norepinephrine has limited empirical support. In addition, issues such as longer waiting times to receive the preferred treatment of norepinephrine may have also contributed to increased mortality rates during the shortage [9]. This leads to another problem that a lack of competition within the generic drug market brings up, where the use of alternatives to cover for shortages can have a domino effect producing additional shortages. With regard

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to Baxter International, the shortage of small-volume saline bags resulted in shortages of the alternatives, such as large-volume saline bags and saline syringes [10]. Shortages of one generic drug can thus compound the already existing shortage problem in other parts of the market.

One seemingly simple solution to the shortage would be to allow for market forces to respond to it. In other words, it would be expected that existing companies would produce more of a particular generic drug to match the market supply's demand. While this is possible, the generic drug market is notably inelastic in both supply and demand. A change in the price of a medication does not necessarily impact production volume. While companies may desire an elastic market, the FDA is required to approve new manufacturing facilities as well as production lines, which elongates the time between when the shortage occurs and when companies are able to put additional generic alternatives on the market [5]. Consequently, the ability of supply to adapt to changes in demand remains constrained. Under recent regulation, it takes nearly a year for companies to receive the approval necessary to produce the generic drug, but drug shortages last approximately 418 days [11]. Therefore, by the time approval has occurred, most of the damage of the drug shortages has likely already occurred. Thus, given the regulation by the FDA, allowing for market forces to respond may address long-term shortages, but it fails to solve short-term drug shortages. Another seemingly simple solution would be for hospitals to stockpile medications when the market is doing well; however, this solution also falls flat for a few reasons. For one, hospitals do not want to increase storage costs of medications and, thus, they buy medications only when absolutely necessary. This phenomenon is referred to just-in-time inventory, as it minimizes the required cost of storing pharmaceuticals [12]. A second issue with stockpiling is that many generics have limited shelf-lives [13]. As a result, stockpiling medications would likely result in the waste of generics that are already short in supply. This can cause further shortages or make existing ones worse, by accelerating the decline of a particular drug on the market [13].

A few laws have been implemented to help prevent generic drug shortages. The Drug Price Competition and Patient Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, played a critical role in establishing bioequivalence as the main criteria for generic drug approval, thus preventing the necessity of costly and time-consuming clinical trials for generic drugs. More recently, during 2014, the Generic Drug User Fee Agreement (GDUFA) requested that companies applying to produce generic medications pay a fee which would help with funding the review process [5]. In addition, the FDA has created a system of prioritizing drug approval, so that medications without any generics on the market or medications that have only one generic drug on the market can be prioritized. As of October 2017, Congress reauthorized GDUFA II, which will help with the regulatory backlog of ANDAs, by increasing the total funding for ANDA evaluations. While these laws have helped, 199 generic medications are still facing a shortage, and additional solutions must be implemented to ensure the viability of the generic drug market [2].

The existing literature has offered a plethora of potential solutions that could be utilized in solving the drug shortage problem. Thomas Bollyky and Aaron Kesselheim at Brooking's Center for Health Policy propose a three-prong solution, of which the first prong has already been implemented by the reauthorization of GDUFA II [5]. The second involves establishing a multinational application system for generic medications. As of now, the regulatory organizations controlling drug sales for each country are largely disconnected from one another. A company is required to submit a separate application in each country that they intend to sell in. With a multinational application system, a company would submit a single request which goes to the regulatory organizations of all participating countries. This would likely increase the number of applications the FDA receives without taking regulatory power out of its hands. A similar sort of system has already been approved in the European Union, indicating that the proper infrastructure required to set up a shared application system is viable. The third and final prong of the Bollyky and Kesselheim's plan is to create a reciprocal drug approval pathway. The United States imports a large portion of the existing pharmaceuticals that are on the market. Yet importing generic medicines that are approved by other countries' regulatory authorities, but not by the FDA, still requires FDA approval. Given the low competition for some key generics, a reciprocal drug approval pathway would allow for the importation of medications which already have approval from a select few regulatory authorities of other countries that have similar generic drug approval standards as the FDA. Bollyky and Kesselheim demonstrate how the latter two prongs of their plan would work, by identifying 69 medications in the United States with insufficient generic competition (which they defined as four or fewer generic medications on the market). They assessed 10 different regulatory industries globally, which had similar standards of drug approval as the FDA, and had English databases with public access. They concluded that 64% of these medications had a suitable generic alternative globally [5]. Providing a system to allow for the use of currently available international generic medications in the United States is critical to prevent future generic drug shortages. Obviously, barriers will exist under this plan, such as potentially increasing the burden on the FDA; however, this plan will likely result in increased competition and a more stable supply of generic medications.

One fairly radical, but potentially effective solution, is to create a nonprofit generic drug producer to solve the root of the problem: too little competition in the market. This is the precise solution five large hospital groups have agreed to pursue in order to stabilize the generic drug supply [14]. These five hospital groups include the Department of Veterans Affairs, Intermountain Healthcare, Ascension, SSM Health, and Trinity Health. As expressed by the executive of the Veterans Health Administration, Carolyn Clancy, the participating hospital groups have no interest in controlling the supply of medications as much as they want to stabilize the drug supply [14]. In fact, the company that will be created will produce only about 20 generic medications which currently are lacking competition in the market [15]. There are many reasons this plan has a chance of succeeding. The firm will already have a market to sell to under the 450 hospitals, one-tenth of the total hospitals in the United States, owned by the five-member organizations. This number does not include the nursing homes, clinics, and other non-hospital health organizations which these hospital groups own and could potentially sell generics to. Furthermore, additional health systems are likely to join this plan in the coming years. While the new firm aims to produce generics as early as the beginning of 2019, there are major barriers to this plan as well [15]. For instance, there is a large start-up cost for the company, as well as difficulty

in predicting and obtaining approval for the generic medications required for future shortages in a reasonable timeframe [16]. Nevertheless, this plan, while difficult to implement, could provide a very possible resolution for many generic drug shortages experienced in the United States.

Generic medications have been invaluable increating a cheaper, more accessible healthcare system for patients. Unfortunately, recent shortages have placed this system in jeopardy. Despite well-intentioned efforts to relieve the pressure drug shortages have created, much work still has to be done in order to create a stable system moving forward. Some potential solutions, such as creating a multinational application among the world's best regulatory agencies, importing reliable bioequivalent alternatives of generics facing shortages, as well as creating a nonprofit generic drug manufacturer, all help address the lack of competition, which is the root problem of the generic drug shortage. If applied, such solutions could be instrumental in helping ease the drug shortage and its associated suffering.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to disclose.

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