The Daraprim and the Pharmaceutical Pricing Paradox

A Broken System?

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INTRODUCTION

On August 10, 2015, at a cost of $55 million, Turing Pharmaceuticals acquired the exclusive U.S. marketing rights to Daraprim, a drug that treats toxoplasmosis (a life-threatening parasitic infection), from Impax Laboratories. [1] Just a few weeks after the acquisition, Turing announced that, effective immediately, the price of Daraprim would be raised from $13.50 a tablet to $750 a tablet, an increase of over 5,500 percent. [2] The overnight price spike has generated considerable censure from healthcare professionals, politicians and the general public. [3] Yet, Turing Pharmaceuticals is not the only company in recent months to substantially increase the price of one of its brand-name drugs. Just nine days after Turing's acquisition of Daraprim, Rodelis Therapeutics announced its acquisition of Cycloserine, a drug used to treat tuberculosis, and subsequently raised the price for 30 capsules of the drug from $500 to $10,800. [4] While public pressure has since forced the price of Cycloserine to be scaled back to $1,050, Turing and Rodelis have shown that pharmaceutical companies can realize substantial upside by targeting old, neglected drugs (often for rare diseases) and refashioning them into high-priced specialty drugs. [5]

In a recent study by the American Association of Retired Persons (AARP), the average prices for brand-name prescription drugs were found to have increased by an

average of 13 percent in 2013, compared to the inflation rate the year of just 1.5 percent. [6] The Daraprim and Cycloserine cases, while extreme illustrations, depict a broader trend of increasing U.S. drug and health care costs to patients. [7] The two manufacturers' pricing decisions illustrate a longstanding tension in the pharmaceutical industry between the need for firms to recoup the high costs associated with bringing drugs to market and keeping drugs affordable for consumers. To date, neither Turing nor Rodelis faces any lawsuits tied to their pricing decisions for Daraprim and Cycloserine respectively. However, given what has transpired with Daraprim and Cycloserine, and the need to keep drug and health care costs down, perhaps action should be taken to deter future price spikes on brand-name drugs. That is, under these circumstances, should the government intervene to curb the considerable price-making power that pharmaceutical companies possess in order to better serve the patients who rely on their brand-name drugs and society at large?

I. BACKGROUND

Originally approved by the Food and Drug Administration (FDA) in 1953, Daraprim was made by GlaxoSmithKline (GSK) until it was sold in October 2010 to CorePharma, a maker of generic pharmaceuticals. [8] In October 2014, Impax Laboratories acquired Daraprim through its $700 million purchase of Tower Holdings and several of its operating subsidiaries, which included CorePharma. [9] Less than a year later, Impax Laboratories sold Daraprim's exclusive U.S. marketing rights to Turing Pharmaceuticals in a deal announced in August 2015. [10] Prior to 2010,

Daraprim cost only $1 a tablet, but, citing the need to turn a profit, CorePharma raised the tablet's price significantly upon its acquisition from GSK. [11]

In a joint letter dated September 8, 2015 and addressed to Turing Pharmaceuticals from the Infectious Disease Society of America (IDSA) and the HIV Medicine Association (HIVMA), the senders noted that the increase in the price of Daraprim would result in an average bill for a toxoplasmosis patient weighing 132 pounds of $634,500 per year. [12] With such high prices, and few viable alternative treatments to Daraprim, some posit that hospitals may find it too expensive to keep Daraprim in stock, which could lead to delays in treatment. [13]

In response to the public outcry and excoriation, Martin Shkreli, Founder and CEO of Turing Pharmaceuticals, defended the 5,500 percent price increase stating that the company needed to turn a profit on the drug in order to modernize Daraprim (a 62 year old drug) and create new alternatives to Daraprim with fewer side effects. [14] While the exclusivity period prohibiting competitors from making or selling Daraprim has long since expired, there are currently no generic alternatives. Perhaps the biggest reason for the absence of generic alternatives is the fact that toxoplasmosis is a relatively rare condition, with only 8,821 prescriptions having being filled in the U.S. in 2014. [15] Furthermore, ever since Daraprim belonged to Impax Laboratories, its distribution has been tightly controlled. This means that companies wishing to create a generic version of Daraprim face considerable difficulty in gaining access to the samples they need for testing and developing such a generic. [16] While the higher price of Daraprim should entice manufacturers to develop a

generic competitor to Daraprim, the limited patient market (and diminutive profits at stake) may discourage potential entrants who are unable to justify the high costs associated with marketing a generic.

Justifications for the High Cost of Brand-Name Drugs

There are several reasons that help to explain why brand-name drugs are so expensive. One reason is that brand-name drug companies have a first-mover advantage in the pharmaceutical market. As in other markets, firms that are first-movers benefit by entering a market with no other direct competitors (by definition). Without having to worry about the behavior and pricing decisions of other firms, the first entrant is able to set prices, establish control of the market and have their name and brand associated with the product category (e.g. Kleenex, Xerox, and Post-It). Thus, even if and when other firms enter the market, consumers may prefer to keep purchasing the first-mover's product rather than switch to an alternative, even if the alternative is cheaper, due to their familiarity with the first mover's product. Unlike many other industries however, the legal system rewards pharmaceutical companies for their innovative efforts with patents and exclusivity periods. Within the realm of brand-name drugs, government regulations effectively prohibit other firms from producing generic forms of the brand-name drug for a specified period of time. [17] Thus, a successful brand-name drug producer gains not only first-mover advantages, such as consumer loyalty and brand recognition, but a limited monopoly for a period of years guaranteed by the U.S. government.

II. REGULATION OF THE PHARMACEUTICAL INDUSTRY

The Unique Challenges of the Pharmaceutical Industry

Similar to the airline and petroleum industries, the pharmaceutical industry is characterized by high entry costs (sometimes referred to as "barriers to entry"), which severely limit the number of firms which are able to effectively compete in the industry. According to one report from the Tufts Center for the Study of Drug Development released in 2014, the cost of bringing a drug to market from the point of inception can reach as high as $2.8 billion. [18] Given the enormous costs associated with pharmaceutical research and development, and the need to encourage drug development as a matter of good public health and public policy, the U.S. government provides regulatory protections to assist pharmaceutical firms. [19] The regulations are specifically designed to help firms recoup the costs of their high-value, high-cost investments and bring more novel drugs to market, especially for rarer diseases which are not as profitable as drugs which treat more common afflictions. [20]

III. REGULATION OF THE PHARMACEUTICAL INDUSTRY

The U.S. Food and Drug Administration (FDA) is a federal agency within the United States that is tasked with "protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation." [21]

Overview of the FDA's Approval Process for Brand-Name Drugs

With respect to human drugs, the FDA has two distinct approval processes, one for new drugs, and a separate, shorter process for generics. For new drugs, drug

companies must first file an Investigational New Drug (IND) application for their specific drug candidate. [22] The IND must include data on the safety and efficacy of the candidate, which means that firms must have completed substantial testing both in the laboratory and on animal subjects prior to the filing of the IND. [23] The FDA reviews the IND in order to ensure that there is sufficient data to support the drug candidate moving forward to clinical trials on human subjects. [24] If the FDA is satisfied with the data in the IND, the drug candidate is put through four phases of clinical trials with each phase designed to gather specific data on the safety and efficacy of the drugs. [25] As the drug advances through the phases, the study is scaled up with an increasing number of participants in each phase. [26] Upon completion of the four clinical phases, the applicant will meet with the FDA to review the results before filing a New Drug Application (NDA), which summarizes the findings to date. [27] If the NDA passes FDA review and is approved, the drug progresses to the two final stages, labeling (to ensure the appropriate information is included on the package) and an inspection of the facility in which the drug candidate will be manufactured. [28]

Overview of the FDA's Approval Process for Generics

By contrast, the approval process for generic forms of brand-name drugs, often referred to simply as "generics," is not nearly as extensive or lengthy. However, an application to market a generic may not be filed until the exclusivity period of the brand-name drug has expired. [29] The length of various exclusivity periods depends on the classification of the brand-name drug and is set out in the New Drug Product

Exclusivity provision of the Code of Federal Regulations (CFR). [30] As an example, brand-name drugs which represent new chemical entities (NCE) are granted a five year exclusivity period, meaning a company wishing to market a generic may not even begin the FDA approval process for generics until five years after the date the FDA approves the brand-name drug's NDA. [31]

For companies wishing to market a generic, the first step involves filing an Abbreviated New Drug Application (ANDA). [32] As its name would suggest, the ANDA is a truncated version of the IND process. In an ANDA, the applicant is only required to demonstrate that the generic produces the same results as the brand-name drug in the human body (a characteristic known as "bioequivalence"). [33] A generic applicant need not include any data gathered from animal studies or clinical (human) studies as such data would be largely duplicative of the brand-name drug developer's efforts. [34] Because of the abbreviated process for generics, companies creating generics incur far lower research and development costs, which allow generics to sell for far lower prices than the brand-name drug. The existence of generics in a market can therefore be a strong agent for change, inducing brand-name drug companies to lower the price of their drug or risk facing reduced sales and profits. In this way, generics can act as a deterrent and a check on brand-name drug companies to keep them from increasing the prices they charge without justification.

IV. PROPOSED SOLUTIONS

Keeping drug costs affordable is an essential and desirable outcome for patients, drug companies, health care providers, insurance companies, and the government. Unlike other consumer products such as books or televisions, prescription drugs are price inelastic goods, which means that changes in their price (in either direction) will not significantly affect the likelihood that consumers will purchase them. [35] Put differently, because of the life-extending nature of the goods they are selling, pharmaceutical companies are able to increase their drug prices without having to worry about a significant drop in consumer demand, which would ordinarily result for most goods. This characteristic of prescription drugs is a crucial one and should inform the way policymakers create solutions to limit the occurrence of future cases like Daraprim. Consequently, many of the proposed solutions that follow herein focus on increasing competition for brand-name drugs in order to attenuate a pharmaceutical company's price-setting power rather than on affecting the demand for a particular therapeutic class of drugs.

Federal Level Reforms

One logical starting point in the fight against high-priced brand-name drugs would be to revise the FDA regulations themselves. [36] According to an estimate from the Manhattan Institute for Policy Research, the value in bringing one generation of new drugs to market one year faster in the United States is approximately $4 trillion, as measured by the increase in life expectancy. [37] To that end, the FDA could modify the reward structure under which pharmaceutical

companies are permitted to benefit for their innovative efforts by shortening exclusivity periods. In doing so, generics could more quickly reach the marketplace, providing a valuable lower-cost alternative for consumers. However, tweaking the exclusivity term may, in some cases, diminish the brand-name manufacturer's incentive to invest in research and at worst, altogether eliminate their incentive to pursue the development of a brand-name drug in the first place.

An alternative to modifying the exclusivity provisions would be to encourage the development of generics and increase the pace in which they are able to reach the market. [38] Targeted reforms to the ANDA regulations could incentivize manufacturers to develop generics and a more efficient FDA review process of ANDA submissions would allow for more timely approvals. [39] However, simplifying or expediting an already abbreviated process may negatively impact the quality of the generic, which would increase the risk of harm to the public and even hurt the reputation of the brand-name drug's safety and efficacy. [40] Indeed, a number of generic drugs were recalled in 2013 for noncompliance with FDA manufacturing standards, prompting Congress to instruct the Office of Inspector General (OIG) to review and evaluate the FDA's oversight of generic drug manufacturers. [41]

Alternatively, a combination of the two reforms described above may prove to be a better approach. Even if the prices of brand-name drugs are brought down, generic manufacturers may need additional incentive to create a generic considering the diminution in profit motive. The IND/NDA process for brand-name drugs could similarly be streamlined in an effort to reduce the research and development cost

burden. Such a measure would still suffer from the same drawbacks and arguably be even riskier than facilitating the ANDA process however, since generics rely on the rigorous testing brand-name drugs undergo as part of their development.

Thus, however well-intentioned any reforms to FDA regulations may be in their efforts to curb rising drug costs, policymakers must strike a balance between providing economic incentives for pharmaceutical companies on the one hand and not unduly diminish their willingness to invest in drug research in an effort to obtain those incentives on the other.

State Transparency Legislation

At the state level, several jurisdictions have proposed bills that would require pharmaceutical companies to provide greater detail and justification for the prices they are charging. [42] The bills aim to put greater pressure on pharmaceutical companies to be transparent in disclosing their costs of drug development and in so doing, force them to defend and justify their pricing decisions to the public. [43] Among other provisions, several bills would require disclosures on the manufacturing, marketing, and advertising costs for a drug, in addition to research and development costs. [44] Under one proposal in Pennsylvania, insurers would reserve the power to refuse to pay for a drug if the manufacturer fails to file the requisite disclosures. [45] In Massachusetts, a state commission would be created with the authority to step in and set price ceilings if they have reason to believe that a drug's price is disproportionate to its benefits in light of its costs and its price in other countries. [46] To date, six states (California, Massachusetts, New York, North Carolina, Oregon,

and Pennsylvania) have pharmaceutical cost transparency bills at various stages in their legislatures. [47]

The state transparency bills represent a good-faith effort to curb the costs of brand-name drugs, but are not without their drawbacks. [48] First, the bills do not account for other values drugs have to our society, such as the benefits drugs convey by keeping people easily treated with drugs out of the hospital and freeing up scarce medical resources for others. Economically, such an outcome is desirable from a resource allocation standpoint. Furthermore, the bills also do not give any weight to the sunk costs associated with the drugs that never make it to market (the vast majority), which pharmaceutical companies must recoup in order to remain profitable. Finally, pharmaceutical companies may argue that the cost of complying with such transparency bills would be unreasonably high, and as a result, they may be incentivized to pass the cost on to consumers, which would undermine the bill's intention.

To date, the proposed transparency bills have received little traction within their state legislatures and most remain in the initial stages of deliberation. [49]

The "Value Framework"

A different approach takes advantage of the power and responsibility doctors hold in informing their patients as to the entire menu of available therapeutic alternatives. [50] A proposal by the American Society of Clinical Oncology (ASCO) dubbed the "value framework" would ask doctors to discuss not only the medicinal properties of the different drugs patients may choose, but the costs of those

treatments as well. [51] The value framework would consider not only the private cost to the patient of the treatment, but also the overall cost a drug imposes on the health system. [52] While asking doctors to become resource allocators is admittedly controversial, the authors of the study believe that giving patients important information on costs will allow them to make better individual decisions, especially if the costs of a course of treatment are disproportionately high compared to the treatment's benefit to the patient. [53]

In an economic sense, such a proposal finds strong support in the concept of informational asymmetry, which holds that transactions in which one side has more or better knowledge or access to information than the other side are prone to economic inefficiencies. [54] The classic example of informational asymmetry is the so-called "Lemons Problem" where sellers in the used car market know considerably more about the history of their vehicles than prospective buyers. [55] With respect to helping patients make the best choice of treatment, doctors are presumed to have better knowledge and information about the drugs they are prescribing and therefore, under the value framework, would have the obligation to correct that imbalance by informing the patients as to the costs of those drugs.

More Permissive Trade Policies

Despite the fact that the United States represents one of the largest and most profitable pharmaceutical drug markets in the world, few foreign drug manufacturers are willing to enter the U.S. market because of the lengthy and costly FDA approval process. Notwithstanding the economic benefits that would result from increased

trade with other nations, encouraging foreign manufacturers to enter the U.S. market is beneficial because their entry would boost the supply of available alternatives to brand-name drugs and therefore put downward pressure on the prices of incumbent brand-name drugs. For instance, by importing cheaper alternatives from Canada, U.S. patients would benefit from having more options to choose from and not having to rely on a single drug for their treatment.

In recognizing the importance for Americans to have access to foreign-made drug products, the FDA has recently instituted a Globalization Initiative to ensure imported drugs are as safe and effective as products made in the United States. [56] In practice, globalization in the area of pharmaceutical drugs is an incredibly lofty and difficult goal, not least owing to the fact each country has a unique set of relevant standards which necessarily results in countless discrepancies and variations amongst these regulations worldwide. One solution, which the FDA is considering, would be to account for, reconcile and ultimate harmonize the standards of each country into one universal drug recognition system. [57] Such a unified system would considerably reduce the regulatory burden on foreign manufacturers and the FDA alike and may work to increase the volume of foreign-made drug imports into the U.S. market. Even with such a harmonized system, foreign manufacturers with FDA approval for their drugs may nevertheless find it difficult to gain market share and traction amongst U.S. consumers who are unfamiliar with their company and products.

VI. CONCLUSION

There is little doubt that pharmaceutical companies (domestic and foreign) seeking to market drugs in the United States operate in an extremely challenging environment, a world shaped in part by the lengthy and expensive regulatory approval process imposed by the FDA. Choosing which diseases to develop therapies for is often a decision based as much on societal need as on the profitability and the patentability of a compound. However, despite the difficulties faced by pharmaceutical companies, the Daraprim and Cycloserine cases clearly demonstrate the extent to which pharmaceutical companies are willing to go to pad their bottom line. Hiding behind the FDA licensing scheme, pharmaceutical companies can exploit the life-saving nature of their products and capitalize on a vulnerable segment of the population by demanding unconscionably high prices for their products. A variety of potential solutions have been proposed to help combat the monotonic increase in drug and health care costs, including revisions to the FDA regulations for drugs, state transparency bills, the implementation of a value framework by doctors, and more permissive trade policies. Ultimately however, the most effective strategies will be those that incentivize the entry of viable alternatives to brand-name drugs into the U.S. market.

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