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Regulatory Solutions to the Problem of High Generic Drug Costs

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Recent reports have highlighted dramatic price increases for several older generic drugs, including a number of essential products used to treat deadly infectious diseases. Although most of these medicines have been widely available at reasonable prices for decades, some manufacturers have seized on unique features of the pharmaceutical marketplace to seek substantial profits. In this Perspective, we examine limitations in current price regulation among public and private payors and consider several reforms that could address the problem of expensive generic drugs through improved competition.

Keywords. drug costs; drug prices; FDA; generic drugs.

Social media erupted in September 2015 with news of Turing's 5000% markup of pyrimethamine, a 62-year-old drug used to treat toxoplasmosis. Overnight, the company's brash founder and chief executive, Martin Shkreli, became the poster child for industry greed run amok. Turing's action is the latest in a series of astronomical increases in the prices of select generic products. Similar markups have been observed for the antibiotic doxycycline (5000%, from \$0.06 to \$3.36 per pill), the antiparasitic albendazole (1900%, from \$5.92 to \$119.58

per typical daily dose), the antidepressant clomipramine (3600%, from \$0.22 to \$8.32 per pill), and the heart failure drug digoxin (900%, from \$0.11 to \$1.10 per pill)—to name but a few [1, 2]. For patients using these products, price increases translate into greater out-of-pocket costs, decreased adherence to medication regimens, and worse health outcomes.

What's to blame? Not patents—old drugs such as pyrimethamine have long since lost enforceable market exclusivity. Instead, such price hikes emerge when market forces result in limited competition among drug suppliers. Such an environment can arise from consolidations or manufacturers moving on to other products as in the case of digoxin, a generic drug that used to be made by 8 generic manufacturers but is now made by only 3. In the case of pyrimethamine, limited competition had long existed, because the drug was made for decades only by GlaxoSmithKline, never attracting generic entrants because of its relatively small sales. Still, it was sold at a modest price (approximately \$1 per pill). However, GlaxoSmithKline sold the product in 2011 to a small, private business venture,

Amedra, which raised the price to \$13.50 per pill before Turing acquired the rights to the product in August 2015. There are no federal or state laws that prevent such price increases for prescription drugs; indeed, companies that naturally have or acquire a monopoly may charge whatever price they can get without fear of breaking antitrust laws.

The United States relies on market forces to set prices, a mechanism that is particularly ineffective when there is only 1 manufacturer, as with pyrimethamine. Even when multiple producers of highly effective drugs for the same disease exist, as with direct-acting antivirals used to treat hepatitis C, current laws restrict how much effect competition can have on lower prices. The federal government is statutorily prohibited from influencing negotiations between individual Medicare Part D plan sponsors and drug manufacturers. In part because of this major limitation, a recent Department of Health and Human Services Office of Inspector General report found that savings from these negotiations are substantially less than savings obtained through the Medicaid drug rebate program [3].

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Public payors are also restrained in their abilities to use formularies to drive down prices because of mandatory coverage requirements [4]. Finally, state Medicaid programs are supposed to obtain additional rebates when the price of brand-name drugs rise faster than inflation, but these statutory rebates will not apply to generic drugs until 2017. [5].

For private payors, the competitive situation is not much better. Although commercial health insurance plans may be able to reduce costs by refusing to cover unreasonably expensive generic drugs, many plans may be reluctant to do so when the offending drug is the first-line treatment, as pyrimethamine is for toxoplasmosis. Some plans may elect to shift a greater fraction of the costs to patients, but such cost shifting can lead to financial distress and medication nonadherence. Although some pharmaceutical manufacturers have set up patient assistance programs to help patients with insurance copays, these programs can have high qualification hurdles and are often time delimited. Even if patient assistance programs are effective, they do not address substantial costs still paid by the insurer, which are subsequently transferred to all beneficiaries in the form of higher premiums.

Some claim that a potential check on skyrocketing generic drug prices is the fact that other manufacturers could produce the same medicine at lower prices. Unfortunately, the generic market is slow to correct itself. All generic drugs marked for sale must be reviewed and approved by the US Food and Drug Administration (FDA) for bioequivalence and manufacturing quality, but chronic underfunding of the FDA Office of Generic Drugs has led to a 3-year-long queue before a generic drug application gets reviewed. Legislation instituting user-fee funding in 2012 sought to ameliorate the problem but has not shortened wait times to any significant degree yet. In addition, costs associated with these fees may have the undesirable effect

of reducing incentives for competition when the overall market is small. For example, the current submission fee per new generic drug application is \$76 030. An additional fee of \$243 905 is charged if FDA inspection is required at a new manufacturing facility.

A variety of proposed solutions could help the growing problem of expensive generic drugs. Senator Bernie Sanders and former Senator Hillary Clinton advocate allowing the federal government to negotiate Medicare Part D drug prices, a power that the Veterans Health Administration already enjoys. Clinton has also called for better funding for the Office of Generic Drugs and a \$250 monthly spending cap for patients, although a cap alone would not shield payors from continuing to pay high prices and then passing them on to enrollees or taxpayers.

Another essential way to tackle rising generic drug prices is by fostering greater market competition. The government—perhaps the Centers for Medicare & Medicaid Services (CMS)—could better monitor the generic drug marketplace to ensure a minimum number of manufacturers of essential medicines. Previous research suggests that adequate generic prices can be maintained with 4 or more producers [6]. When the threat of falling below this threshold emerges, CMS could work with the FDA to allow temporary importation of products by manufacturers vetted by stringent regulatory authorities around the world. An expedited review process could be created for approval of new generic drug applications that address an important public health need. This process could be modeled after the numerous expedited review pathways that exist for brand-name drugs. To incentivize new entrants into a flagging market, the FDA could also waive generic drug user fees. Although all of these measures would likely require Congressional authorization, broad bipartisan support exists among the electorate to change the status quo.

More than 85% of the 4 billion annual prescriptions in the United States are filled with generic drugs. When the system works, the use of generics has generated large cost-savings for patients and payors, increased medication adherence, and improved public health. However, for cases in which companies have driven up the price of drugs simply because they can, a strategy must be developed that helps patients access needed medications as quickly, affordably, and safely as possible. Although public shaming can play a role—as it did in prompting Shkreli to reconsider the price of pyrimethamine—a comprehensive plan is needed to address the other cases and help prevent future crises from emerging.

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