



Off-patent drugs at brand-name prices: a puzzle for policymakers

Naren P. Tallapragada*

Department of Systems Biology, Harvard Medical School, USA

*Corresponding author. E-mail: ntallapragada@fas.harvard.edu

ABSTRACT

In August 2015, Turing Pharmaceuticals acquired the marketing rights to Daraprim (pyrimethamine), a drug used to treat parasitic infections like malaria and toxoplasmosis. Soon after, Turing caused an uproar when it announced that it would raise the price per tablet of Daraprim from \$13.50 to \$750, a 5500% price hike for a drug that has been on the market for over 60 years and off patent since the 1970s. Old, off-patent drugs are becoming increasingly expensive; Daraprim is the archetypal example. Turing had the power to set a high price for Daraprim because the drug's limited patient population, the absence of competing manufacturers, and a lack of therapeutic alternatives all created an effective monopoly. Similar forces have driven up the prices of other off-patent drugs that treat diseases as diverse as heart failure and multi-drug-resistant tuberculosis. Thus, policymakers will have to consider how the high cost of off-patent drugs impacts public health as well as public spending. In this Note I outline the extent of the high-cost off-patent drug problem, drawing special attention to the problem's negative effects on both health outcomes and government budgets. After discussing some of the problem's underlying causes, I present several solutions to the problem that policymakers could consider, with a focus on proposals like reference pricing and expanded compounding that have received relatively little media attention.

INTRODUCTION

Prescription drugs under patent command premium prices. Drug development is risky, expensive, and time-consuming.¹ High prices allow pharmaceutical companies not only to recoup their development costs but also to turn healthy profits that satisfy their investors and fund research on other drugs in their pipelines. Through patents and other

¹ Gary P. Pisano, *Can Science Be a Business?*, 84 HARV. BUS. REV. 114 (2006).

market exclusivities, the federal government grants drug makers limited monopolies on their products with the understanding that eventually drugs will lose this protection and will go down in price. So, what is a policymaker to do when the price of an off-patent drug goes up instead?

This question is hardly hypothetical. In August 2015, Turing Pharmaceuticals acquired the marketing rights to Daraprim (pyrimethamine), a drug used to treat parasitic infections like malaria and toxoplasmosis. Within one month, Turing announced that it would raise the price per tablet of Daraprim from \$13.50 to \$750—a 5500 per cent price hike for a drug that has been on the market for over 60 years and off patent since the 1970s.² Facing bad press, social media backlash, and even the outrage of presidential candidates—but, notably, no immediate legal sanctions—Turing pledged it would roll back its price increase before settling on only minor adjustments to its original pricing strategy.³

Turing Pharmaceuticals is not alone in trying to purchase the rights to old drugs and squeeze higher revenues out of them—a strategy that detractors label ‘drug profiteering’. Since 2013 similar moves by other companies have inflated the prices of drugs that treat not only rare diseases like toxoplasmosis but also common conditions like heart failure and growing threats like multidrug-resistant tuberculosis.⁴ These price increases are of national concern since the profits that they generate could well be at the expense of public health and the general welfare.

Yet recent scrutiny from lawmakers and the public has not necessarily changed the calculus for drugmakers considering Turing-like tactics. Fundamentally, off-patent drugs can be extremely lucrative for companies that purchase the rights to manufacture and market them. These companies stand to make substantial returns on relatively small investments,⁵ especially if they can charge high prices for the drugs that they acquire. Indeed, since they are legally obliged to act in the interest of their shareholders,⁶ corporations are likely to raise the prices of off-patent drugs to the full extent the market will bear.

To continue with the Turing example, the company has the power to set a high price for Daraprim because the drug’s limited patient population, the absence of

² Andrew Pollack, *Once a Neglected Treatment, Now an Expensive Specialty Drug*, *N.Y. Times*, Sept. 21, 2015, at B1.

³ In November 2015, Turing announced it would cut the price that hospitals pay for Daraprim by 50 per cent. However, since the majority of Daraprim is dispensed outside of hospitals, Turing stands to retain most of the projected revenue from its original price hike. See Associated Press, *Turing Reneges On Drug Price Cut, Rival’s Version Sells Well*, *WASH. POST*, Nov. 25, 2015, https://www.washingtonpost.com/business/economy/turing-reneges-on-drug-price-cut-rivals-version-sells-well/2015/11/25/d2c22bd8-93cd-11e5-b5e4-279b4501e8a6_story.html.

⁴ Pollack, *supra* note 2, at B1.

⁵ Purchasing the rights to an old drug is generally much cheaper than developing a new drug. Turing paid Impax Laboratories \$55 million to acquire the rights to market Daraprim in the United States. Impax Laboratories, *Impax Announces Sale of Daraprim® to Turing Pharmaceuticals AG*, <http://investors.impaxlabs.com/Media-Center/Press-Releases/Press-Release-Details/2015/Impax-Announces-Sale-of-Daraprim-to-Turing-Pharmaceuticals-AG/default.aspx> (accessed Jan. 15, 2016). Compare this figure to the average cost of \$2.6 billion to bring a new drug to market. Tufts University, *How the Tufts Center for the Study of Drug Development Pegged the Cost of a New Drug at \$2.6 Billion*, http://csdd.tufts.edu/files/uploads/cost_study_background.pdf (accessed Jan. 14, 2016).

⁶ The oft-repeated claim that corporations are legally obligated to maximize their profits is not strictly true. ‘... Modern corporate law does not require for-profit corporations to pursue profit at the expense of everything else, and many do not.’ *Burwell v. Hobby Lobby Stores, Inc.*, 134 S.Ct. 2751 (2014).

competing manufacturers, and a lack of therapeutic alternatives have all created an effective monopoly. However, considering all of these forces, it is unclear that Turing engaged in anticompetitive behavior to obtain its market position. Thus, federal and state governments might not be able to use antitrust law to challenge Turing or companies like it. Instead, governments may need to use unconventional approaches to encourage potential competitors and to rein in the prices of off-patent drugs.

In this Note, I focus on policy solutions that have attracted less media attention, like expanded compounding, over those that have already been discussed at length elsewhere, like drug reimportation from Canada.⁷ First, however, I outline the extent of the high-cost off-patent drug problem, drawing special attention to the negative impact of high drug costs on public health outcomes and public spending, and I discuss some of the problem's underlying causes.

THE PROBLEM

Old, off-patent drugs are becoming increasingly expensive. Rising prices for off-patent drugs have come in two forms: (i) increased rates for single-source drugs—that is, drugs with only one manufacturer—driven by savvy investors who spot opportunities to earn monopoly profits; and (ii) spikes in the price of multisource generic drugs due to manufacturer mergers and manufacturing disruptions.⁸

Both types of price increases have been alarmingly large—often tenfold or more—but I focus in this Note on the case of single-source drugs that have recently changed hands. Canadian company Valeant Pharmaceuticals purchased two drugs commonly used to treat cardiovascular conditions—Isuprel (isoprenaline) and Nitropress (sodium nitroprusside)—and raised their prices by up to 500 per cent, seemingly overnight.⁹ Rodelis Therapeutics bought cycloserine, a drug used to treat multidrug-resistant tuberculosis, from an affiliate of nonprofit Purdue University and raised the price of a course of treatment from \$500 to \$10,800—the most substantial hike yet.¹⁰ What Turing, Valeant, Rodelis, and others share is the view that many off-patent drugs are undervalued assets, at least relative to prices that insurers and patients with no therapeutic alternatives are willing to pay. By this logic the original owners of these off-patent drugs underpriced their products because they lacked the profit motive to charge more, as in the case of Purdue and cycloserine, or they neglected them in favor of more lucrative drugs in their product portfolio, as in the case of GlaxoSmithKline, the long-time manufacturer of Daraprim.¹¹ However, this economic argument in favor of higher prices disregards the negative effects of high drug prices on health outcomes¹² and on public spending through programs like Medicare and Medicaid.¹³

⁷ For more on drug reimportation, see eg Niteesh K. Choudhry & Allan S. Detsky, *A Perspective on US Drug Reimportation*, 293 J. AM. MED. ASS'N. 358 (2005).

⁸ Jonathan D. Alpern, William M. Stauffer & Aaron S. Kesselheim, *High-Cost Generic Drugs—Implications for Patients and Policymakers*, 371 NEW ENG. J. MED. 1859 (2014).

⁹ Pollack, *supra* note 2, at B1.

¹⁰ *Id.*

¹¹ *Id.*

¹² See Michael T. Eaddy et al., *How Patient Cost-Sharing Trends Affect Adherence and Outcomes*, 37 PHARM. THERAPEUTICS 45 (2012).

¹³ See eg Centers for Medicare & Medicaid Services, *Medicare Drug Spending Dashboard 2014*, https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/Medicare-Drug-Spending/Drug_Spending_Dashboard.html (accessed Jan. 15, 2016).

Like many off-patent drugs, Daraprim, Nitropress, and cycloserine are considered ‘essential medicines’¹⁴ that even the most basic healthcare system should have on hand. These drugs allow for timely responses to infectious disease outbreaks and enable modern intensive care. Low costs for these treatments encourage their widespread availability and adoption. High costs can saddle society with a heavy disease burden due to reduced medication adherence—that is, fewer patients starting or sticking to a course of necessary prescribed medication.¹⁵ Thus, keeping off-patent drug costs low can often be considered a public health imperative.

Arguably the rationale that would support low prices for off-patent drugs also supports lower prices for expensive innovator drugs with clear public health benefits—for example, the hepatitis C treatment Sovaldi (sofosbuvir). Up to five million Americans suffer from a chronic hepatitis C infection, which is the leading cause for liver cancer and liver transplantation in the United States.¹⁶ As of January 2016, the average wholesale price for Sovaldi is \$1200 per pill, or \$100,800 for a 12-week course of treatment.¹⁷ To date private insurers and government payers have covered Sovaldi, but the cost of treatment has been a significant strain on their budgets. Between January and March 2014 alone, Medicaid in the state of Massachusetts spent \$23.3 million on Sovaldi.¹⁸ In an attempt to contain costs, payers now cover treatment with Sovaldi only for patients with advanced liver disease.¹⁹

From the perspective of both public health and public spending, the high price of Sovaldi has led to suboptimal outcomes. However, from the perspective of the free market, Sovaldi’s status as an innovator drug justifies its high price. As I discuss in the remainder of this Note, off-patent drugs are just as affected as innovator drugs by this tension between legitimate public and private interests.

CAUSES OF THE PROBLEM

The high cost of off-patent drugs is, at its heart, about shortages: most commonly, a shortage of patients to take these drugs and/or a shortage of drugmakers to make them.

As a treatment for a parasitic disease of tropical origin, Daraprim is the archetypal example of a drug with a limited patient population in the United States.²⁰ Although it is estimated that 22.5 per cent of adults in the USA carry the parasite

¹⁴ The World Health Organization (WHO) maintains a ‘Model List of Essential Medicines’ to fulfill public health needs as diverse as infectious disease control and treating mental illness. Most countries have national lists of essential medicines based in part on the WHO’s list, but the United States is a notable exception. State Medicaid programs have preferred drug lists, but these lists have limited overlap with the WHO list and with each other. See Timothy P. Millar et al., *Applying the Essential Medicines Concept to US Preferred Drug Lists*, 101 AM. J. PUB. HEALTH 1444 (2011).

¹⁵ See M. Christopher Roebuck et al., *Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending*, 30 HEALTH AFF. 91 (2011). See also M. Christopher Roebuck et al., *Increased Use Of Prescription Drugs Reduces Medical Costs In Medicaid Populations*, 34 HEALTH AFF. 1586 (2015).

¹⁶ Centers for Disease Control and Prevention, *Hepatitis C FAQs for the Public*, http://www.cdc.gov/parasites/toxoplasmosis/health_professionals/ (accessed Jan. 14, 2016).

¹⁷ Truven Health Analytics, *RedBook—Micromedex Medication, Disease, and Toxicology Management*, www.micromedexsolutions.com (accessed Jan. 15, 2016).

¹⁸ Robert Weisman, *Demand for Expensive Hepatitis C Drug Strains Insurers*, BOSTON GLOBE, Jun. 1, 2014.

¹⁹ *Id.* See also United Healthcare Community & State, *Prior Authorization Guideline for Sovaldi*, https://www.uhcommunityplan.com/content/dam/communityplan/healthcareprofessionals/pharmacyprogram/Sovaldi_Prior_Authorization.pdf (accessed Jan. 15, 2016).

²⁰ The broad-spectrum anti-parasitic albendazole is another example, see Alpern et al., *supra* note 8, at 1860.

Toxoplasma gondii,²¹ most of these carriers rarely get ill. However, individuals who are immunocompromised—due to comorbid HIV infection, immunosuppression following an organ transplant, or chemotherapy, for example—can experience recurring bouts of disease with severe symptoms like seizures and confusion. Even so, only about 2000 Americans take Daraprim each year.²²

Toxoplasmosis being a rare disease does not ipso facto make treatments for the disease unprofitable. Indeed, over the past decade pharmaceutical companies have profited massively from ‘orphan drugs’ that treat rare cancer variants and enzymatic disorders.²³ The key difference here is that treatment with Daraprim lasts just six weeks, which limits the potential value of its sales relative to orphan drugs that must be taken for life. In 2010, sales of Daraprim totaled just \$667,000 from \$12,700 prescriptions.²⁴ By contrast, many orphan drugs cost hundreds of thousands of dollars per patient per year.²⁵ Given this disparity, the market is unlikely to prioritize the development of therapeutic alternatives to Daraprim.²⁶

Generic competition is similarly unlikely. In principle, the newly high price of Daraprim would encourage generic drugmakers to produce substantially cheaper bioequivalent competitors. In practice, however, several barriers to entry keep generic competitors out of the market despite favorable price signals—eg the limited patient population and treatment duration relative to other drugs that could be produced, as discussed above, and restricted distribution tactics that hinder the regulatory approval of generics.²⁷

Makers of single-source drugs like Daraprim will continue to possess de facto monopolies on the manufacture and sale of these drugs until at least one competitor is granted approval to sell a generic alternative. In most cases, the assumption is that more than one generic competitor will enter the market and prices will drop precipitously as a result, even though consolidation in the generic drug industry has cut down the number of potential players.²⁸ The reality, however, is that sometimes no generic competitors enter the market and the prices never drop. Daraprim remains without a generic competitor in 2016, about four decades after the patent on pyrimethamine expired, and its price is higher than ever.

²¹ Centers for Disease Control and Prevention, *Parasites—Toxoplasmosis (Toxoplasma infection)*, <http://www.cdc.gov/parasites/toxoplasmosis/> (accessed Dec. 4, 2015). *Toxoplasma gondii* can be acquired by eating undercooked meat or by exposure to cat litter. See *id.*

²² Robert Langreth & Drew Armstrong, *Clinton’s Tweet on High Drug Prices Sends Biotech Stocks Down*, BLOOMBERG BUSINESS, <http://www.bloomberg.com/news/articles/2015-09-21/clinton-s-tweet-on-high-drug-prices-sends-biotech-stocks-down> (accessed Dec. 30, 2015).

²³ Profit margins on orphan drugs have been reported to exceed 80 per cent. M. Ian Phillips, *Big Pharma’s New Model in Orphan Drugs and Rare Diseases*, 1 EXPERT OP. ORPHAN DRUGS 1 (2013). Notable examples of orphan drugs include Gleevec, a treatment for chronic myelogenous leukemia and Cerezyme, a treatment for the metabolic disorder Gaucher’s disease. See *id.*

²⁴ Pollack, *supra* note 2, at B1.

²⁵ See Langreth & Armstrong, *supra* note 22.

²⁶ I mention therapeutic alternatives here not to suggest that pyrimethamine is clinically ineffective but instead to point out that high drug prices result in part from patients’ lack of choices to treat toxoplasmosis and many other conditions.

²⁷ See Ameet Sarpatwari, Jerry Avorn, & Aaron S. Kesselheim, *Using a Drug-Safety Tool to Prevent Competition*, 370 NEW ENG. J. MED. 1476 (2014).

²⁸ Alpern et al., *supra* note 8, at 1860.

Off-patent single-source drugs like Daraprim are ripe for price jumps precisely because they lack competitors. Whoever owns the rights to one of these drugs has all the power to set its price until the government encourages competitors to emerge or asserts the public interest in regulating seemingly legal monopoly profits.

POTENTIAL POLICY PRESCRIPTIONS

In this section, I evaluate two kinds of policy solutions that the government could employ to rein in the cost of off-patent single-source drugs: explicit price controls and moves to promote competition. The list of policy prescriptions here is by no means an exhaustive one, and I focus only on specific aspects of these policies that I think have received comparatively little attention from scholars and the media.

Explicit drug price controls and reference pricing

Explicit price controls for off-patent drugs are a natural response to the high cost of off-patent drugs, though they are rarely discussed in the United States. Price controls in the USA have a complicated history, especially in response to perceived ‘price gouging’.²⁹ The federal government last tried imposing widespread price controls to reduce inflation in the early 1970s. Then, Congress passed the Economic Stabilization Act of 1970,³⁰ which authorized³¹ the President to freeze prices and wages temporarily in an attempt to stabilize them. President Nixon exercised this authority with mixed results; initial progress against inflation eventually led to meat and fuel shortages. Opponents of pharmaceutical price controls could point to this historical example to claim that capping prescription drug prices (and thus, spending) would lead to shortages of vital drugs and could even cause the expensive drug development pipeline to run dry.³²

As a counterpoint to this argument, even Switzerland—home to pharmaceutical giants like Novartis and Roche—sets maximum allowable prices on drugs for sale within its borders.³³ Indeed, unlike in the United States, the governments of many other OECD countries³⁴ make frequent use of government fiat and negotiating power to drive down the cost of prescription drugs—branded and generic, patented and off patent alike.³⁵ Their methods are too diverse to enumerate in full, but here I compare and contrast three tactics with those employed by the US government.

The first, reference pricing, is a widespread method of calculating a country’s drug reimbursement rates as some function of (i) that drug’s prices in several peer nations

²⁹ The existing body of case law on price gouging has restricted the authority to limit price gouging largely to the States in times of emergency such as a natural disaster. See ADAM VANN & KATHLEEN ANN RUANE, CONG. RESEARCH. SERV., RS22236, GASOLINE PRICE INCREASES: FEDERAL AND STATE AUTHORITY TO LIMIT ‘PRICE GOUGING’ (2011).

³⁰ Economic Stabilization Act of 1970, Pub. L. No. 91-379, 84 Stat. 799 (1970).

³¹ In *Amalgamated Meat Cutters v. Connally*, 337 F. Supp. 737 (D.D.C. 1971), the US District Court for the District of Columbia held that the grant of power to impose price controls from Congress to the Executive Branch did not violate the nondelegation doctrine.

³² THOMAS A. ABBOTT & JOHN A. VERNON, NAT’L. BUR. ECON. RES., WORKING PAPER 11114, THE EFFECT OF PRICE CONTROLS ON PHARMACEUTICAL RESEARCH. THE COST OF U.S. PHARMACEUTICAL PRICE REDUCTIONS: A FINANCIAL SIMULATION MODEL OF R&D DECISIONS (2005).

³³ Ezekiel Emanuel, *The Solution to Drug Prices*, N.Y. TIMES, Sept. 9, 2015, at A31.

³⁴ The Organization for Economic Co-operation and Development (OECD) is a global association of 34 developed countries, including the United States. OECD, <http://www.oecd.org/> (accessed Dec. 30, 2015).

³⁵ Gretchen A. Jacobson, *Pharmaceuticals Pricing: U.S. and European Strategies*. 8 EUR. AFF. (2007).

and/or (ii) the average price of therapeutically comparable drugs in that country itself. Approach (ii) is actually very similar to how Medicaid computes Federal Upper Limits to reimbursement,³⁶ so reference pricing could be practical in America. The second, value-based pricing, relates drug prices to quality-adjusted life years (QALYs),³⁷ a metric of disease burden that captures improved health due to treatment. Norway's use of cost-per-QALY to pick one of many therapeutically comparable drugs has translated into major savings, like paying 71 per cent less than Medicare for the same osteoporosis treatment.³⁸ By statute,³⁹ however, Medicare explicitly cannot consider cost-per-QALY when calculating its reimbursements.⁴⁰ The third, the imposition of profit controls, requires market intervention by the government at a scale and scope well beyond the American norm. The United Kingdom limits drugmaker profits by capping its annual spending on pharmaceuticals and requiring drugmakers to foot the bill or cut drug prices going forward if spending exceeds this cap.

Admittedly, state-run and state-funded healthcare systems like those in Norway and the UK facilitate extensive government regulation of prescription drug prices, and neither country has a pharmaceutical lobby as active as the United States.⁴¹ One could argue more generally that high drug prices in America subsidize low prices elsewhere. Indeed, a Department of Commerce report from 2004 concluded that American consumers would benefit most from the elimination of pharmaceutical price controls abroad, not the imposition of price controls at home.⁴² Still, the role of the Center for Medicare and Medicaid Services (CMS) as the dominant payer for American healthcare should give it substantial leverage in dealing with pharmaceutical companies. If Medicare eventually were allowed to negotiate drug prices with drug makers—as several lawmakers have proposed⁴³—being able to reference lower prices for the same drugs in peer countries could strengthen Medicare's negotiating position.

Nevertheless many scholars have argued that Medicare's ability to negotiate drug prices would be fundamentally impaired by its inability to walk away from many negotiations.⁴⁴ Medicare Part D is required to cover 'all or substantially all' drugs in six

³⁶ Centers for Medicare & Medicaid Services, *Federal Upper Limits*, <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Federal-Upper-Limits.html> (accessed Dec. 4, 2015).

³⁷ 'One year in perfect health equals one QALY. Four years in so-so health equals two or three QALYs.' Jeanne Whalen, *What is a QALY?*, WALL ST. J., Dec. 1, 2015.

³⁸ Jeanne Whalen, *Why the U.S Pays More Than Other Countries for Drugs*. WALL ST. J., Dec. 1, 2015.

³⁹ Patient Protection and Affordable Care Act, Pub L. No. 111-148, 124 Stat. 119,1025 (2010). See also Peter J. Neumann & Milton C. Weinstein, *Legislating against Use of Cost-Effectiveness Information*, 363 NEW ENG. J. MED 1495 (2010).

⁴⁰ The ban on cost-per-QALY use reflects a pervasive American fear of health care rationing. See also Neumann & Weinstein, *supra* note 39, at 1495.

⁴¹ M. Asif Ismail, *Drug Lobby Second to None*, CENTER FOR PUBLIC INTEGRITY, <http://www.publicintegrity.org/2005/07/07/S786/drug-lobby-second-none> (accessed Dec. 30, 2015).

⁴² PHARMACEUTICAL PRICE CONTROLS IN OECD COUNTRIES: IMPLICATIONS FOR U.S. CONSUMERS, PRICING, RESEARCH AND DEVELOPMENT, AND INNOVATION, U.S DEPARTMENT OF COMMERCE INTERNATIONAL TRADE ADMINISTRATION (2004).

⁴³ Prescription Drug Affordability Act of 2015, S. 2023, 114th Cong. §1 (2015). See also Hillary Clinton's plan in Patrick Healy & Margot Sanger-Katz, *Hillary Clinton Proposes Cap on Patients' Drug Costs as Bernie Sanders Pushes His Plan*, N.Y. TIMES, Sept. 22, 2015, at A13.

⁴⁴ See eg Richard G. Frank & Joseph P. Newhouse, *Should Drug Prices Be Negotiated Under Part D Of Medicare? And If So, How?* 27 HEALTH AFF. 33 (2008).

protected classes⁴⁵ that tend to be among the most expensive. If negotiations or fiat cannot lower off-patent drug prices, perhaps government encouragement of market forces could have the same effect.

FDA incentives for generic drugmakers

The FDA could begin to address the lack of market competition for expensive off-patent drugs by maintaining a list of single-source off-patent drugs, much like the list it currently maintains of drugs in short supply.⁴⁶ Companies who apply to produce these drugs could be rewarded with expedited processing of their applications and fee waivers,⁴⁷ though such incentives may require Congressional authorization and others may be needed as well.⁴⁸ Importantly, these actions could not be taken in response to the cost of the drug alone, as the FDA explicitly cannot consider costs when approving a drug or its generic competitors.⁴⁹ However, the FDA does have substantial power to relieve drug shortages.⁵⁰ Access to a drug does decrease with substantial increases in price. Is that limited access tantamount to a shortage, and would the expedited approval of generic competition constitute appropriate relief?

The FDA recognizes the importance of a steady supply of many medicines; it requires that manufacturers promptly notify the agency if they intend to stop producing prescription products that are ‘life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition’.⁵¹ The FDA can alleviate resulting drug shortages by taking actions like reimporting drugs,⁵² or expediting the approval of new drug suppliers.⁵³ Especially with Congressional authorization, the FDA might be able to exercise its shortage power to expedite generic competition for single-source off-patent drugs—especially since public health experts consider many of these drugs to be essential medicines.⁵⁴ That said, the FDA might be able to increase drug supply without Congressional involvement by encouraging the expansion of compounding pharmacies, though this policy option is not without controversy.

⁴⁵ The six protected classes are anti-retrovirals, immunosuppressants for organ recipients, anti-depressants, anti-psychotics, anti-convulsants, and anti-neoplastics. See David Nather, *Washington Has Big Hopes, But Little Power, to Negotiate Drug Prices*, STAT, <http://www.statnews.com/2016/01/06/medicare-negotiate-drug-prices/> (accessed Jan. 9, 2016).

⁴⁶ US Food and Drug Administration, *FDA Works to Lessen Drug Shortage Impact*, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm258152.htm> (accessed Jan. 20, 2016).

⁴⁷ The \$76,030 fee to submit an Abbreviated New Drug Application to the FDA [Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2016, 80 Fed. Reg. 46,015 (Aug. 3, 2015).] is almost 10 per cent of the \$1–2 million cost to demonstrate bioequivalence for a generic drug. Henry Grabowski, Iain Cockburn & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1293 (2006). Faster approval could also benefit drugmakers by giving their generic drugs a longer time on the market.

⁴⁸ Alpern et al., *supra* note 8, at 1861.

⁴⁹ VINAYAK K. PRASAD & ADAM S. CIFU, ENDING MEDICAL REVERSAL: IMPROVING OUTCOMES, SAVING LIVES 142 (2015).

⁵⁰ Alpern et al., *supra* note 8, at 1861.

⁵¹ Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products, 80 FED. REG. 38,915 (Jul. 8, 2015).

⁵² US Food and Drug Administration, *supra* note 46.

⁵³ Exec. Order No. 13,588, 3 C.F.R. 13,588 (2011).

⁵⁴ Alpern et al., *supra* note 8, at 1861.

Expanded compounding for small patient populations

In October 2015, Imprimis Pharmaceuticals (in conjunction with the payer Express Scripts) announced it would sell a Daraprim competitor for less than \$1 per tablet, or far less than the \$750 that Turing demands.⁵⁵ Imprimis is a compounding pharmacy, which means that it fills doctor-prescribed, patient-specific formulations of mixtures of drugs.⁵⁶ Though compounding was originally intended for patients with needs unmet by the market,⁵⁷ custom-compounded versions of off-patent drugs may be viable alternatives to their expensive commercial counterparts, especially if the patient population is small.

But compounded substitutes alone cannot cure the problem of high-priced off-patent drugs. Compounding pharmacies are limited in what they can provide relative to traditional dispensaries. By statute, compounders may not produce ‘drug products that are essentially copies of a commercially available drug product’.⁵⁸ In the case of Imprimis’s Daraprim competitor, this limitation is actually an asset. The compounded tablet contains not just pyrimethamine but also a form of folic acid called leucovorin that reduces pyrimethamine’s adverse side effects.⁵⁹ Of course, not all drugs have such natural synergistic partners, so in general it may be difficult to work around the ban on copies.⁶⁰ Additionally, compounded drugs are not FDA-approved, nor are their manufacturing processes necessarily FDA-regulated⁶¹ so over-reliance on compounding may expose the public to very real risks of contamination and adulteration.⁶²

In response to recent scandals,⁶³ Congress established standards and safeguards for compounding to protect consumers’ health and safety. Under the Drug Quality and Security Act,⁶⁴ a compounder can seek certification as an ‘outsourcing facility’ that the FDA inspects regularly to ensure that compounding occurs under the supervision of a licensed pharmacist according to current good manufacturing practices (cGMP). Though certification as an outsourcing facility does not guarantee that a compounder’s drugs are safe, it does help consumers, physicians, and payers pass judgment on the quality and trustworthiness of compounders.

⁵⁵ Express Scripts, *Express Scripts Champions \$1 per Pill Access to an Alternative for Daraprim*, <http://lab.express-scripts.com/insights/drug-options/express-scripts-champions-1-per-pill-access-to-an-alternative-for-daraprim> (accessed Jan. 15, 2016).

⁵⁶ US Food and Drug Administration, *Compounding and the FDA: Questions and Answers*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm> (accessed Dec. 4, 2015).

⁵⁷ For example, medicines free of allergens or in easier-to-consume liquid form. See *id.*, at Q3.

⁵⁸ 21 U.S.C. § 353a(b)(1)(D) (2013).

⁵⁹ For example, bone marrow toxicity. See Centers for Disease Control and Prevention, *supra* note 21, at ‘Resources for Health Professionals.’

⁶⁰ 21 U.S.C. § 353a(b)(1)(D) (2013).

⁶¹ US Food and Drug Administration, *supra* note 56, at Q4.

⁶² Most infamously, the New England Compounding Center (NECC) caused a multistate fungal meningitis outbreak that killed 64 and sickened over 800. Its improper manufacturing practices led to contamination of the injectable steroid methylprednisolone, which it produced and sold nationwide effectively as an unlicensed drug company. See Kurt Eichenwald, *Killer Pharmacy: Inside a Medical Mass Murder Case*, NEWSWEEK, Apr. 16, 2015. The fallout from the NECC debacle prompted the passage of the Drug Quality and Security Act in 2013, 21 U.S.C. § 353a(b)(1)(D) (2013). See Besu F. Teshome et al., *How Gaps in Regulation of Compounding Pharmacy Set the Stage for a Multistate Fungal Meningitis Outbreak*, J. AM. PHARM. ASSOC. 441 (2014).

⁶³ Teshome et al., *supra* note 62, at 442.

⁶⁴ Drug Quality and Security Act, Pub L. No. 113-54, 127 Stat. 587 (2013).

In the face of market failures that have discouraged drugmakers from producing generic competitors to off-patent drugs that serve small patient populations, expanded compounding by certified compounders could expand access to drugs very quickly and practically. Many of the same active pharmaceutical ingredients in off-patent drugs are available for compounders to purchase in bulk.⁶⁵ With its \$1 per dose Daraprim competitor, Imprimis has demonstrated that compounding can be cost-effective and that payers are willing to cover compounded drugs if their value proposition is clear. The FDA should continue to allow arrangements like the one between Imprimis and Express Scripts that could increase drug access while decreasing costs. However, out of an abundance of caution, the rigor of the FDA's inspections should scale up with the number of patients to which a compounder provides drugs.

CONCLUSION

Since the Daraprim saga began in September 2015, the high prices of pharmaceuticals in general, and of off-patent drugs in particular, have become political issues and topics of everyday conversation in the United States. The media and the public have been quick to condemn Turing and its leadership for what they see as rampant corporate greed, but they have been slower to accept that the public interests and private incentives that exist in tension in the Turing story are both legitimate. The American economy is set up to reward players who best exploit market opportunities, and in some sense Turing simply fulfilled its obligations to its shareholders by raising the price of undervalued Daraprim.

That said, policymaking clearly has a role to play to ensure that private profits do not come at unbearable costs to public health and the general welfare. This Note discussed how the federal government might rein in high drug prices, through explicit price controls that restrain the market or through pro-competitive policies that use the market to expand the supply of off-patent drugs that are currently single-sourced. Some of the questions and considerations raised here may apply not only to small molecule drugs but also more broadly to increasingly prevalent biologic treatments and their generic biosimilars. However, policymakers choose to reconcile high drug costs with public health and public spending concerns, their decisions over the next decade could transform how we make, take, and pay for all drugs—on or off patent.

⁶⁵ American Pharmacists Association, *Frequently Asked Questions About Pharmaceutical Compounding*, <http://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding> (accessed Jan. 15, 2016).