

Generic but Expensive: Why Prices Can Remain High for Off-Patent Drugs

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Brand-name prescription drugs are sold at extremely high prices in the US because patents and other market exclusivities provided by the government allow manufacturers to exclude direct competition. This period of market exclusivity was intended for pharmaceutical manufacturers to recoup costs associated with research and development of those products and make profits. The other intended outcome of this system is that the market exclusivity period for brand-name drugs should be self-limited, with competition being able to flourish after the market exclusivities end. Such competition has been most effectively supplied by generic drug manufacturers that produce Food and Drug Administration (FDA)-approved bioequivalent versions of the brand-name product. The market entry of these generic drugs—with market uptake augmented by automatic substitution of brand-name prescriptions at the pharmacy—remains the only market intervention that lowers prescription drug prices consistently and substantially.

Generic manufacturers can make their drugs available at considerably lower cost because of various market advantages they have over brand-name drugs. When this process does not operate as intended, drug prices do not fall after market exclusivity expiration, or prices for generic drugs may actually increase. In this paper, we examine the variety of factors that mitigate the cost savings associated with introduction of interchangeable generic drugs, especially older, off-patent drugs. We then consider policy solutions that may help stabilize the generic drug marketplace, diminishing the frequency and impact of generic price increases.

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INTRODUCTION

Brand-name prescription drugs are sold at extremely high prices in the United States because patents and other market exclusivities provided by the government allow manufacturers to exclude direct competition. This period of market exclusivity was intended for pharmaceutical manufacturers to recoup costs associated with research and development of those products and make profits.¹ The other intended outcome of this system is that the market exclusivity period for brand-name drugs should be self-limited, with competition being able to flourish after market exclusivity ends. Such competition has been most effectively supplied by generic drug manufacturers that produce Food and Drug Administration (FDA)-approved bioequivalent versions of the brand-name product.² The market entry of these generic drugs—with market uptake augmented by automatic substitution of brand-name prescriptions at the pharmacy—remains the only market intervention that lowers prescription drug prices consistently and substantially.³ Drugs with just three interchangeable generic competitors attain a 40% median reduction from brand-name price, and those with six manufacturers attain a 62% median reduction.⁴ In 2018, generic drugs represented 90% of all prescriptions dispensed in the United States, but accounted for only 22% of total drug spending.⁵ Generic drugs also accounted for an estimated savings of \$293 billion in 2018, including savings of \$137 billion to Medicare and Medicaid, with total savings of \$2 trillion over the previous decade.⁶

Generic manufacturers can make their drugs available at considerably lower cost because of various market advantages they have over brand-name drugs. First, generic manufacturers have an abbreviated pathway to market in which they can receive FDA approval upon demonstrating bioequivalence to the brand-name version, which involves less clinical testing than is required for new drug approval. Second, upon market entry, generics can achieve high levels of market penetration because state drug product selection laws allow pharmacists to dispense them when a patient receives a prescription for the brand-name version. As such, generics need not rely on changing physician

1. Aaron S. Kesselheim et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 J. AM. MED. ASS'N INTERNAL MED. 1658, 1659 (2017).

2. Kerstin Noëlle Vokinger et al., *Strategies that Delay Market Entry of Generic Drugs*, 177 J. AM. MED. ASS'N INTERNAL MED. 1665, 1665 (2017).

3. Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 J. AM. MED. ASS'N 858, 861 (2016).

4. Chintan V. Dave et al., *Prices of Generic Drugs Associated with Numbers of Manufacturers*, 377 NEW ENG. J. MEDICINE 2597, 2598 (2017).

5. See ASS'N FOR ACCESSIBLE MEDS., THE CASE FOR COMPETITION: 2019 GENERIC DRUG & BIOSIMILARS ACCESS & SAVINGS IN THE U.S. REPORT 8 (2019).

6. *Id.* at 9–10.

prescribing practices—often influenced by substantial marketing budgets of brand-name manufacturers—to gain market share.

When this process does not operate as intended, drug prices do not fall after market exclusivity expiration. Prices for generic drugs may actually increase. For example, some drugs may not attract many generic competitors—perhaps because fewer patients use the prescription—which reduces the size of the potential revenue stream. A 2017 study demonstrated that between 2008 and 2014, prices of generic drugs with three or fewer competitors remained considerably higher than those in more competitive markets.⁷ In some cases, pharmaceutical manufacturers have acquired marketing rights to off-patent products with little to no generic competition, subsequently increasing the price of those products abruptly and substantially, which has resulted in public and political outcry.⁸ As part of its investigation into the problem of high generic drug prices, the U.S. Senate Special Committee on Aging produced a bipartisan report identifying sole-source drug status and small patient market size as two key factors leading to generic drug price increases.⁹ Such products can be susceptible to disruptions in drug supply, leading to shortages and price increases that often persist even after the shortage is resolved.¹⁰

Other factors may also contribute to generic drug price increases. Recent antitrust litigation alleges that a variety of anticompetitive practices by several generic manufacturers have contributed to increases in the price of many common generic drugs.¹¹ Another cause of intentional disruption to the generic drug marketplace came as a result of the FDA's Unapproved Drugs Initiative (UDI), which awarded three years of market exclusivity to manufacturers who conducted studies of older, off-patent drugs.¹² The program, which ran from 2006 to 2015, resulted in higher prices and an increase in both the number and duration of drug shortages because generic competitors were forced to discontinue production.¹³

These examples underscore the important point that generic drug cost reductions emerge through robust competition among generic manufacturers.

7. See Dave et al., *supra* note 4, at 2598.

8. See, e.g., Stephanie Armour & Jonathan D. Rockoff, *Valeant, Turing Boosted Drug Prices to Fuel Preset Profits*, WALL ST. J. (Feb. 2, 2016, 3:35 PM), <https://www.wsj.com/articles/valeant-turing-boosted-drug-prices-to-fuel-preset-profits-1454445342>.

9. S. REP. NO. 114-429, at 1, 4 (2016).

10. Inmaculada Hernandez et al., *Changes in Drug Pricing After Drug Shortages in the United States*, 170 ANNALS INTERNAL MED. 74, 74 (2019); see also Michail Alevizakos et al., *The Impact of Shortages on Medication Prices: Implications for Shortage Prevention*, 76 DRUGS 1551, 1551 (2016).

11. *In re Generic Pharm. Pricing Antitrust Litig.*, 338 F. Supp. 3d 404 (E.D. Pa. 2018); Michael S. Sinha et al., *Antitrust, Market Exclusivity, and Transparency in the Pharmaceutical Industry*, 319 J. AM. MED. ASS'N 2271, 2271 (2018).

12. See 21 U.S.C. § 355(j)(5)(F)(iii) (2018); see also Ravi Gupta et al., *The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States*, 23 J. MANAGED CARE & SPECIALTY PHARMACY 1066, 1066 (2017); Aaron Hakim et al., *High Costs of FDA Approval for Formerly Unapproved Marketed Drugs*, 318 J. AM. MED. ASS'N 2181, 2181 (2017).

13. Gupta et al., *supra* note 12, at 1066.

However, even if generic competition has been established and the price of the drug has settled at a level closer to its production cost, prices can increase once again if generic competitors leave the market and remaining competitors seek to leverage increased market share. The severity and frequency of price increases affecting the generic drug market is becoming a source of alarm. One study found price increases of over 400% for at least fifty older generic medications between 2012 and 2015.¹⁴ Between 2010 and 2015, prices increased by 100% or more for 315 of 1441 (22%) generic drugs sold in the United States.¹⁵ Price increases can detrimentally impact the ability of patients to access these products and lead to negative health outcomes, all while increasing the cost to government and private payors.

Patients, legislators, and the FDA have called for novel approaches to foster generic price competition. In this paper, we examine the variety of factors that mitigate the cost savings associated with introduction of interchangeable generic drugs, especially older, off-patent drugs. We then consider policy solutions that may help stabilize the generic drug marketplace and diminish the frequency and impact of generic price increases.

I. CONSOLIDATED MARKETS

When brand-name market exclusivity ends—usually due to the expiration of one or more patents protecting the drug—generic competitors can begin to enter the market. Since they are interchangeable at the pharmacy level, generic manufacturers predominantly compete with each other by driving down prices close to the cost of production, which results in steeper price reductions as more competitors enter the market for a particular product.¹⁶ Since the passage of the Drug Price Competition and Patent Restoration Act of 1984 (Hatch-Waxman Act),¹⁷ generic competition has been associated with substantially

14. Ana D. Vega et al., *Commentary on Current Trends in Rising Drug Costs and Reimbursement Below Cost*, 25 *MANAGED CARE* 41, 43–44 tbl.1 (2016).

15. U.S. GOV'T ACCOUNTABILITY OFF., GAO-16-706, *GENERIC DRUGS UNDER MEDICARE: PART D GENERIC DRUG PRICES DECLINED OVERALL, BUT SOME HAD EXTRAORDINARY PRICE INCREASES* 12 (2016).

16. *Generic Competition and Drug Prices*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm> (last visited Apr. 15, 2020).

17. Drug Price Competition and Patent Restoration Act of 1984, Pub L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, & 42 U.S.C.). After passage of The Hatch-Waxman Act in 1984, the number of generics in the small-molecule drug market has risen from 15% to 90%. See *FDA Approves More Generic Drugs, but Competition Still Lags*, PEW TRUSTS (Feb. 25, 2019), <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/02/fda-approves-more-generic-drugs-but-competition-still-lags> (last visited Apr. 15, 2020). The act catalyzed a major shift in the role that generics play in regulating drug price in the pharmaceutical market. Of note, the Hatch-Waxman Act implicitly acknowledges the limited price decreases associated with small numbers of manufacturers. See *id.* The first generic manufacturer to file a paragraph IV certification and successfully invalidate brand-name drug patents receives a 180-day period of generic marketing exclusivity, during which other generic competitors are foreclosed from entering the market. Drug Price Competition and Patent Restoration Act of 1984, 98 Stat. at 1589. During this government-mandated duopoly period, the generic manufacturer is free to set prices at near brand-name level. See *FDA Approves More Generic Drugs, but Competition Still Lags*, *supra*.

lower drug costs. But in certain cases, over the last three decades in the U.S. pharmaceutical market, robust competition has not ensued after market exclusivity ends. Factors that contribute to such an outcome include financial disincentives to enter the generic manufacturer market, decreased competition due to market withdrawals from rival generic manufacturers, and merger and acquisition activity between manufacturers that decreases the number of manufacturers for a particular drug or set of drugs. Finally, the FDA's short-lived UDI program further induced consolidation, disrupting an often-robust generic marketplace for older drugs while re-establishing a market monopoly. In each of these settings, prices are affected by manufacturers maintaining near-monopoly pricing power.

A. NICHE DRUG MARKETS

Niche drug markets are often characterized by limited competition, in part because niche drugs may be difficult to manufacture or may benefit smaller patient populations, as is true with drugs to treat rare diseases. As such, niche drugs tend to face limited potential for generic manufacturer entry—if they face generic competition at all. Niche drug markets are often served by three or fewer generic manufacturers. These less-competitive markets pose an obstacle to price reduction once a brand-name drug's market exclusivity period expires because, under near-monopolistic market conditions, generic manufacturers have less incentive to lower prices. Some generic manufacturers in these markets raise their prices gradually over time, while in other cases, manufacturers have used strong market positioning to raise prices in dramatic fashion.

Niche drug markets for older, off-patent drugs typically emerge in response to conditions that result in manufacturers leaving the market. These conditions may include limited profitability, limited efficacy compared to newer treatments, less desirable routes of administration or dosing regimens compared to newer-in-class products,¹⁸ and inability to generate sufficient revenue to compensate for costly and complex manufacturing processes.¹⁹ In many ways, niche drug markets follow a similar pattern to that of drugs for

18. Of note, if a drug has limited therapeutic benefit or onerous dosing regimens compared to other in-class drugs, there may be too few patients to support competitive market conditions despite high disease prevalence in the United States, and despite having more than three manufacturers. For instance, captopril (Capoten, approved 1981), a first-generation angiotensin-converting enzyme (ACE) inhibitor approved in 1981, was effective but required multiple doses per day. *Captopril (Oral Route)*, MAYO CLINIC <https://www.mayoclinic.org/drugs-supplements/captopril-oral-route/proper-use/drg-20069213> (last updated Feb. 1, 2020). After captopril went off-patent, second-generation ACE inhibitors with improved dosing regimens displaced the use of captopril. Jonathan D. Alpern, *High-Cost Generic Drugs—Implications for Patients and Policymakers*, 371 *NEW ENG. J. MEDICINE* 1859, 1860 (2014). The use of captopril decreased and the number of manufacturers of the drug listed in the FDA's Orange Book dropped more than half from 2000 to 2012 (from 22 to 10). Between November 2012 and November 2013, the price of captopril rose by more than 2800%, from 1.4 cents to 39.9 cents per pill. Alpern, *supra*.

19. Céline Pulcini et al., *Ensuring Universal Access to Old Antibiotics: A Critical but Neglected Priority*, 23 *CLINICAL MICROBIOLOGY & INFECTION* 590, 591 (2017).

rare diseases,²⁰ as there may be too few patients receiving the drug to support robustly competitive markets. The limited earning potential of these niche markets is often reflected in corporate pricing strategies for these products.²¹

Recent studies have found an association between manufacturers in a drug market and pricing. A 2006 FDA study noted a steady decrease in average relative price of generic drugs as the number of generic manufacturers increased.²² A 2017 analysis replicated that effect for a cohort of drugs from 2008 to 2014, but noted a more muted effect of earlier entrants on generic price.²³ The largest decrease in price—17%—was observed between generic drugs with three manufacturers and those with four manufacturers.²⁴ A separate study of generic market competition levels from 2008 to 2013 found that over a six-year period, baseline level of market competition was associated with increased drug price by the end of the study period.²⁵ Finally, among a cohort of 1113 generic drugs on the market from 2008 to 2016, 235 (21%) had three or fewer manufacturers.²⁶ In April 2017, there were 170 oral drug formulations approved by the FDA for which market exclusivity had ended that had three or fewer FDA-approved generic versions.²⁷ Perhaps more concerning, critical medicines are among these drugs with too few manufacturers. A 2016 study found that seventeen anti-infective medications

20. Established under the Orphan Drug Act of 1983, orphan-designated drugs are those that treat populations of 200,000 or fewer in the United States at the time of FDA approval. Ameet Sarpatwari et al., *Evaluating the Impact of the Orphan Drug Act's Seven-Year Market Exclusivity Period*, 37 HEALTH AFF. 732, 732 (2018). These products receive an extended regulatory exclusivity period of seven years upon approval. *Id.* Though the seven-year exclusivity period was intended to increase research and development into drugs to treat rare diseases, a recent study suggests that the incentive effect of the seven-year period has diminished over time. *See id.* at 736.

21. A 2015 report on orphan drug prices and a 2017 analysis of oncologic orphan products found that the price of these drugs rose exponentially as the number of patients who have the condition decreased. *See* Igho J. Onakpoya et al., *Effectiveness, Safety and Costs of Orphan Drugs: An Evidence-Based Review*, 5 BRIT. MED. J. OPEN e007199 (2015); IQVIA INST., ORPHAN DRUGS IN THE UNITED STATES: GROWTH TRENDS IN RARE DISEASE TREATMENTS (2018). Exceptionally high prices were common for so-called “ultra-orphan” diseases. *See* Onakpoya et al., *supra*, at e007202.

22. *Generic Competition and Drug Prices*, *supra* note 16.

23. Dave et al., *supra* note 4, at 2598 fig.1.

24. *Id.* at 2597–98.

25. Chintan V. Dave et al., *High Generic Drug Prices and Market Competition: A Retrospective Cohort Study*, 167 ANNALS INTERNAL MED. 145, 148 (2017). This study defined “quadropoly,” “duopoly,” and “near-monopoly” competition levels using the Herfindahl-Hirschman Index (HHI), the U.S. Department of Justice’s preferred method of quantifying market competition. HHI calculates market competition levels by summing the squares of the market shares of individual firms (generic manufacturers). Index values range from approaching 0 (reflecting an extremely competitive generic market) to 10,000 (a monopoly). Drug competition levels were assigned to HHI values as follows: quadropoly (HHI 2500), duopoly (HHI 5000), near-monopoly (HHI 8000), and monopoly (HHI 10,000). *Id.* at 146–47. Compared to drugs with baseline quadropoly competition, genericized drugs with duopoly, near-monopoly, and monopoly competition levels in 2008 were associated with relative price differences of 29.2%, 75.8%, and 115.9% respectively in 2013. *Id.* at 149.

26. This 2008 to 2016 cohort was derived from the authors’ database used in Dave et al., *supra* note 12.

27. Ravi Gupta et al., *Affordability and Availability of Off-Patent Drugs in the United States—The Case for Importing from Abroad: Observational Study*, THE BMJ (Mar. 19, 2018), <https://www.bmj.com/content/360/bmj.k831>.

on the World Health Organization (WHO) Essential Medicines List were produced by three or fewer manufacturers.²⁸ In niche drug markets, each manufacturer holds tremendous power to set the price for the drug.

Table 1 shows a list of recent price increases among generic drugs, many of which exist in niche markets. For instance, at the time of its price increases of close to 1000% from 2012 to 2014, digoxin was only manufactured by three companies.²⁹ Similarly, when one of the two manufacturers producing glycopyrrolate temporarily halted production due to quality control issues, the remaining manufacturer raised prices by about 334%.³⁰ Once a manufacturer of a particular drug becomes the sole source, prices can increase substantially, unfettered by the threat of competition. The 2016 U.S. Senate Special Committee on Aging report noted that sole-source manufacturers “could exercise *de facto* monopoly pricing power, and then impose and protect astronomical price increases.”³¹ This was the case for many drugs listed within the Senate report, including pyrimethamine, tiopronin, penicillamine, trientine, isoproterenol, sodium nitroprusside, and seromycin.³² For many of these drugs, internal company documents revealed strategies aimed at maximizing price and profitability via price gouging.³³

B. MERGERS AND ACQUISITIONS

Another factor that contributes to high generic drug prices is market consolidation, which most frequently occurs via mergers of pharmaceutical manufacturers or acquisitions of pharmaceutical product lines.³⁴ In the generics sector, market consolidation can leave certain generic drugs susceptible to price increases. Subpoenaed email exchanges between corporate officials have uncovered corporate pricing strategies after mergers and acquisitions; corporate executives will often reevaluate the drug’s competition and demand, raising prices accordingly.³⁵ This may be to recoup the costs of the merger or acquisition or to obtain maximal revenues from a noncompetitive marketplace.³⁶ Merger activity attracts particular scrutiny by the Federal Trade

28. Jonathan D. Alpern et al., *Essential Medicines in the United States—Why Access Is Diminishing*, 374 *NEW ENG. J. MEDICINE* 1904, 1906 (2016).

29. Elisabeth Rosenthal, *Rapid Price Increases for Some Generic Drugs Catch Users by Surprise*, *N.Y. TIMES* (July 8, 2014), <https://www.nytimes.com/2014/07/09/health/some-generic-drug-prices-are-soaring.html>.

30. Jacqueline LaPointe, *Hospitals Saw 23% Rise in Inpatient Prescription Drug Spending*, *REVCYCLE INTELLIGENCE* (Oct. 12, 2016), <https://revcycleintelligence.com/news/hospitals-saw-23-rise-in-inpatient-prescription-drug-spending>; see also James King, *How Pharma Execs Jacked Up the Prices of 5 Other Critical Drugs*, *VOCATIV* (Sept. 22, 2015, 4:02 PM), <https://www.vocativ.com/233557/how-pharma-execs-jacked-up-the-prices-of-5-other-critical-drugs/index.html>.

31. S. REP. NO. 114-429, at 4 (2016) (emphasis added).

32. *Id.* at 6 tbl.1.

33. *Id.* at 39–41, 44–45, 62–63, 86–87.

34. Ravi Gupta et al., *The Impact of Off-Patent Drug Acquisitions on Prices*, 33 *J. GEN. INTERNAL MED.* 1007, 1007 (2018).

35. See S. REP. NO. 114-429, at 44–45.

36. See *id.* at 45.

Commission when it involves acquisitions of direct competitor products, as in 2005 when Ovation Pharmaceuticals acquired the sole competitor to an indomethacin formulation used in neonatal cardiac care.³⁷

A 2018 analysis of recent pharmaceutical merger and acquisition activity found that the median price for a cohort of thirty-seven off-patent, brand-name drugs (with either monopoly or duopoly levels of competition) more than doubled after acquisition.³⁸ As shown in Table 1, generic drug price increases often follow merger or acquisition activity. In fact, the 2016 U.S. Senate report noted that manufacturers such as Retrophin, Turing, and Valeant attributed their price increases on acquired product lines to profit motives.³⁹ Subpoenaed internal company documents revealed that executives pursued acquisitions with the explicit intent to raise the price in consolidated niche drug markets with few or no competitors.⁴⁰ Retrophin acquired tiopronin because it was “woefully underpriced;” Valeant admitted to a “patient as hostage” model of drug pricing, focused on acquiring drugs for rare diseases and raising the price dramatically.⁴¹

Other studies demonstrate that targeted acquisition of non-patent-protected products is a common business strategy. A 2017 study of market consolidation found that in 2008, nearly half (546 of 1120 drugs) were at duopoly or near-monopoly levels of competition, and by 2013, the average level of market concentration for the cohort remained at duopoly-level.⁴² There was also a noticeable uptick in mergers and acquisitions among generic manufacturers from 2014 to 2016, increasing from twenty-two deals to forty-two deals.⁴³

C. FDA UNAPPROVED DRUGS INITIATIVE

From 2006 to 2015, the FDA launched the UDI, which led to the unintended consequence of increased prices among older drugs that were no longer protected by any patent-based exclusivities. The program sought to encourage testing of drugs marketed in the United States prior to 1938 that were grandfathered into the market and had never undergone official FDA

37. Press Release, U.S. Fed. Trade Comm’n, FTC Sues Ovation Pharmaceuticals for Illegally Acquiring Drug Used to Treat Premature Babies with Life-Threatening Heart Condition (Dec. 16, 2008), <https://www.ftc.gov/news-events/press-releases/2008/12/ftc-sues-ovation-pharmaceuticals-illegally-acquiring-drug-used>.

38. See Gupta et al., *supra* note 34, at 1008 tbl.1. Of note, the authors also observed a trend toward higher prices for acquired brand-name drugs compared to non-acquired brand name drugs, though the difference was not statistically significant. *Id.* at 1008.

39. See S. REP. NO. 114-429, at 32–73.

40. *See id.*

41. *Id.* at 45, 58.

42. See Dave et al., *supra* note 25, at 148. Duopoly levels of competition were defined as those with HHI greater than 5000. Near-monopoly levels of competition were defined as those with HHI greater than 8000. *Id.* at 146.

43. Marc-André Gagnon & Karena D. Volesky, *Merger Mania: Mergers and Acquisitions in the Generic Drug Sector from 1995 to 2016*, 13 GLOBALIZATION & HEALTH 62, 66 fig.2 (2017).

review for efficacy or safety.⁴⁴ The FDA reached out to manufacturers of the products, encouraging those interested in conducting clinical trials to conduct studies and bring the product through the formal regulatory approval process, in exchange for 3 years of market exclusivity.⁴⁵ The UDI enabled manufacturers to force competitors to stop production, creating monopoly market conditions that would facilitate dramatic price increases.

In total, thirty-four previously unapproved prescription drugs received exclusivities through the UDI.⁴⁶ In one study of the program, the average wholesale price of twenty-six drugs increased by a median of 37% over the two years prior to, and after, approval via the UDI pathway.⁴⁷ The price of certain drugs rose more dramatically; for example, vasopressin increased in price by 1138% (from \$12.83 per vial to \$158.83) and neostigmine increased in price by 531% (from \$27.74 per vial to \$175.14 per vial).⁴⁸

While the UDI contributed to higher prices for some critical drugs, it did not incentivize manufacturers to undertake important new studies of these drugs before submitting them for FDA approval. In fact, nearly 90% of the drugs approved via the UDI already had evidence-based support for their use.⁴⁹ One of those drugs, colchicine, was in widespread use in the United States since the 19th century as a treatment for gouty arthritis.⁵⁰ In 2007, URL Pharma ran a week-long trial of colchicine on 185 patients that confirmed the drug's efficacy under a new dosing regimen.⁵¹ Upon entering the market, URL Pharma forced other colchicine products off the market and raised the price by over 5000% (from \$0.09 to \$4.85 per pill).⁵² Another consequence of colchicine's dramatic price increases was that the financial burden to payers and patients often led to missed doses and relapses for patients with familial Mediterranean fever, a secondary indication for colchicine therapy.⁵³

Upon receipt of a three-year UDI exclusivity term for neostigmine in 2013, Éclat Pharmaceuticals asked the FDA via Citizen Petition to mandate market withdrawal of generic neostigmine against five other manufacturers, asserting that the neostigmine products by those manufacturers were "marketed

44. Many of these drugs were approved prior to the 1938 Federal Food, Drug, and Cosmetic Act, which mandated safety testing for the first time as a requirement of drug approval. They were grandfathered by the statute and allowed to remain on the market.

45. See sources cited *supra* note 12.

46. *Id.* at 1069.

47. *Id.* at 1069–71.

48. Philip J. Almeter et al., *U.S. Food and Drug Administration Disruption of Generic Drug Market Increases Hospital Costs*, 127 ANESTHESIA & ANALGESIA 1414, 1416 (2018).

49. See Gupta et al., *supra* note 12, at 1066.

50. Aaron S. Kesselheim & Daniel H. Solomon, *Incentives for Drug Development—The Curious Case of Colchicine*, 362 NEW ENG. J. MEDICINE 2045, 2045 (2010).

51. *Id.*

52. *Id.* at 2046; see also *Mut. Pharm. Co. v. Watson Pharm. Inc.*, No. CV 09-5700 PA, 2009 WL 3401117, at *1 (C.D. Cal. Oct. 19, 2009) (noting that the price had raised from \$9 per bottle to \$485 per bottle).

53. Wayne W. Grody & Terri Getzug, *Colchicine's Other Indication—Effect of FDA Action*, 363 NEW ENG. J. MEDICINE 2267, 2267–68 (2010).

with incomplete labeling that may raise potential safety risks.”⁵⁴ With competitor products removed from the marketplace, Éclat and its parent company Flamel Technologies subsequently increased the price of its neostigmine product on two occasions between 2013 and 2015.

The UDI ended in 2015 without evidence that the program had been successful in generating new knowledge about the drugs approved via the initiative.⁵⁵

II. DECREASED DRUG SUPPLY

Apart from niche markets and consolidation, sudden drug shortages can also lead to market conditions that enable generic price increases. In times of shortage, demand remains constant as supply diminishes; such conditions allow manufacturers to increase prices as shortages begin and persist, often keeping prices elevated even after the shortage resolves. Other settings, such as market discontinuation of a competitor with sizeable market share, can lead to shortages of other drugs in the short-term, as supply can no longer keep up with demand.

A. DRUG SHORTAGES

Drug shortages are defined by the FDA as “situation[s] in which the total supply of all clinically interchangeable versions of an FDA-regulated drug [are] inadequate to meet the current or projected demand at the patient level.”⁵⁶ In 1999, the FDA introduced the Drug Shortage Staff program—a group within the FDA’s Center for Drug Evaluation and Research (CDER) charged with detecting potential and actual drug shortages in the United States.⁵⁷ In 2013, the FDA drafted a “Strategic Plan for Preventing and Mitigating Drug Shortages” as part of a congressional mandate within the FDA Safety and Innovation Act (FDASIA).⁵⁸ As part of the Strategic Plan, the FDA began

54. ÉCLAT PHARMACEUTICALS LLC, No. FDA-2013-P-1000, CITIZEN PETITION REQUESTING THAT THE COMMISSIONER OF FOOD AND DRUGS TAKE IMMEDIATE ENFORCEMENT ACTION AGAINST UNAPPROVED DRUG PRODUCTS BEING ILLEGALLY MARKETED AS AN ALTERNATIVE TO AN EXISTING FDA-APPROVED DRUG PRODUCT, AND TO SECURE THE REMOVAL OF THESE PRODUCTS FROM THE MARKET 1 (Aug. 13, 2015), <https://www.fdanews.com/ext/resources/files/archives/10113-01/09-05-13-EclatPetition.pdf>.

55. Other approvals and regulatory exclusivities have had the effect of pushing and keeping competitors off the market. For instance, Sun Pharma, the sole manufacturer of the drug dichlorphenamide (initially approved in 1958), received orphan drug approval and seven years of market exclusivity for use in treating periodic paralysis, thereby precluding manufacturers from producing generic versions of the drug for other uses, including glaucoma. *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=314210> (last visited Feb. 11, 2020).

56. Rachel B. Morgan, *Drug Shortages: Preserving the Drug Supply*, NAT’L CONF. ST. LEGISLATURES (Nov. 7, 2013), <http://www.ncsl.org/research/health/drug-shortages-preserving-the-drug-supply.aspx>.

57. Valerie Jensen, *Preventing and Mitigating Drug Shortages—FDA’s and Manufacturers’ Roles*, U.S. FOOD & DRUG ADMIN. (Mar. 21, 2016), <https://www.fda.gov/downloads/drugs/newsevents/ucm493617.pdf>.

58. U.S. FOOD & DRUG ADMIN., STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES (2013), <https://www.fda.gov/media/86907/download>.

formally tracking and publishing lists of drug shortages to better inform patients and prescribers.⁵⁹ Manufacturers are now required to report shortages to the FDA,⁶⁰ and the American Society of Health-Systems Pharmacists (ASHP) also maintains an updated list of drug shortages.⁶¹ While the FDA can offer regulatory guidance to facilitate needed drug production in times of shortage, the agency cannot compel a pharmaceutical manufacturer to resume production of a drug, increase production of a drug, or alter patterns of drug distribution.⁶²

From 2005 to 2011, shortages of generic drugs more than quadrupled (from 61 to more than 250 drugs),⁶³ while the number of drugs affected by shortages nearly tripled between 2007 and 2012 (154 to 456).⁶⁴ This trend may be slowing: the FDA reported that the number of new and persisting drug shortages has stabilized over the last five years.⁶⁵ The FDA attributes this reduction in drug shortages to its prevention and mitigation strategies.⁶⁶

Shortages among generic drugs are associated with drug price increases. A study of 917 drugs in shortage from December 2015 to December 2016 found price increases of 7.3% before the shortage and 16% after the shortage.⁶⁷ Niche market drugs in shortage exhibited greater price increases than those in more competitive markets: market prices increased 12.1% pre-shortage and 27.4% post-shortage, as compared to 2.5% pre-shortage growth and 4.8% post-shortage growth for drugs with more than three manufacturers.⁶⁸ Another study of twenty-nine generic injectable drug shortages resolved between 2010 and 2015 found that the change in quarterly average sales price increased substantially after the shortage began.⁶⁹ After six months, there was a 22.6% increase and after one year, a 33.7% increase, as compared to decreases of 7% six months and 26.2% one year pre-shortage.⁷⁰

The duration of drug shortages also impacts the severity of price increases. In a study of 309 drugs in shortage from 2008 to 2014, researchers

59. *Id.* at 18–19.

60. *Drug Shortages Infographic*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm441579.htm> (last updated Oct. 22, 2019).

61. *Drug Shortages List*, AM. SOC'Y OF HEALTH-SYS. PHARMACISTS, <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages> (last visited Apr. 15, 2020).

62. See Jensen, *supra* note 58.

63. U.S. FOOD & DRUG ADMIN., U.S. DEP'T HEALTH & HUMAN SERVS., REPORT ON DRUG SHORTAGES FOR CALENDAR YEAR 2017 2 (2018) [hereinafter REPORT ON DRUG SHORTAGES FOR CALENDAR YEAR 2017]; U.S. FOOD & DRUG ADMIN., U.S. DEP'T HEALTH & HUMAN SERVS., REPORT ON DRUG SHORTAGES FOR CALENDAR YEAR 2016 2 (2017).

64. U.S. GOV'T ACCOUNTABILITY OFF., GAO-14-194, DRUG SHORTAGES: PUBLIC HEALTH THREAT CONTINUES, DESPITE EFFORTS TO HELP ENSURE PRODUCT AVAILABILITY 13 (2014).

65. See REPORT ON DRUG SHORTAGES FOR CALENDAR YEAR 2017, *supra* note 63, at 3 fig.1.

66. *Id.* at 1.

67. See Hernandez et al., *supra* note 10, at 74.

68. *Id.*

69. P. Hur et al., *Generic Injectable Shortages and Trends in Average Sales Price in the United States*, 19 VALUE IN HEALTH A4, A4 (2016).

70. *Id.*

found that as shortages persisted, prices continued to increase in a stepwise fashion.⁷¹ As compared to drugs without shortages, median price increases for drugs with shortages were 6% for a shortage duration lasting less than 6 months, 10.9% for a shortage duration lasting 6 to 12 months, 14.2% for a shortage duration lasting 12 to 18 months, and 14% for shortage duration lasting greater than 18 months.⁷²

Price increases during the shortage period are concerning, not just because they increase costs during that time period, but also because price increases commonly persist well after the shortage is resolved. A study of inpatient Medicare Part B generic and brand-name drugs in a shortage found a 4.3% quarterly price increase during a shortage and 4.1% increase in the post-shortage period, as compared to a 0.5% reduction in price growth pre-shortage.⁷³ According to the analysis, drugs in shortage had 2150% greater price growth than other readily available products.⁷⁴

In the past two years, there have been several notable price increases associated with generic injectable drug shortages. Injectable opioids have been in chronic shortage after Pfizer, the dominant manufacturer, reduced production in the wake of the opioid epidemic.⁷⁵ Other notable injectable drugs that have faced recent shortage and price increases include the intravenous drugs diltiazem, potassium chloride, ondansetron, and cefepime. Unforeseen disruptions to manufacturing can also limit availability of generic products. In September 2017, destruction of generic manufacturing facilities in Puerto Rico during Hurricane Maria resulted in shortages of intravenous saline infusions.⁷⁶

Prevention of drug shortages therefore remains a key tool for preserving low generic drug prices. However, it can be challenging to pinpoint the reasons for a shortage, which may be multifactorial.⁷⁷ For example, even the UDI program appears to have contributed to drug shortages during the program's existence.⁷⁸ One study exploring the causes of shortages found that three-in-four shortages with a known cause related to manufacturing issues, particularly raw material acquisition and manufacturing delays.⁷⁹ Generics are most

71. Chintan V. Dave et al., *Predictors of Drug Shortages and Association with Generic Drug Prices: A Retrospective Cohort Study*, 21 VALUE IN HEALTH 1286, 1288 (2018).

72. *Id.* at 1289 tbl.3.

73. See Alevizakos et al., *supra* note 10, at 1554.

74. *Id.*

75. Casey Ross, *Hospitals Are Confronting a New Opioid Crisis: An Alarming Shortage of Pain Meds*, STAT (Mar. 15, 2018), <https://www.statnews.com/2018/03/15/hospitals-opioid-shortage/>.

76. Chana A. Sacks et al., *The Shortage of Normal Saline in the Wake of Hurricane Maria*, 178 J. AM. MED. ASS'N INTERNAL MED. 885, 885 (2018).

77. Erin R. Fox et al., *ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems*, 66 AM. J. HEALTH-SYS. PHARMACY 1399, 1400–02 (2009); Rob Stein, *Shortages of Key Drugs Endanger Patients*, WASH. POST (May 1, 2011), https://www.washingtonpost.com/national/shortages-of-key-drugs-endanger-patients/2011/04/26/AF1aJJVF_story.html.

78. See Gupta et al., *supra* note 12, at 1072. The median shortage duration in the two years before and after voluntary approval or UDI action increased from 31 days (IQR = 0-339) to 217 days (IQR = 0-406), though due to the small sample size, the finding was just below the threshold of significance ($p=0.053$). *Id.*

79. See Dave et al., *supra* note 71, at 1288.

susceptible to manufacturing disruptions in cases of more than 90% single-source manufacturing and sole source raw materials.⁸⁰ Of the 117 drug shortages reported in 2012, the FDA identified a variety of reasons: manufacturing issues (37%), raw material unavailability (27%), and delay and capacity issues (27%) were the major causes.⁸¹ Other less common causes included increased demand (5%), loss of manufacturing site (2%), and discontinuation (2%).⁸² A 2013 analysis of generic injectable drugs found similar justifications for shortages.⁸³

Certain characteristics of drugs also raise the risk of a shortage. Perhaps the single greatest predictor of a drug's predisposition to shortage is the product's formulation type. Generic injectable drugs appear to be disproportionately affected by shortages. A recent report found that, as compared to tablets, solutions and extended-release capsules were more likely to be associated with drug shortages.⁸⁴ According to the American Society of Healthcare-System Pharmacists, in July 2018, there were 174 generics in shortage and 137 of these drugs (78.7%) were injectable.⁸⁵ In March 2019, there were 226 generics in shortage and 155 of these drugs (68.6%) were injectable.⁸⁶ The FDA has confirmed that "a high percentage of drug shortages have been, and continue to be, sterile injectables, including chemotherapy, anesthesia, and other acute drugs."⁸⁷

Another reliable predictor of shortage was the generic drug's pre-shortage price. When compared to medium- and high-priced generic drugs, low-priced drugs had a greater risk of drug shortages.⁸⁸ This study did not find an association between risk of shortage and market competition levels or market size, respectively.⁸⁹ This finding suggests that factors that may exacerbate the price increases associated with shortage—such as small market size and low competition levels—may not be useful in predicting the likelihood of impending shortage.

Among the drugs listed in Table 1, benazepril/HCTZ, cycloserine, dextroamphetamine, digoxin, divalproex, doxycycline, epinephrine autoinjector, indomethacin, mechlorethamine, and penicillamine have appeared on the FDA's drug shortage list at some point since 2016.

80. Erin R. Fox, Remarks at the Federal Trade Commission: Understanding Competition in Prescription Drug Markets Workshop: Medication Access—Perspective from a Purchaser (Nov. 8, 2017).

81. See Jensen, *supra* note 57.

82. *Id.*

83. See Morgan, *supra* note 56.

84. See Dave et al., *supra* note 71, at 1288. Odds ratio of 1.67 for generic injectable drugs (95% CI 1.00-2.79) and 2.64 for generic extended-release capsules (95% CI 1.58-4.42). *Id.*

85. See AM. SOC'Y OF HEALTH-SYS. PHARMACISTS, *supra* note 61.

86. *Id.*

87. See U.S. FOOD & DRUG ADMIN., *supra* note 60.

88. Dave et al., *supra* note 71, at 1288.

89. *Id.*

B. MARKET WITHDRAWALS

Companies must notify the FDA six months before permanently discontinuing drug products that are “life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition.”⁹⁰ According to the FDA, among all drug shortages with known explanations, shortages due to product discontinuations were low in 2012 (7%).⁹¹

Market withdrawals can impact pricing. Sodium nitroprusside was FDA-approved in 1974 as a potent, rapid acting antihypertensive agent; patents covering the drug expired in 1981,⁹² and two manufacturers entered the market within the next year.⁹³ The brand-name manufacturer, Hoffman-La Roche, voluntarily withdrew its product from the market in September 1996, leaving only three sodium nitroprusside products on the market.⁹⁴ From 2008 to 2011, Abbott and Teva produced the only two sodium nitroprusside products, and by 2012, Teva ceased manufacture of its generic, leaving Abbott’s product as the sole marketed product.⁹⁵ In December 2013, the drug was sold to Marathon Pharmaceuticals, which sold it to Valeant in February 2015, along with other drugs,⁹⁶ for \$350 million.⁹⁷ That day, Valeant tripled the price from \$2148 to \$8808 per ten, two milliliter vials.⁹⁸

Market withdrawals may also have the effect of creating shortages of drugs within the same therapeutic class.⁹⁹ For example, Merck’s anthelmintic agent thiabendazole was first approved in 1967 to treat gastrointestinal

90. 21 C.F.R. § 600.82 (2020).

91. See Morgan, *supra* note 56.

92. *Original NDA and Original BLA Approvals September 1981*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process&rptName=2&reportSelectMonth=9&reportSelectYear=1981&nav> (last visited Apr. 15, 2020).

93. U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 3-158 (3d ed. 1982).

94. Hoffmann-La Roche, Inc., et al., 61 Fed. Reg. 40,649 (Aug. 5, 1996) (withdrawing approval of 87 new drug applications, 18 abbreviated antibiotic drug applications, and 103 abbreviated new drug applications); U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 3-470 (17th ed. 1997); U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 3-449 (16th ed. 1996).

95. Bracco Diagnostics et al., 78 Fed. Reg. 43,210 (July 19, 2013) (withdrawing approval of fifty-two new drug applications and seventy-seven abbreviated new drug applications); U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 6-301 (32d ed. 2012).

96. *Dems Seek Info on Valeant Drug Price Spikes*, MOD. HEALTHCARE (Aug. 15, 2015, 1:00 AM), <https://www.modernhealthcare.com/article/20150815/NEWS/150819923>.

97. Joseph Walker, *Revolt Against Sky-High Drug Prices Prompts a Pioneer to Cash Out*, <https://www.wsj.com/articles/bipartisan-backlash-on-drug-prices-prompts-one-company-to-cash-out-1493754978> (last updated May 2, 2017, 11:59 PM).

98. See S. REP. NO. 114-429, at 6 tbl.1 (2016).

99. See Alpern et al., *supra* note 18, at 1860.

infections like tapeworm and hookworm.¹⁰⁰ By 1974, Janssen Pharmaceuticals began manufacturing a second-in-class therapeutic alternative, mebendazole.¹⁰¹ Generic entry occurred for mebendazole in 1995, and in 1996, SmithKline Beecham obtained approval for a third product, albendazole, with the same mechanism of action.¹⁰² When thiabendazole fell out of use because of frequent and severe side effects,¹⁰³ generic mebendazole and brand-name albendazole became the primary treatments for combating these soil-transmitted helminths. From 2007 to 2010, mebendazole and albendazole were both sole-source products: Teva produced mebendazole and GlaxoSmithKline—a corporate descendant of SmithKline Beecham—produced albendazole.¹⁰⁴ In 2010, GlaxoSmithKline sold albendazole’s marketing rights to Amedra Pharmaceuticals, and a year later, Teva Pharmaceuticals discontinued mebendazole for business reasons.¹⁰⁵ This left albendazole as the only anthelmintic product on the market. From 2010 to 2013, Amedra leveraged its market position to increase the price of albendazole from \$5.92 to \$119.58 per day (over 2000%).¹⁰⁶

III. ANTICOMPETITIVE PRACTICES

In addition to high drug prices arising from niche markets, consolidations, and decreased drug supply, manufacturers can engage in anticompetitive practices that enable price increases. For example, to sustain price increases in the generic market, some generic manufacturers have used their market positions to negotiate exclusive deals with payors that preclude coverage of competitors.¹⁰⁷ For its extended-release formulation of dextroamphetamine (a drug first FDA-approved in 1975), Shire Pharmaceuticals signed contracts with insurers Humana and UnitedHealthcare mandating that the insurers cover their product only.¹⁰⁸ Mylan Pharmaceuticals used a similar tactic to sell its epinephrine auto-injector (EpiPen) anaphylaxis treatment (a drug-device

100. *Drugs@FDA: FDA-Approved Drugs*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=016096> (last visited Apr. 15, 2020).

101. See U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 3-200 (17th ed. 1997).

102. *Id.*

103. David I. Grove, *Treatment of Strongyloidiasis with Thiabendazole: An Analysis of Toxicity and Effectiveness*, 76 TRANSACTIONS ROYAL SOC’Y OF TROPICAL MED. & HYGIENE 114, 114 (1982).

104. See U.S. FOOD & DRUG ADMIN., U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, (27th ed. 2007); U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (28th ed. 2008); U.S. DEP’T HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (29th ed. 2009); U.S. DEP’T HEALTH & HUMAN SERVS. APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (30th ed. 2010).

105. See Alpern et al., *supra* note 18, at 1860.

106. *Id.*

107. Charles Ornstein & Katie Thomas, *Take the Generic, Patients Are Told. Until They Are Not.*, N.Y. TIMES (Aug. 6, 2017), <https://www.nytimes.com/2017/08/06/health/prescription-drugs-brand-name-generic.html>.

108. See *id.*

combination containing epinephrine, which was first synthesized in 1904)¹⁰⁹; contracts with school districts at discounted prices precluded districts from purchasing rival epinephrine products.¹¹⁰ Some manufacturers negotiate deals with payers that preclude competitor coverage through bundling of rebates. In 2016, for example, Shire Pharmaceuticals launched Xiidra, an ophthalmic solution for dry eye containing cyclosporine (a drug first FDA-approved in 1983). After Shire launched Xiidra, Allergan—the first manufacturer of ophthalmic cyclosporine—made deals with Medicare Part D plans that foreclosed Xiidra from entering the market.¹¹¹ Finally, restricted distribution systems also limit competition by preventing potential competitors from obtaining samples they might need to do the necessary tests to earn FDA approval, such as occurred with Turing’s Daraprim Direct program (for the drug pyrimethamine, first used clinically in 1953).¹¹²

Forty-four state attorney generals brought antitrust litigation, with claims relating to a number of generic drugs and involving several generic pharmaceutical manufacturers.¹¹³ The complaint alleges collusion by generic manufacturers in two ways: agreements to divide the market geographically, and agreements to maintain or raise prices in coordination—in some cases on the same day.¹¹⁴ For example, on April 4, 2014, Teva, Mylan, Actavis, Lupin, Novartis’ Sandoz, Taro Pharmaceuticals, and others raised the price of twenty-two generic drugs, including the antibiotic cephalexin (+90–185%), the antifungal ketoconazole (+110%) and the non-steroidal anti-inflammatory diflunisal (+182%).¹¹⁵ Teva was reported to have colluded with “every significant competitor” via phone or text from 2013–2014.¹¹⁶

Teva Pharmaceuticals, in particular, made several dramatic one-day price increases. For instance, on July 3, 2013, Teva allegedly colluded to raise the price of twenty-one drugs, including the overactive bladder treatment oxybutynin chloride (+1500%); the antifungal nystatin (+1570%); and the antihypertensive nadolol (+2762%).¹¹⁷ In the summer of 2013 alone, the lawsuit estimates that antitrust tactics netted Teva an extra \$937 million in

109. M.R. Bennett, *One Hundred Years of Adrenaline: The Discovery of Autoreceptors*, 9 CLINICAL AUTONOMIC RES. 145, 145 (1999).

110. Ike Swetlitz & Ed Silverman, *Mylan May Have Violated Antitrust Law in Its EpiPen Sales to Schools*, *Legal Experts Say*, STAT (Aug. 25, 2016), <https://www.statnews.com/2016/08/25/mylan-antitrust-epipen-schools/>.

111. David Balto, *Drug “Rebate Walls” Should Be Dismantled by the FTC’s Antitrust Arm*, STAT (Dec. 4, 2018), <https://www.statnews.com/2018/12/04/ftc-dismantle-drug-rebate-walls/>.

112. Michael A. Carrier et al., *Using Antitrust Law to Challenge Turing’s Daraprim Price Increase*, 31 BERKELEY TECH. L.J. 1379, 1381 (2016).

113. *See, e.g., In re Generic Pharma. Pricing Antitrust Litig.*, 368 F. Supp. 3d 814 (E.D. Pa. 2019); *Complaint, Connecticut v. Teva Pharma. USA*, 2019 WL 2126100 (D. Conn. May 10, 2019) (No. 3:19-cv-00710-MPS).

114. *Complaint, supra* note 113, at 2.

115. *Id.* at 224, 234, 237.

116. *Id.* at 35.

117. *Id.* at 182, 173, 152.

additional revenue per quarter.¹¹⁸ The lawsuit notes that, in part because of such activity, between July 2013 and July 2014, “[t]he prices of more than 1,200 generic medications increased an average of 448 percent.”¹¹⁹ The lawsuit also revealed the casual nature of the inter-generic collusion. Companies had their own lingo, calling the market the “sandbox”—where it was implied manufacturers would “play nice.”¹²⁰ As manufacturers divided the market by territory, they made sure that each company got its “fair share.”¹²¹ Deals were negotiated by phone, email, and text, and at industry functions. Sales representatives would attend “girls nights out”—ostensibly events for women in the industry—and discuss sensitive information, according to the complaint.¹²²

Such anticompetitive practices undermine efforts to lower generic prices through greater generic manufacturer entry into niche drug markets. These examples demonstrate that sustained antitrust oversight may be necessary to ensure robust generic competition. In the coming years, maintaining generic competition may also be more difficult because fewer manufacturers are willing to produce low-cost generic drugs and the generic pharmaceutical industry has consolidated.¹²³

IV. POLICY SOLUTIONS

As seen in Figure 1, to ensure the sustainability of reasonable prices for generic drugs, it is critical to understand the interconnected nature of the factors influencing generic drug price increases. Consolidation of drug markets via mergers and acquisitions (Factor 1) reduces the number of manufacturers and can create niche drug market conditions (Factor 2). In such markets, there is a monopoly (or near-monopoly) on manufacturing, meaning that the drug may be prone to shortage (Factor 3) due to limited raw material availability, manufacturing plant closures, or safety recalls. Mergers and acquisitions (Factor 1) that consolidate market share into the hands of a few large manufacturers can also make those drug markets prone to shortage (Factor 3). This may be due to reduced production, discontinuation of a product line, or the process of shifting manufacturing to new facilities, or differential access to raw materials.¹²⁴ Finally, regulatory policy decisions (Factor 4) can interact with any of the other three domains. The UDI created monopolies and led to greater rates of shortages. The FDA is also the gatekeeper for new generic

118. *Id.* at 211.

119. *Id.* at 50.

120. *Id.* at 41.

121. *Id.* at 33.

122. *Id.* at 32.

123. Ravi Gupta et al., *Generic Drugs in the United States: Policies to Address Pricing and Competition*, 105 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 329, 331–32 (2019); see also Ernst R. Berndt et al., *The Landscape of U.S. Generic Prescription Drug Markets, 2004–2016* 3 (Nat’l Bureau of Econ. Research, Working Paper No. 23640, 2017), <https://www.nber.org/papers/w23640.pdf>.

124. See Gagnon & Volesky, *supra* note 43, at 67.

manufacturers seeking to enter the market, compete on prices, or help resolve shortages.

FIGURE 1. INTERPLAY OF FACTORS INCREASING THE RISKS FOR CHANGES IN GENERIC DRUG PRICES

4 Factors That Enable Generic Price Spikes

- 1) Niche Drug Markets
- 2) Mergers & Acquisitions
- 3) Drug Shortage
- 4) Regulatory Policy

- FDA Generic Approval Times
- Unapproved Drugs Initiative



The FDA now expedites review of ANDA applications for drugs with three or fewer manufacturers, an acknowledgment that niche drugs that are vulnerable to pricing strategies could limit patient access to important medications.¹²⁵ The FDA also established a semi-annual list of “Off-Patent, Off-Exclusivity Drugs without an Approved ANDA” to stimulate competition in the generic drug marketplace and offers to hold early-stage meetings with generic manufacturers seeking to enter these markets.¹²⁶

Ensuring robust generic drug markets and reasonable prices will involve policy action in a number of areas: (1) stimulating generic competition; (2) preventing and mitigating drug shortages; (3) generic drug importation; (4) non-profit generic manufacturing; (5) greater antitrust enforcement; (6) federal initiatives; and (7) state-based initiatives.

A. STIMULATING GENERIC COMPETITION

Fostering competition in the generic drug marketplace will be critical to limiting the potential for generic drug shortages and price increases. This will require a strong pipeline of generic drug applications coupled with efficient FDA review of those applications.

Until recent years, generic drug applications could take about three years on average to be reviewed by the FDA.¹²⁷ The FDA’s capacity to review

125. Press Release, U.S. Food & Drug Admin., FDA Tackles Drug Competition to Improve Patient Access (June 27, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm564725.htm>.

126. *List of Off-Patent, Off-Exclusivity Drugs Without an Approved Generic*, U.S. FOOD & DRUG ADMIN. (last updated Dec. 13, 2019), <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/list-patent-exclusivity-drugs-without-approved-generic>.

127. THE PEW CHARITABLE TRUSTS, *supra* note 17. Note: When assessing the likelihood of market competition after price increases on its recently-acquired drugs like pyrimethamine, Turing sought to exploit FDA’s three-year delay in ANDA approvals. *See* S. REP. NO. 114-429, at 35 (2016).

generic drug applications markedly increased after 2015 with the passage of the Generic Drug User Fee Amendment (GDUFA), which established a system of user fees to subsidize the FDA's generic drug review process.¹²⁸ In 2014, the FDA released guidance expediting applications for generic drugs in critical need and with the potential to mitigate shortages.¹²⁹ As part of this initiative, the FDA prioritized "first generics" for which there is no generic approved, "sole-source" drugs with only one FDA-approved supplier, and drugs in shortage.¹³⁰ Generic review times have dropped to less than a year on average, and GDUFA was reauthorized under the FDA Reauthorization Act (FDARA) of 2017 (GDUFA II). There may be additional opportunities to improve the generic drug application process; for example, ANDAs have historically taken three to four review cycles before the FDA approves the application.¹³¹ For new drug applications, by comparison, 88% were approved on the first review cycle in 2017.¹³² GDUFA II created a pre-ANDA review program to address this inefficiency.

Besides prioritizing "first generics" for "sole-source" drugs, the FDA introduced the Drug Competition Action Plan in June 2017 to promote greater generic competition in niche drug markets. As noted previously, the program expedites regulatory review for generic drug markets consisting of three or fewer manufacturers.¹³³ Another provision of FDARA focused on expediting the review of so-called "competitive generic therapies"—products that lack significant competition.¹³⁴ Products fitting this description would be eligible for new 180-day periods of generic market exclusivity, based on the assumption that artificially inflated generic prices during this period would provide incentive for additional market entry, followed by more sustainable lower prices and mitigated risk of future drug shortages.¹³⁵ The first competitive generic therapy designation was awarded in August 2018.¹³⁶

128. *Id.* at 26.

129. *Manual of Policies and Procedures: Prioritization of the Review of Original ANDAs, Amendments, and Supplements*, U.S. FOOD & DRUG ADMIN. (June 27, 2017), <https://www.fda.gov/files/about%20fda/published/Prioritization-of-the-Review-of-Original-ANDAs--Amendments--and-Supplements.pdf>.

130. *Id.*

131. *Generic Drug User Fee Amendments: Accelerating Patient Access to Generic Drugs: Hearing on Examining Generic Drug User Fee Amendments, Focusing on Accelerating Patient Access to Generic Drugs Before the S. Comm. on Health, Educ., Labor, and Pensions*, 114th Cong. 6 (2016) (statement of Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration).

132. Patrick Frey, Remarks at the Food & Drug Admin. & Ctr. for Medicare and Medicaid Servs. Summit (Dec. 5, 2017), <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM587690.pdf>.

133. See U.S. Food & Drug Admin., *supra* note 125.

134. U.S. FOOD & DRUG ADMIN., U.S. DEP'T HEALTH & HUMAN SERVS., COMPETITIVE GENERIC THERAPIES: GUIDANCE FOR INDUSTRY 3 (2019), <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm631401.pdf>.

135. *Id.* at 1.

136. Press Release, U.S. Food & Drug Admin., FDA Approves First Generic Drug Under New Pathway Aimed at Enhancing Market Competition for Sole Source Drugs (Aug. 8, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm616167.htm>.

B. PREVENTING AND MITIGATING DRUG SHORTAGES

The FDA works closely with manufacturers to address the underlying causes of shortages to mitigate the public health risk associated with these events. In addressing manufacturing and product quality issues contributing to shortage, the FDA will often evaluate the process of manufacturing the drug, including quality standards of the manufacturing facility.¹³⁷ According to the FDA, manufacturing problems can range from the wrong expiration date on a package to contamination or sterility issues.¹³⁸ The FDA also convenes other generic manufacturers producing the drug to determine if they have the capacity and the willingness to increase short-term production to help alleviate shortages.¹³⁹

As part of the FDA's 2013 "Strategic Plan for Preventing and Mitigating Drug Shortages,"¹⁴⁰ the agency offered strategies to strengthen its response after the onset of shortage. Strategies to mitigate drug shortages include improved data collection and response tracking databases, close work with manufacturers on remediation efforts that can rapidly alleviate shortages, and best practices to avoid future shortages.¹⁴¹ The FDA is also working to identify ways to promote and sustain manufacturing improvements, to detect early warning signals of supply chain disruption, and to engage stakeholders on issues relating to drug shortages.¹⁴² In July 2018, the FDA established a Drug Shortages Task Force to explore long-term solutions the agency can take to prevent shortages.¹⁴³ According to the agency, the Task Force works closely with pharmaceutical and health care industry representatives, patient representatives, Congress, and other federal partners while soliciting public input through stakeholder meetings.¹⁴⁴ Most recently, in October 2019 the FDA's Drug Shortages Task Force released a report titled "Drug Shortages: Root Causes and Possible Solutions," which offers three recommendations: (1) improved understanding causes and costs of shortages; (2) creation of a ratings system for quality management of individual manufacturing facilities to incentivize more reliable production; and (3) payment incentives, including private sector contracting, to ensure a steady supply of essential drugs.¹⁴⁵

137. See Jensen, *supra* note 57.

138. *Frequently Asked Questions About Drug Shortages*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages> (last updated July 5, 2018).

139. See Jensen, *supra* note 57.

140. See U.S. FOOD & DRUG ADMIN., *supra* note 58.

141. *Id.* at 4–6.

142. *Id.*

143. Press Release, Statement by FDA Commissioner Scott Gottlieb, M.D., on Formation of a New Drug Shortages Task Force and FDA's Efforts to Advance Long-Term Solutions to Prevent Shortages (July 12, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613346.htm>.

144. *Id.*

145. U.S. FOOD & DRUG ADMIN., DRUG SHORTAGES: ROOT CAUSES AND POTENTIAL SOLUTIONS 7–9 (2019), <https://www.fda.gov/media/132059/download>.

C. GENERIC DRUG IMPORTATION

In December 2019, the U.S. Department of Health and Human Services (HHS) proposed a rule to allow certain prescription drugs to be imported from Canada.¹⁴⁶ According to HHS, the rule is designed to permit importation "under specific conditions that ensure the importation poses no additional risk to the public's health and safety."¹⁴⁷ The rule would give states and select non-federal government entities the ability to submit importation proposals to the FDA for review and authorization.¹⁴⁸ Importation programs would be eligible for co-sponsorship with a pharmacist, a wholesaler, or another state or non-federal governmental entity.¹⁴⁹

Besides this HHS rule proposal to allow Canadian drug importation, other recent attempts have been made to legalize drug importation through federal law-making. Several recent bills introduced in Congress seek to expand the FDA's ability to enable well-regulated importation of prescription drugs from outside the United States, particularly in the case of shortages or extreme price increases. In January 2019, Senator Bernie Sanders (I-VT) and Representatives Elijah Cummings (D-MD) and Ro Khanna (D-CA) introduced the Affordable and Safe Prescription Drug Importation Act, which would allow importation of any generic prescription drug for which the U.S. price is higher than the average price in Canada, the United Kingdom, Germany, France, and Japan and for which federal officials have determined the price is excessively high.¹⁵⁰ A related amendment had been introduced in January 2017 by Senators Sanders and Amy Klobuchar (D-MN), seeking to allow U.S. citizens to purchase prescription medications from approved Canadian pharmacies.¹⁵¹ Importation of generic drugs could dramatically lower drug costs in the short-term.¹⁵² The threat of importation could also deter strategies such as those used by Turing and Valeant to raise prices for off-patent drugs in the United States.¹⁵³ Yet skepticism about drug importation persists: four recent FDA

146. Press Release, Dep't of Health & Hum. Servs., Trump Administration Takes Historic Steps to Lower U.S. Prescription Drug Prices (Dec. 19, 2019) <https://www.hhs.gov/about/news/2019/12/18/trump-administration-takes-historic-steps-to-lower-us-prescription-drug-prices.html>.

147. *Id.*

148. *Id.*

149. *Id.*

150. Affordable and Safe Prescription Drug Importation Act, S. 97, 116th Cong. (2019); *see also* Press Release, Bernie Sanders, Sweeping Plan to Lower Drug Prices Introduced in Senate and House (Jan. 10, 2019), <https://www.sanders.senate.gov/newsroom/press-releases/sweeping-plan-to-lower-drug-prices-introduced-in-senate-and-house>.

151. Affordable and Safe Prescription Drug Importation Act, S. 469, 115th Cong. (2017); *see also* Jeff Stein, *How Cory Booker Went from Progressive Hero to Traitor in Under 2 Days*, VOX (Jan. 14, 2017, 9:50 AM), <https://www.vox.com/policy-and-politics/2017/1/14/14262732/cory-booker-senate-democrats>.

152. *See* Thomas J. Bollyky & Aaron S. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* (Brookings Inst., Hutchins Ctr. on Fiscal & Monetary Policy at Brookings, Working Paper No. 29, 2017).

153. Matthew Cohen et al., *Policy Options for Increasing Generic Drug Competition Through Importation*, HEALTH AFF. BLOG (Jan. 7, 2019), <https://www.healthaffairs.org/doi/10.1377/hblog20190103.333047/full/>.

Commissioners expressed concern, noting that the agency could never be certain of the safety of imported drugs.¹⁵⁴

Realizing price reduction from safe importation should be attainable under current regulatory standards. The United States already imports 40% of its “finished product” pharmaceuticals from overseas.¹⁵⁵ An estimated 80% of active ingredients are imported as well,¹⁵⁶ though these drug products are generally repackaged and sold by U.S.-based drug manufacturers.¹⁵⁷ In the absence of federal action on wholesale importation, a new bill from Senators Charles Grassley (R-IA) and Klobuchar, the Preserve Access to Affordable Generics Act, seeks to allow individuals to import drugs from Canada for personal use.¹⁵⁸ Although such wholesale importation of drugs is not currently permitted, the FDA does sanction limited importation during emergency shortages.¹⁵⁹ Over the past decade, the agency has allowed temporary importation from Canada, Ireland, Australia, and the United Kingdom.¹⁶⁰ Notably, a clause in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 authorizes the FDA to import drugs from Canada, but that provision has never been invoked.¹⁶¹

Large-scale importation, if allowed, could offer an important counterweight to prevent companies from predatory price increases on certain sole-sourced U.S. drugs. In July 2018, the FDA announced the formation of a working group to explore importation options for such “sole-source medicines with limited patient availability, but no blocking patents or exclusivities.”¹⁶² A 2018 study found that nearly half of the forty-four off-patent drugs made by a single U.S. manufacturer were already available from a different manufacturer in at least one of seven foreign countries with similar regulatory standards as the United States (European Union, Canada, Australia, New Zealand, Switzerland, South Africa, and Israel).¹⁶³

Importation may therefore serve an important role in deterring unreasonable price increases due to monopolies or near-monopolies on generic

154. *Id.*

155. *Id.*

156. *Id.*

157. *See id.*

158. Preserve Access to Affordable Generics Act, S. 124, 115th Cong. (2017); Press Release, Amy Klobuchar, Klobuchar, Grassley Introduce New Bipartisan Legislation to Crack Down on Pharmaceutical Pay-for-Delay Deals (Dec. 19, 2018), <https://www.klobuchar.senate.gov/public/index.cfm/2018/12/klobuchar-grassley-introduce-new-bipartisan-legislation-to-crack-down-on-anticompetitive-pay-for-delay-deals-affecting-biosimilars-as-well-as-generic-drugs>.

159. *See* Jensen, *supra* note 57.

160. *See* Cohen et al., *supra* note 153.

161. *Id.*

162. Press Release, Statement by FDA Commissioner Scott Gottlieb, M.D., on the Formation of a New Work Group to Develop Focused Drug Importation Policy Options to Address Access Challenges Related to Certain Sole-Source Medicines with Limited Patient Availability, but No Blocking Patents or Exclusivities (July 19, 2018), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-formation-new-work-group-develop-focused-drug>.

163. *See* Gupta et al., *supra* note 27, at 3–4.

drug production. While importation could lower prices for drugs facing dramatic price increases, competing factors may limit this effect. For instance, if the United States were to allow drug importation, pharmaceutical companies might simply adjust global prices, which could mitigate the cost-savings of importing drugs while reducing foreign incentives to export to the United States.¹⁶⁴ Even if foreign countries and manufacturers were willing to export drugs, differences in population size and manufacturing capacity may make long-term exportation to the United States infeasible. Canada, a country often touted as a potential source of drug importation, has an estimated population of 37 million—about 11% of the estimated U.S. population of 327 million.¹⁶⁵ Given such differences in population, the US may not be able to rely on Canadian imports to curtail long-term generic drug shortages.

D. NON-PROFIT GENERIC MANUFACTURING

New business models may also address problems with niche generic drug markets. In recent years, non-traditional generic drug manufacturers have emerged, including non-profit companies and drug compounding facilities. The first large U.S. non-profit to begin manufacturing generic drugs was Civica Rx, a consortium of four health care institutions working with the Department of Veterans Affairs to bring affordable generic products to particularly capricious and volatile markets.¹⁶⁶ Civica Rx plans to initially focus on inpatient products which may involve sterile manufacturing.

In the past few years, large hospitals—including Massachusetts General Hospital in Boston, Druid City Hospital Health System in Alabama, and others—have built compounding facilities that combine drugs with multiple active ingredients in-house, avoiding costly brand-name and generic drugs sold for the same purpose.¹⁶⁷ A similar model exists in Sweden, where

164. Aaron S. Kesselheim & Niteesh K. Choudhry, *The International Pharmaceutical Market as a Source of Low-Cost Prescription Drugs for U.S. Patients*, 148 ANNALS INTERNAL MED. 614, 617 (2008). There would be significant challenges incentivizing foreign countries to export drugs. As current FDA Commissioner Scott Gottlieb noted in 2016, drug companies that produce sole-source drugs often control global production lines as well, and they are:

“[N]ot going to simply ramp up the production lines to accommodate new demand, if it means that the drugs will be imported into the U.S. to skirt their tiered pricing. Nor will the foreign countries allow their local supply to be skimmed off, only to create local shortages of important medicines.”

Arlene Weintraub, *FDA to Consider Drug Importation in Battle Against High Drug Prices*, FORBES (July 19, 2018, 10:18 AM), <https://www.forbes.com/sites/arleneweintraub/2018/07/19/fda-to-consider-drug-importation-in-battle-against-high-drug-prices/> (internal quotation marks omitted) (quoting Dr. Scott Gottlieb).

165. Jonathon Gatehouse, *Canada's Population Tops 37 Million After Record Two-Year Surge*, CBC NEWS (June 14, 2018, 2:15 PM), <https://www.cbc.ca/news/thenational/national-today-newsletter-trump-sued-canada-population-1.4700759>.

166. See Press Release, Intermountain Healthcare, *Leading U.S. Health Systems Announce Plans to Develop a Not-for-Profit Generic Drug Company* (Jan. 18, 2018, 6:02 AM), <https://intermountainhealthcare.org/news/2018/01/leading-us-health-systems-announce-plans-to-develop-a-not-for-profit-generic-drug-company/>.

167. *A Windfall from In-House Compounding: \$900,000 Savings Projected*, PHARMACOLOGY TECH. REP. (Aug. 25, 2017), <https://www.pharmacytechnologyreport.com/Hazardous-Drugs-Handling/article/09-17/A->

the government set up a generic manufacturer (called Apoteket) to produce any unavailable drugs.¹⁶⁸ In the United States, legislators have proposed establishing government-sanctioned generic manufacturers for prescription drugs that are unaffordable or unavailable. In 2018, Senator Elizabeth Warren (D-MA) and Representative Jan Schakowsky (D-IL) introduced the Affordable Drug Manufacturing Act, which would establish an Office of Drug Manufacturing within the Department of Health and Human Services, charged with “lowering prices, increasing competition, and addressing shortages in the market for prescription drugs.”¹⁶⁹ The Office would target manufacturing in three specific cases: 1) when “no company is manufacturing the drug;” 2) when “one or two companies produce the drug, and the price has spiked or the drug is in shortage[;]” and 3) when “one or two companies produce the drug, the price is a barrier to patient access, and the drug is an ‘essential medicine’ by the World Health Organization.”¹⁷⁰ The Office’s first task would be to lower insulin prices, with a mandate to begin production of insulin within one year.

E. GREATER ANTITRUST ENFORCEMENT

Increased enforcement of anticompetitive practices by the FTC could address some of the practices that enable generic drug price increases. The FTC could also continue to scrutinize mergers and acquisitions in the generic pharmaceutical sector to protect against market consolidation in certain generic drug marketplaces. It did so in 2016, when Teva was required to divest seventy-nine generic drugs before merger with Allergan’s generic business,¹⁷¹ as well as in 2018, when it required Amneal and Impax to divest ten generic drugs before their merger.¹⁷² The Senate Finance Committee’s 2016 report on

Windfall-From-InHouse-Compounding/42386; see also *Hospital Pharmacies Step Up Compounding Efforts in Wake of Meningitis Outbreak*, WBUR NEWS (Nov. 28, 2012), <http://www.wbur.org/news/2012/11/28/mgh-pharmacy-compounding>.

168. Marc-André Gagnon, *Drug Shortages: Searching for a Cure*, 7 HEALTHCARE POL’Y 10, 15 (2012).

169. Elizabeth Warren & Jan Schakowsky, *Affordable Drug Manufacturing Act*, <https://www.warren.senate.gov/imo/media/doc/One-Pager%20-%20Affordable%20Drug%20Manufacturing%20Act1.pdf> (last visited Apr. 15, 2020). The bill was reintroduced in December 2019, accompanied by a joint report explaining how an Office of Drug Manufacturing would function and offering a list of “hundreds of examples of drugs that are potential candidates for public manufacturing under the bill.” See Press Release, Senator Elizabeth Warren and Representative Jan Schakowsky, Schakowsky, Warren Reintroduce Affordable Drug Manufacturing Act, Legislation to Radically Reduce Drug Prices through Public Manufacturing of Prescription Drugs (Dec. 20, 2019) <https://www.warren.senate.gov/newsroom/press-releases/schakowsky-warren-reintroduce-affordable-drug-manufacturing-act-legislation-to-radically-reduce-drug-prices-through-public-manufacturing-of-prescription-drugs>.

170. *Id.*

171. Press Release, U.S. Fed. Trade Comm’n., FTC Requires Teva to Divest Over 75 Generic Drugs to Settle Competition Concerns Related to its Acquisition of Allergan’s Generic Business (July 27, 2016), <https://www.ftc.gov/news-events/press-releases/2016/07/ftc-requires-teva-divest-over-75-generic-drugs-rival-firms-settle>.

172. *FTC Conditions for Amneal Merger with Impax*, PHARMA LETTER (Apr. 30, 2018), <https://www.thepharmalletter.com/article/ftc-conditions-for-amneal-merger-with-impax>.

off-patent prescription drug price increases calls on Congress to strengthen the FTC's authority to review and prevent such increases.¹⁷³

F. TAXATION

Some experts have suggested taxing drug price increases that exceed health care inflation thresholds.¹⁷⁴ This additional tax revenue would then be used to fund greater FTC oversight or go toward other initiatives aimed at lowering drug prices. A 2017 bill from Senators Sherrod Brown (D-OH) and Kirsten Gillibrand (D-NY), the Stop Price Gouging Act, was introduced to enact such a tax on drug companies.¹⁷⁵ Under the bill, drug makers would face an excise tax if their price increases exceeded the annual rise in the consumer price index for medical care.¹⁷⁶ The tax would capture between 50 and 100% of the revenue generated from such price increases, with exceptions for good cause—such as if the price is still quite low (for example, less than \$10 for a thirty-day supply), or if there are other available alternatives.¹⁷⁷ In 2019, Minnesota state legislators introduced a similar proposal.¹⁷⁸

G. GENERIC DRUG PRICE NEGOTIATION

Granting the federal government greater negotiating power in determining the price of generic products on its formularies may also curb anticompetitive pricing of pharmaceutical drugs. The Elijah E. Cummings Lower Drug Costs Now Act of 2019, which was introduced in September 2019 and passed the House in December 2019, would require the Centers for Medicare & Medicaid Services (CMS) to negotiate prices for certain drugs, including high-priced generic products.¹⁷⁹

H. STATE-BASED INITIATIVES

In the absence of federal intervention, several states have developed legislation to address the problems. However, federal pre-emption continues to limit the implementation of these efforts. In 2013, Maine passed the Pharmacy Act, allowing residents to import medications from pharmacies in Canada, the UK, New Zealand, or Australia; the law was invalidated two years later as exceeding state authority.¹⁸⁰ Vermont (2018) and Colorado (2019) ratified

173. See S. REP. NO. 114-429, at 10 (2016).

174. Dylan Scott, *Congress is Grilling Pharma CEOs. Here Are 8 Ideas for Bringing Down Drug Prices*, VOX (Feb. 26, 2019, 10:30 AM), <https://www.vox.com/policy-and-politics/2019/1/14/18176707/congress-drug-prices-hearing-pharmaceutical-ceos>.

175. Stop Price Gouging Act, S. 1369, 115th Cong. (2017). The bill was reintroduced in 2019. Stop Price Gouging Act, S. 378, 116th (2019).

176. *Id.*

177. *Id.*

178. Excess Prices Tax; Prescription Drugs, H. F. 2819, 91st Leg. (Minn. 2019).

179. Elijah E. Cummings Lower Drug Costs Now Act, H.R. 3, 116th Cong. (2019).

180. Michael Fralick et al., *The Price of Crossing the Border for Medications*, 377 NEW ENG. J. MEDICINE 311, 312 (2017).

similar legislation approving imports from Canada, but neither law has been implemented.¹⁸¹ As of April 2020, twenty-three other states have introduced similar proposals.¹⁸²

Several states have passed anti-price gouging laws. The first such law, which went into effect in October 2017 in Maryland, barred “unconscionable increases” in prescription drug prices.¹⁸³ In April 2019, the Fourth Circuit Court of Appeals invalidated the law, as it would violate the Interstate Commerce Clause by regulating drug sales outside of the state;¹⁸⁴ the Supreme Court denied certiorari.¹⁸⁵ Similar legislation had been in the works in Louisiana and Illinois at the time of the Fourth Circuit’s ruling.¹⁸⁶ Other state initiatives to lower drug price include drug pricing transparency laws in California (2017),¹⁸⁷ Nevada (2017),¹⁸⁸ and Oregon (2018).¹⁸⁹ Many of these state proposals specifically target price-gouging for essential, off-patent generic medicines.¹⁹⁰

Other state initiatives seek to lower drug prices through payment reform. In 2019, California Governor Gavin Newsom (D-CA) introduced a proposal to allow the state’s Medicaid program, Medi-Cal, to negotiate

181. Katie Jickling, *Vermont to Advise Feds on Plan to Import Rx Drugs from Canada*, VTDigger (Nov. 27, 2019), <https://vtdigger.org/2019/11/27/vermont-to-advise-feds-on-plan-to-import-rx-drugs-from-canada/>; Justin Wingerter, *Colorado Will Try to Import Canada’s Prescription Drugs*, DENVER POST, <https://www.denverpost.com/2019/05/17/colorado-import-canada-prescription-drugs/> (last updated May 17, 2017, 3:44 PM).

182. *2020 State Legislative Action to Lower Pharmaceutical Costs*, NAT’L ACAD. FOR STATE HEALTH POL’Y, <https://nashp.org/rx-legislative-tracker-2019/> (last updated Apr. 15, 2020). Such states include Louisiana (2018), Utah (2018), Connecticut (2019), Florida (2019), Maine (2019), Minnesota (2019), Oklahoma (2019), and West Virginia (2019). *Id.*

183. Carolyn Y. Johnson, *A Maryland Law to Prevent “Unconscionable” Price Hikes on Old Drugs Has Been Struck Down*, WASH. POST (Apr. 13, 2018, 2:53 PM), <https://www.washingtonpost.com/news/wonk/wp/2018/04/13/a-maryland-law-to-prevent-unconscionable-price-hikes-on-old-drugs-has-been-struck-down/>.

184. Ovetta Wiggins, *Fourth Circuit Appeals Court Strikes Down Maryland’s Drug Price-Gouging Law*, WASH. POST (Apr. 13, 2018, 3:01 PM), https://www.washingtonpost.com/local/md-politics/fourth-circuit-appeals-court-strikes-down-marylands-drug-price-gouging-law/2018/04/13/6b192130-3f4c-11e8-a7d1-e4efec6389f0_story.html.

185. Lev Facher, *Supreme Court Deals a Fatal Blow to Maryland Drug “Price Gouging” Law*, STAT (Feb. 19, 2019), <https://www.statnews.com/2019/02/19/supreme-court-declines-case-on-maryland-drug-price-gouging-law/>.

186. *See* Johnson, *supra* note 183.

187. Victoria Colliver, *California’s Drug Transparency Law Yields Early Surprises*, POLITICO (Mar. 25, 2018, 7:30 PM), <https://www.politico.com/story/2018/03/25/california-drug-transparency-law-440090>.

188. Lydia Ramsey, *Nevada Just Passed One of the Strictest Drug Pricing Transparency Laws in the Country*, BUS. INSIDER (June 15, 2017, 1:02 PM), <http://www.businessinsider.com/nevada-passes-insulin-drug-pricing-transparency-bill-2017-6>.

189. Zachary Brennan, *Oregon Governor Signs Drug Price Transparency Bill*, REG. AFF. PROFS. SOC’Y (Mar. 13, 2018), <https://www.raps.org/news-and-articles/news-articles/2018/3/oregon-bill-on-drug-price-transparency-headed-to-g>.

190. *See* NAT’L ACAD. FOR STATE HEALTH POLICY, *supra* note 182. Such states include like those introduced in Colorado (2018), Minnesota (2018), New Hampshire (2018), New Jersey (2018-2019), Virginia (2018), Wisconsin (2018), and Indiana (2019). *Id.*

prescription drug prices on behalf of its 13 million beneficiaries.¹⁹¹ The proposal mimics efforts at the federal level to enable drug price negotiation by the Centers for Medicare and Medicaid Services.¹⁹² In 2018 and 2019, several states enacted legislation prohibiting pharmacy benefit managers (PBMs) from enforcing so-called “gag clauses” penalizing pharmacists for informing patients of lower cost drug products.¹⁹³ Likewise, many bills have passed requiring greater price transparency and disclosure from PBMs.¹⁹⁴

Another state-based initiative to lower generic prices is volume-based purchasing—states would buy drugs in bulk and redistribute to their residents. To date, seven states have proposed such legislation, including New Mexico, which established an Interagency Pharmaceuticals Purchasing Council in April 2019 to “review and coordinate cost-containment strategies for the procurement of pharmaceuticals.”¹⁹⁵ States have also passed “affordability review” legislation seeking to identify over-priced drugs and leverage state negotiating power to bring down costs for state residents.¹⁹⁶ The strategy, applicable to both generic and brand-name drug prices, has been proposed in thirteen states and became law in Maryland without the governor’s signature.¹⁹⁷ The Maryland statute, passed in May 2019, established a Prescription Drug Affordability Board, which will “study the entire pharmaceutical distribution and payment system” and draft a plan of action for how to set limits on drug prices.¹⁹⁸ The legislation also set guidelines for determining which brand-name and generic drugs need pricing limitations.¹⁹⁹

CONCLUSION

Though generic entry routinely leads to lower prices, many off-patent drugs are expensive and have experienced dramatic price increases. Manufacturers often rely upon various profit-maximizing strategies. For example, mergers and acquisitions can consolidate generic drug markets, making those markets vulnerable to shortages and susceptible to drug price increases. The FDA’s Unapproved Drugs Initiative had the unintended effect of increasing prices via re-introduction of market exclusivity for previously

191. Ed Silverman, *California Governor Moves to Bolster Negotiating Power for Lower Drug Prices*, STAT (Jan. 8, 2019), <https://www.statnews.com/pharmalot/2019/01/08/california-drug-prices-executive-order/>.

192. *Id.*

193. See NAT’L ACAD. FOR STATE HEALTH POLICY, *supra* note 182.

194. *Id.*

195. S.B. 8, 53d Leg., 2d Sess. (N.M. 2018).

196. NAT’L ACAD. FOR STATE HEALTH POLICY, *supra* note 182.

197. *Addressing the Prescription Drug Affordability Crisis: A Golden Opportunity for State Lawmakers*, FAMILIESUSA https://familiesusa.org/wp-content/uploads/2019/12/Rx_Drug-Affordability-1.pdf.

198. Jane Horvath, *Maryland Passes Nation’s First Prescription Drug Affordability Board Legislation*, NAT’L ACAD. FOR ST. HEALTH POL’Y (Apr. 15, 2019), <https://nashp.org/maryland-passes-nations-first-prescription-drug-affordability-board-legislation/>.

199. *Id.*

competitive generic markets. Although the FDA has made progress toward timely approval generic drug applications, delays prolong a brand manufacturer's effective market exclusivity period beyond the expiration of a product's regulatory or patent exclusivity.

Strategies that encourage more robust generic competition while limiting the ability of manufacturers to unilaterally raise prices in vulnerable markets may provide financial savings to both payors and patients. Such strategies may include importation of generic drugs during drug shortages, and continued action by the FDA in preventing and mitigating drug shortages, ensuring timely ANDA review and approval, increasing competition from non-traditional generic manufacturers, and greater FTC enforcement of anticompetitive business practices in the pharmaceutical sector.

TABLE 1. NOTABLE PRICE INCREASES AND THREATENED INCREASES FOR OFF-PATENT DRUGS SINCE 2000

Generic Drug Name	Indication for Use	FDA Approval (Year)	Niche Market ^a	M&A ^b	Shortage or Discontinuation ^c	Price Increase	Period of Price Increase
Albuterol	Bronchospasm in asthma/chronic obstructive pulmonary disease (COPD)	1981	Yes	No	No	\$11 to \$434 per 100 pills	2013 to 2014
Benazepril/HCTZ	Hypertension	1991	Yes	No	Yes	\$34 to \$149 per bottle of 100 20-25mg tablets	
Calcium-EDTA	Lead poisoning	1953	Yes	Yes	No	\$950 to \$26,927 per package of vials	2013 to 2014
Chlorambucil [1]	1) Lymphatic leukemia; 2) Lymphosarcoma; 3) Hodgkin lymphoma	1957	Yes	No	No	N/A	2012 to 2015
Clomipramine	1) Depression; 2) Panic attacks; 3) Obsessive-compulsive disorder	1989	No	No	No	\$0.34 to \$8.43 per capsule	2013 to 2014
Corticotropin [2]	1) Infantile seizures; 2) Multiple sclerosis; 3) Rheumatoid arthritis; 4) Lupus erythematosus	1952	Yes	No	No	\$40 to ~\$40,000 per vial	2001 to 2019
Cycloserine	Active pulmonary and extrapulmonary tuberculosis	1964	Yes	Yes	Yes	\$500 to \$10,800 per 30 capsules	One-time, August 2016
Dichlorphenamide [3]	Primary hyperkalemic periodic paralysis	1958	Yes	Yes	No	\$50 to \$15,000 per 100 pills	2001 to 2017
Digoxin	1) Mild to moderate congestive heart failure; 2) Atrial fibrillation	1954	Yes	No	Yes	\$0.11 to \$1.10 per pill	2012 to 2014

Divalproex ER	1) Bipolar mania; 2) Epilepsy; 3) Migraine prophylaxis	1983	No	No	Yes	\$31 to \$235 per bottle of 80 pills	2013 to 2014
Doxycycline [4]	Bacterial infections (e.g. typhus fever, STDs, respiratory tract infections)	1967	No	No	Yes	\$4 to \$191 per fifty 100 mg tablets	2013 to 2014
Epinephrine autoinjector	1) Anaphylaxis; 2) Hypotension associated with septic shock	1987	Yes	No	Yes	\$103.50 to \$608.61 per twin pack	2009 to 2016
Glycopyrrolate	Preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions	1961	Yes	No	No	\$65 to \$1,277 per ten vials	2013 to 2014
Indomethacin	1) Rheumatoid arthritis; 2) Ankylosing spondylitis	1963	Yes	Yes	Yes	\$90 to \$1,500 per three vials	2005 to 2006
Isoproterenol [5]	1) Mild to serious episodes of heart block; 2) Cardiac arrest; 3) Bronchospasm during anesthesia	1956	Yes	Yes	No	\$2,183 to \$13,097 per ten 5 mL vials	One-time, February 2015
Lomustine	1) Primary and metastatic brain tumors; 2) Hodgkin lymphoma	1976	Yes	Yes	No	\$50 to \$768 per dose	2013 to 2017
Mebendazole	Gastrointestinal infection (e.g. hookworm and roundworm)	1974	Yes	Yes	No	\$1.60 to \$442 per dose	2011 to 2016
Mechlorethamine	1) Palliative treatment of Hodgkin lymphoma (Stages III and IV); 2) Lymphosarcoma; 3) Lymphocytic leukemia	1949	Yes	Yes	Yes	\$77 to \$548 per month	One-time, February 2006
Naloxone [6]	Respiratory depression in opioid overdose	1971	Yes	No	No	\$1.84 to \$31.66 per two vials	2005 to 2014
Neostigmine [7]	1) Myasthenia gravis; 2) Postoperative distention and urinary retention; 3) Reversal of non-depolarizing neuromuscular	1931 (patented)	Yes	Yes	No	\$25 to \$121 per bottle	2013 to 2014

	blocking agents						
Penicillamine [8]	1) Wilson disease; 2) Cystinuria; 3) Rheumatoid arthritis	1970	Yes	Yes	Yes	\$445 to \$26,188 per treatment	2010 to 2015
Pravastatin	Hyperlipidemia;	1991	No	No	No	\$27 to \$196 per bottle	2013 to 2014
Praziquantel [9]	Parasites (e.g. <i>Schistosoma mekongi</i> and liver flukes)	1982	Yes	Yes	No	N/A	2015
Procarbazine	Hodgkin lymphoma (stage III and IV)	1969	Yes	No	No	\$0.60 to \$55 per pill	2004 to 2005
Pyrimethamine	Toxoplasmosis	1953	Yes	Yes	No	\$13.50 to \$750 per dose	One-time, August 2015
Sodium nitroprusside [10]	Acute hypertensive crisis	1981	Yes	Yes	No	\$2,148 to \$6,445 per ten 2 mL vials	One-time, February 2015
Tiopronin	Prevention of nephrolithiasis	1988	Yes	Yes	No	\$1.50 to \$30 per dose	One-time, August 2014
Trientine	Wilson disease	1985	Yes	Yes	No	\$652 to \$21,267 per treatment	2010 to 2015

^a As defined in this Article, a “niche market” is one with three or fewer manufacturers for a given drug.

^b Defined as merger or acquisition activity related to the drug within a year of the relevant price increase (or threatened increase).

^c Defined as being listed in the “FDA’s Drug Shortages” section of the U.S. Food and Drug Administration website. *Current and Resolved Drug Shortages and Discontinuations Reported to FDA*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm> (last visited Apr. 15, 2020).

[1] Chlorambucil manufacturer threatened to destroy supply and raise prices in Italy.²⁰⁰

200. See Nick Mulcahy, *Destroy Them: One Way to Up Price of Generic Cancer Drugs*, MEDSCAPE (Apr. 17, 2017) <https://www.medscape.com/viewarticle/878652>; see also Alex Keown, *Drug Giant Aspen*

- [2] Includes a one-time increase of 12,900% in 2007 (Questcor).²⁰¹
- [3] Most significant increase by Sun in 2015 when it gained an orphan drug designation for periodic paralysis.²⁰²
- [4] Doxycycline's percent increases varied from 5000% to 8200% depending on dosage strength, number of pills, and capsule/tablet formulations (Sen. Sanders letter to Sun Pharma described increases in "average market price").²⁰³
- [5] Isoproterenol was since raised to \$17,901 for ten 5 mL vials, representing a cumulative 720% increase.²⁰⁴
- [6] At the time, the three manufacturers of naloxone each produced a different formulation: Hospira (intravenous); Adapt (intranasal); Evzio (intramuscular). Kaleo's product also increased in price by 500% from 2014 to 2016.²⁰⁵
- [7] Flamel also increased the price by 446% from 2014 to 2015.²⁰⁶
- [8] Includes a one-time increase of 300% for penicillamine in July 2015.²⁰⁷
- [9] In 2014, Turing threatened to purchase the product and increase its price from \$100 per treatment to \$100,000 per treatment.²⁰⁸

Pharmicare Plotted to Destroy Cancer Medicine to Jack Up Prices, *BIOSPACE* (Apr. 17, 2017) <https://www.biospace.com/article/drug-giant-aspen-pharmicare-plotted-to-destroy-cancer-medicine-to-jack-up-prices/>.

201. Andrew Pollack, *Questcor Finds Profits, at \$28,000 a Vial*, *N.Y. TIMES* (Dec. 29, 2012).

202. Troy Brennan, *Manipulating the Orphan Drug Act: What an Orphan Designation for an Old Drug Means for Payors*, *CVS HEALTH* (Feb. 21, 2017) <https://payorsolutions.cvshealth.com/insights/manipulating-orphan-drug-act>; Carolyn Y. Johnson, *High prices make once-neglected 'orphan' drugs a booming business*, *WASH. POST* (Aug. 4, 2016) https://www.washingtonpost.com/business/economy/high-prices-make-once-neglected-orphan-drugs-a-booming-business/2016/08/04/539d0968-1e10-11e6-9c81-4be1c14fb8e8_story.html.

203. Letter from Representative Elijah Cummings, Ranking Member on the Comm. on Oversight and Gov't Reform for the U.S. House of Representatives, & Senator Bernie Sanders, Chairman of the Subcomm. on Primary Health & Aging for the U.S. Senate, to Dilip S. Shanghvi, Managing Dir. for Sun Pharm. Indus., Inc., 2 (Oct. 2, 2014), <https://www.sanders.senate.gov/download/letter-to-mr-sanghvi-managing-director-sun-pharmaceutical-industries-inc?inline=file>.

204. Sen. Susan M. Collins & Sen. Claire McCaskill, *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System*, SPECIAL COMM. ON AGING FOR THE U.S. SENATE 64 (2016) <https://www.aging.senate.gov/imo/media/doc/Drug%20Pricing%20Report.pdf>.

205. Ravi Gupta et al., Perspective, *The Rising Price of Naloxone—Risks to Efforts to Stem Overdose Deaths*, *NEW ENG. J. MEDICINE* (Dec. 8, 2016), <https://www.nejm.org/doi/full/10.1056/NEJMp1609578>; Meredith Cohn, *Maryland pharmaceutical company buys maker of overdose Narcan for \$735 million*, *BALTIMORE SUN* (Aug. 29, 2018, 4:45 PM), <https://www.baltimoresun.com/business/bs-bz-emergent-buys-narcan-maker-20180829-story.html>.

206. Eric Sagonowsky, "Random," *Unpredictable" Drug Price Hikes Send Costs Skyward at U.S. Hospitals, Report Says*, *FIERCEPHARMA* (Oct. 12, 2016, 11:06 AM) <https://www.fiercepharma.com/pharma/drug-price-hikes-lead-to-skyrocketing-costs-at-u-s-hospitals-report-says>; NORC, *TRENDS IN HOSPITAL INPATIENT DRUG COSTS: ISSUES AND CHALLENGES* 19 (2016) <https://www.aha.org/system/files/2018-01/aha-fah-rx-report.pdf>.

207. See Collins & McCaskill, *supra* note 204, at 54; Zachary Brennan, *Senate Committee Offers Inside Look at the Rise and Fall of Valeant Pharmaceuticals*, *REGULATORY AFFAIRS PROF'LS SOC'Y: REGULATORY FOCUS* (Mar. 9, 2016) <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/5/senate-committee-offers-inside-look-at-the-rise-and-fall-of-valeant-pharmaceuticals>.

[10] Sodium nitroprusside was since raised to \$8809 for ten 2 mL vials, representing a cumulative 310% increase.²⁰⁹

208. Adam Feurstein, *Ousted Retrophin CEO Sold Stock While Urging Investors to Buy*, STREET (Nov. 25, 2014, 12:41 PM) <https://www.thestreet.com/investing/stocks/ex-retrophin-ceo-sold-stock-while-publicly-urging-investors-to-buy-12965617>.

209. See Collins & McCaskill, *supra* note 204, at 6.