



United States Senate Committee on
**Homeland Security &
Governmental Affairs**

U.S. Senator Gary Peters | Ranking Member

A PRICE TOO HIGH

Cost, Supply, and Security Threats
to Affordable Prescription Drugs

A HSGAC MINORITY STAFF REPORT

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Cost, Supply, and Security Threats to Affordable Prescription Drugs

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EXECUTIVE SUMMARY

Hardworking families across the country are struggling to afford the medicine and care they need to live healthy lives. Rising prescription drug costs, a growing number of drug shortages, and mounting concerns about the source and supply of our drugs are creating a threefold public health crisis that puts Americans at risk.

Recent studies have shown that millions of Americans are skipping doses of their medications due to rising costs. Yet over the past 30 years, the pharmaceutical industry has paid more than \$35 billion to settle drug pricing related lawsuits alleging violations ranging from “off-label marketing” to deliberately overcharging taxpayer funded health programs through Medicare and Medicaid. In addition, restrictive patent, pricing, and litigation strategies have contributed to delays in the introduction of new and more affordable drugs and have helped maintain high prices for brand name drugs. Average prices for the twelve top selling brand name drugs in the United States increased 68% between 2012 and 2018. The list price in 2017 for a one-year supply of Humira, the top selling drug in the U.S., was over \$58,000 – more than the annual median household income in Michigan.

At the same time, active drug shortages in the United States are now at their highest levels in almost five years. An increasing number of essential medications used in hospitals, as well as common prescription medications sold at local pharmacies, have at one time or another been unavailable, in short supply, or in limited circumstances, rationed by hospitals, doctors, and pharmacists. These shortages include drugs as varied as intravenous (“IV”) saline solution, lifesaving cancer treatments, and even basic drugs like sodium bicarbonate, which is essentially a sterilized version of the same baking soda that can be found on every supermarket shelf in America. In a 2017 national survey of nearly 300 health care practitioners, 71% indicated that because of drug shortages, they were unable to provide patients with recommended medication or treatment. As a result, shortages are making it harder for hospitals and health care providers to give patients the care they need, when they need it.

Finally, our overdependence on foreign pharmaceutical supply chains is a growing risk to national security. The U.S. is the largest consumer of pharmaceutical products in the world. However, over 80% of the active ingredients in prescription drugs sold throughout the U.S. now come from foreign countries, primarily China and India. China is the largest supplier in the world of the key ingredients in drugs, known as active pharmaceutical ingredients or API. According to Rosemary Gibson, a Senior Advisor at the Hastings Center with an expertise in health care reform and patient safety, “[i]f China shut the door on exports of medicines and their key ingredients and raw materials, U.S. hospitals and military hospitals and clinics would cease to function within months, if not days.”

Compounding these concerns, the U.S. is losing the ability to manufacture essential medications at home. Currently, U.S. domestic manufacturing capabilities have declined to the point where the U.S. is largely dependent on other countries to manufacture and supply most antibiotics, other key emergency medications, and even the needles and syringes necessary for administering these medications. Despite the significant amount of pharmaceutical production and manufacturing of both API and finished drug products that has shifted from the U.S. to other

countries over the past two decades, the Food and Drug Administration (FDA) only inspected one in five pharmaceutical manufacturing facilities abroad last year. The FDA is responsible for ensuring the safety, efficacy, and security of our drug products in the United States. Despite its best efforts, however, popular prescription blood pressure medications (manufactured in China) and common over-the-counter heartburn medications (manufactured in India), for example, have recently undergone a series of recalls after a chemical previously used to make rocket fuel was found in the drugs.

To better understand these economic, health, and security risks, U.S. Senator Gary Peters, Ranking Member of the Senate Homeland Security and Governmental Affairs Committee, directed minority staff to examine the causes of rising drug prices, drug shortages, dependence on foreign supply chains, and resulting threats to patients, consumers, and health care systems. While not exhaustive, this focus addresses three key pieces of the larger puzzle contributing to rising health care costs and public health concerns.

This report details the minority staff's findings and provides recommendations to address the threefold crisis of unaffordable prescription drugs, widespread shortages of prescription and hospital-administered drugs, and overreliance on foreign sources and supplies of drugs sold in the United States.

Findings of Fact and Recommendations

Findings of Fact

Drug Pricing

1. **Brand name drug prices continue to increase at record levels:** Of the twelve top selling brand name drugs in the U.S., prices increased 68% from 2012 to 2018. The number one selling brand name drug Humira, a widely prescribed biologic for treatments including rheumatoid arthritis and Crohn's disease, more than tripled in price from 2006 to 2017.
2. **The United States is the largest market in the world for pharmaceutical company sales:** Pharmaceutical sales in the U.S. exceed \$475 billion annually.
3. **Protective business practices are contributing to decreases in market entry for lower priced drugs:** Brand name drug companies have sustained high prices and limited competition, in part, through exploiting certain patent protections and exclusivity periods. From 2005 to 2015, 78% of new drug patents were based on drugs already in existence. One study estimates that an additional two years of market exclusivity for brand name drugs costs the U.S. health care system over \$30 billion in potential savings.
4. **Generic drugs have lowered costs but present risks:** In 2018, generic drug competition amounted to \$293 billion in overall savings. Generic drugs make up nearly 90% of prescriptions in the U.S., but less than a quarter of all prescription drug costs. From 2001 to 2011 drug recalls increased by over 500%. As one example, in 2018 and 2019, three generic blood pressure medications were recalled after a chemical used to make rocket fuel was discovered in the drug.

Drug Shortages

1. **The number and duration of drug shortages continues to rise:** Drug shortages increased by 300% from 2005 to 2014. The number of active shortages in the second quarter of 2019, 282, exceeded the number of active shortages at any point in 2018 according to the American Society of Health-System Pharmacists. Life-saving drugs formerly required by the Federal Aviation Administration to be carried onboard every U.S. flight are now exempt from being included in medical kits due to shortages. These include epinephrine (used to treat cardiac arrest), atropine (used to treat slow heart rates) and dextrose (used to raise low blood sugar for people with diabetes).
2. **Market consolidation is contributing to drug shortages and price increases:** From 1995 to 2015, sixty pharmaceutical companies merged into ten. A 2017 GAO report found that less competition was associated with higher drug prices, particularly for generic drugs. Less competition in the branded marketplace can impact innovation, new drug approvals, and prices throughout the industry. In some instances, sole-source suppliers have led to higher prices and market fragility that make certain drug products susceptible to shortages.

3. **U.S. drug manufacturers have increasingly declined to invest in new equipment:** Over half of the companies surveyed in a 2017 Pew Charitable Trust report stated that they chose not to upgrade manufacturing equipment – a critical component in resilient manufacturing of sterile injectables – for low margin, low volume products because of cost.
4. **Drug manufacturers are not required to provide critical manufacturing details to the FDA:** The FDA has no timely insight into the volume of drug products produced by each manufacturer and other critical information that could help address shortages. Currently, manufacturers only provide volume information retrospectively and are not required by law to provide information on inventory on hand, percentage of market controlled, or drug shortage risk management plans.

National Security Implications and Supply Chain Vulnerability

1. **U.S. dependence on foreign sources of prescription drugs increases security risks:** Currently, for prescription drugs sold in the U.S., over 80% of the active pharmaceutical ingredients (API) – the key ingredients used in the production of drugs – come from overseas, primarily China and India. Experts including the former Department of Homeland Security Under Secretary for Science and Technology have testified before Congress that the United States has failed to assess its growing dependence on foreign sources of drugs as a national security threat.
2. **The U.S. is losing its ability to independently manufacture generic antibiotics:** In 2004, the last U.S. plant that manufactured active ingredients for antibiotics like penicillin closed. The FDA has found that the majority of facilities that manufacture API for most critical medical countermeasures against biological, chemical, influenza, and radiation threats, now originate in foreign countries. For example, 96% of facilities that manufacture API for ciprofloxacin and 82% of those for doxycycline, two critical antibiotics used to counteract anthrax and other biological threats, are now located in foreign countries.
3. **The FDA lacks adequate oversight of foreign manufacturing facilities:** The FDA inspects or samples less than 1% of all regulated products before allowing them into the U.S. While surveillance inspections in the U.S. are unannounced, the FDA provides notice before conducting the majority of inspections at foreign facilities.
4. **U.S. based pharmaceutical manufacturing is declining:** Within the past two decades, pharmaceutical manufacturing has shifted overseas due to lower labor, construction, regulatory, and environmental costs. According to the FDA, approximately 80% of the manufacturing facilities that produce API are now located outside of the United States.

Recommendations

1. **Improve price transparency:** Pharmaceutical manufacturers, middlemen responsible for negotiating drug prices, and other actors behind the financial engineering of drug prices do not share the net price (the actual cost of the drug after any rebates, discounts, or incentives) with the public, who can only see the list price. Congress should require disclosure of the net price of drug products to improve transparency and accountability. Congress should also evaluate the effectiveness of rebates and whether elements of those rebates should be passed on to the consumer.
2. **Increase approvals for an affordable supply of drugs in shortage:** Congress should require the FDA to prioritize approvals for critical drugs currently in shortage and waive certain fees in if manufacturers agree to bring those drugs to market at pre-shortage levels to stabilize the market and ensure an affordable supply. Congress should also create incentives for negotiating better long-term affordable prices through contracting practices that ensure high-volume, sustainable production of safe, accessible, quality medication.
3. **Reward quality in manufacturing and sufficiently resource and authorize unannounced inspections worldwide:** The FDA should revise its pharmaceutical manufacturing evaluation system from a pass/fail rubric to a sliding scale (e.g., one through five stars) to reward quality. The results should be public so consumers, patients, and health care systems can access the information and use it when making decisions about what drugs to buy. All FDA inspections, regardless of location, should be unannounced, and the FDA should be resourced to ensure it can deploy a sufficient number of trained and qualified inspectors abroad.
4. **Prohibit unjustified price increases by pharmaceutical companies:** Congress should pass the Stopping the Pharmaceutical Industry from Keeping Drugs Expensive (SPIKE) Act and the Forcing Limits on Abusive and Tumultuous Prices (FLAT) Act, both co-sponsored by Senator Peters, which would require pharmaceutical companies to submit justification for their price increases above a certain threshold and shorten market exclusivity periods for prescription drugs that engage in price hikes.
5. **Level the playing field for generics:** Congress should encourage new and affordable generic competition by prohibiting unfair and manipulative patent and regulatory exclusivity practices. Congress should also pass the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, which would prevent unfair drug company practices by allowing innovators to purchase drug samples for a commercially reasonable price and bring civil actions if a sample is withheld. It would also broaden FDA authority to approve generics and biosimilars.
6. **Allow Medicare to negotiate drug prices:** Congress should pass the Empowering Medicare Seniors to Negotiate Drug Prices Act, which would strike the “noninterference clause” that prohibits the government from negotiating drug prices under Medicare Part D.

7. **Allow for personal use importation where safe and viable:** Americans have resorted to traveling outside of the U.S. to obtain prescription medications at an affordable cost. Congress should consider passing the Safe and Affordable Drugs from Canada Act, a bipartisan bill that would allow individuals to safely import prescription drugs from Canada into the United States.
8. **Require pharmaceutical companies and manufacturers to report needed data to the FDA and list key information on drug labels:** The Food and Drug Administration Safety and Innovation Act (FDASIA) should be amended to require manufacturers to report the percentage of the market currently held by the manufacturer, inventory on hand and in distribution channels, and interruptions or discontinuances of manufacturing for certain key ingredients. Congress should expand FDA authority to impose fines for noncompliance. In addition, information about active ingredients and manufacturing facilities, including the country of origin, should be listed on prescription labels.
9. **Require pharmaceutical manufacturers to submit annual redundancy and contingency plans to the FDA:** Pharmaceutical companies should be required to submit annual redundancy and contingency plans for critical lifesaving and emergency medications to help reduce the impacts of drug shortages.
10. **Require pharmaceutical manufacturers to provide key quarterly data:** The government does not have insight into the real-time manufacturing capacity of pharmaceutical companies bringing drugs to the U.S., creating gaps in information necessary to assess safety and security risks. Pharmaceutical companies should be required, on a quarterly basis, to provide to the Department of Homeland Security and the Department of Health and Human Services with information on the location, volume, and production capacity for each drug produced at a company's manufacturing facilities.
11. **Require DHS and HHS to conduct an annual risk assessment:** DHS and HHS should be required to publish an annual risk assessment of the national security implications regarding the diversification of the pharmaceutical industry's supply chain, relevant market intelligence, and potential threats. The risk assessment should classify severity of risks and propose specific solutions.
12. **Help bring pharmaceutical manufacturing for critical drugs back to the U.S.:** The FDA should be given authority to provide incentives for pharmaceutical companies that bring manufacturing for certain critical drugs back to the U.S. Congress should also provide incentives for pharmaceutical companies to partner with academic institutions to further advancements in continuous pharmaceutical manufacturing in the United States.

I. INTRODUCTION

The United States is the largest consumer of pharmaceutical products in the world. In 2018, pharmaceutical sales in the U.S. exceeded \$475 billion.¹

While pharmaceutical drug consumption in the U.S. is hundreds of billions of dollars higher than in any other country, at the same time, the U.S. has the highest number of disease, disability, premature death, and hospital admissions for preventable diseases of any developed country in the world.² In addition, minority and low income populations in the U.S. experience disparities in health, healthcare, and access to care at rates much higher than for the rest of the population.³ The drivers of high drug costs, increasing shortages, and drug supply concerns examined in this report are a narrow but interrelated part of the larger public health crisis exemplified by these adverse health outcomes and disparities in access and care. The recommendations in this report are intended to contribute needed solutions to address the economic, health, and safety threats faced by Americans today.

In preparation for this report, minority staff conducted interviews with over thirty healthcare and industry experts, including doctors, pharmacists, patients, hospitals, university administrators, academics, pharmaceutical company executives, and officials with the U.S. Food and Drug Administration (FDA) and the U.S. Department of Health and Human Services. Minority staff also reviewed relevant Government Accountability Office reports, hospital and industry field studies, and other peer-reviewed articles, research, and congressional testimony to assess the current pricing, shortages, and pharmaceutical supply chain and distribution landscape and determine needed recommendations for reform.

II. DRUG PRICING

The complexity of drug pricing reflects the complexity of the drug marketplace. Brand name and generic drugs have vastly different costs and can exist in the marketplace at different points in time after a new drug is approved by the FDA.⁴ Dr. Aaron Kesselheim, an expert in drug pricing and health policy who currently serves as Director of the Program on Regulation, Therapeutics, and Law at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School has described the lifecycle of drugs (post-FDA approval) as having three phases, generally: the brand name exclusivity period, the period of transition to a generic market in

¹ IQVIA, Pharmaceutical Trends: Top 10 Pharmaceutical Markets Worldwide, 2018 (Dec. 2018) (https://www.iqvia.com/-/media/iqvia/pdfs/canada/2018-trends/top10worldwidesales_en_18.pdf?la=en&hash=4F53F349B98F3D8D8477A791F03B93EC).

² Bradley Sawyer and Daniel McDermott, *How does the quality of the U.S. healthcare system compare to other countries?* Kaiser Family Foundation Health System Tracker (Mar. 28, 2019).

³ *The costs of inequality: Money = quality health care = longer life*, The Harvard Gazette (Feb. 22, 2016) (<https://news.harvard.edu/gazette/story/2016/02/money-quality-health-care-longer-life/>).

⁴ Branded products include either traditional small molecule drugs, which are chemically synthesized or biologics, which are derived from a living organism and have a more complex structure. Generic drugs are identical to a branded small molecule drug. Biosimilars are products deemed to be “highly similar” to the original biologic. See Congressional Research Service, *Frequently Asked Questions About Prescription Drug Pricing and Policy* (R44832) (Apr. 24, 2018).

which other manufacturers begin to enter the market, and finally, the multisource market period in which multiple generic and brand name manufacturers can exist.⁵

Drug pricing involves a number of participants – manufacturers, wholesalers, health plans, academic and federally funded institutions, employers, pharmacy benefit managers, pharmacies and others, all of which influence pricing. Unwinding the “drug pricing maze” can be difficult given its complexities and limited publicly accessible data.⁶

A. Causes and Drivers

The price and value of a drug fluctuates throughout its lifecycle. The two main forces that impact drug pricing are marketplace competition and negotiation power. During the brand name exclusivity period, U.S. purchasers have little negotiating power to push back against drug prices set by patent-holding manufacturers.⁷ The combination of market exclusivity and insufficient negotiating power results in opportunistic pricing, allowing companies to set exceedingly high prices that would be unsustainable in other consumer markets. As Dr. Kesselheim has explained “[t]he United States is characterized by a fractured buyers’ market for prescription drugs.”⁸ In essence, the U.S. government is not able to act as a unified force in negotiating drug prices and private payers often do not have sufficient tools to exercise effective negotiating power with brand name pharmaceutical companies.

The predominant payers for health care in the U.S. are private insurers, Medicare, Medicaid, the Veterans Health Administration, the Department of Defense, state prisons, and the Federal Employee Health Benefits Program. Some of these payers have the authority to negotiate drug prices but others do not. The Medicare Modernization Act of 2003, for example, included a “noninterference” clause, which prohibits the Secretary of the Department of Health and Human Services from directly negotiating drug prices with drug manufacturers and pharmacies under Medicare Part D. As such, for the 43 million Americans enrolled in Medicare Part D (outpatient prescription drug benefits), the HHS Secretary is restricted from negotiating drug prices, and any negotiating happens via private health payers that offer Part D plans.⁹

⁵ Dr. Aaron Kesselheim, Director of the Program On Regulation, Therapeutics, and Law and practicing physician at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Aug. 28, 2019) (hereinafter “Interview with Dr. Aaron Kesselheim”).

⁶ Robert Ripley, Vice President and Chief Pharmacy Officer for Trinity Health, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Sept. 9, 2019) (hereinafter “Interview with Robert Ripley”).

⁷ Aaron S. Kesselheim, Jerry Avorn, and Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, Journal of American Medicine Association (Aug. 2016) (noting the “[p]rimary counterweight against market exclusivity is the negotiating power of the payer”).

⁸ Interview with Dr. Aaron Kesselheim.

⁹ Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Pub. L. No. 108-172); Kaiser Family Foundation, *Medicare Part D in 2018: The Latest on Enrollment, Premiums, and Cost Sharing* (May 17, 2018) (<https://www.kff.org/medicare/issue-brief/medicare-part-d-in-2018-the-latest-on-enrollment-premiums-and-cost-sharing/>).

This prohibition eliminates the vast bargaining power that HHS could exercise in negotiating drug prices, further strengthening pharmaceutical companies' pricing power. From 2011-2015, Medicare spending on branded drugs increased 62%.¹⁰ By contrast, the Department of Veterans Affairs' Veterans Health Administration (VA), which does not have this same restriction in price negotiations, has more successfully utilized its market power — serving over nine million veterans — to directly negotiate drug prices with manufacturers. Unlike HHS, the Veterans Health Administration is able to set a ceiling on prices manufacturers can charge the VA and its purchasers, negotiate for discounts on prescription drugs, and exclude certain medications from its formularies.¹¹

B. Brand Name Drugs

While the FDA is responsible for ensuring the safety and clinical effectiveness of drug products, it does not have the authority to assess affordability of drug prices and does not take prices into account as part of its drug approval process.¹² As Dr. Kesselheim has explained, “brand name drug companies have the ability in the U.S. to set the price of a drug at whatever level they believe is fair.”¹³ This helps explain why brand name drug prices are so much higher in the U.S. than in other countries around the world that have more negotiating power over how drug prices are set. It also explains why of the 49 top-selling brand name drugs in the U.S., most of which have been on the market since 2012, 78% “have seen an increase in insurer and out-of-pocket costs [by more than half], and 44% have more than doubled in price.”¹⁴

The number one selling brand name drug, Humira, a widely prescribed biologic for treatments including rheumatoid arthritis, psoriasis, and Crohn's disease, more than tripled in price from 2006 to 2017. Although it was originally approved by the FDA in 2002, in 2017, the list price for a one-year supply was over \$58,000 – more than the annual median household income in Michigan. Humira's 2018 global sales totaled almost \$20 billion – four times the value of the Dallas Cowboys.¹⁵ The average prices for the twelve top selling brand name drugs in the

¹⁰ Robin Feldman, *Drugs, Money, & Secret Handshakes: The Unstoppable Growth of Prescription Drug Prices* (2019).

¹¹ Mike McCaughan, *Prescription Drug Pricing #8, Veterans Health Administration*, Health Affairs (Aug. 10, 2017). See also Brett Venker, Kevin B. Stephenson, and Walid F. Gellad, *Assessment of Spending in Medicare Part D If Medication Prices From the Department of Veterans Affairs Were Used*, JAMA Internal Medicine (Jan. 14, 2019).

¹² Congressional Research Service, *Frequently Asked Questions About Prescription Drug Pricing and Policy* (R44832) (Apr. 24, 2018).

¹³ Interview with Dr. Aaron Kesselheim.

¹⁴ Nathan E. Wineinger, et al., *Trends in Prices of Popular Brand-Name Prescription Drugs in the United States*, Journal of American Medical Association Network Open (May 31, 2019).

¹⁵ *Protect at all Costs: How the Makers of the World's Bestselling Drug Keeps Prices Sky-High*, Fortune Magazine (Jul. 18, 2019) (<https://fortune.com/longform/abbvie-humira-drug-costs-innovation/>). See also United States Census Bureau, *QuickFacts Michigan* (Jul. 1, 2018) (<https://www.census.gov/quickfacts/MI>). Note that the list price for Humira depends on what condition the drug is being used to treat.

U.S. increased 68% between 2012 and 2018.¹⁶ The underlying causes of these and other massive price increases are multi-faceted and interrelated.

1. Financial Engineering

Drug pricing does not follow the typical laws of economics. Ernst Berndt, Thomas McGuire, and Joseph Newhouse, professors of applied economics, health economics, and health policy and management at MIT's Sloan School of Management and Harvard Medical School, described how supply prices are set in one context by negotiations for what manufacturers will receive while demand prices "those paid by patients ... are specified as part of the insurance contract for the great majority of [the U.S. population] that has health care"¹⁷ Erin Fox, Senior Director of Drug Information and Support Services at the University of Utah, and Linda Tyler, Chief Pharmacy Officer and Associate Dean for the University of Utah College of Pharmacy, explained the effect of this imbalance on consumers: "supply cannot change quickly, demand is relatively static, and consumers are not in charge of which product is purchased."¹⁸

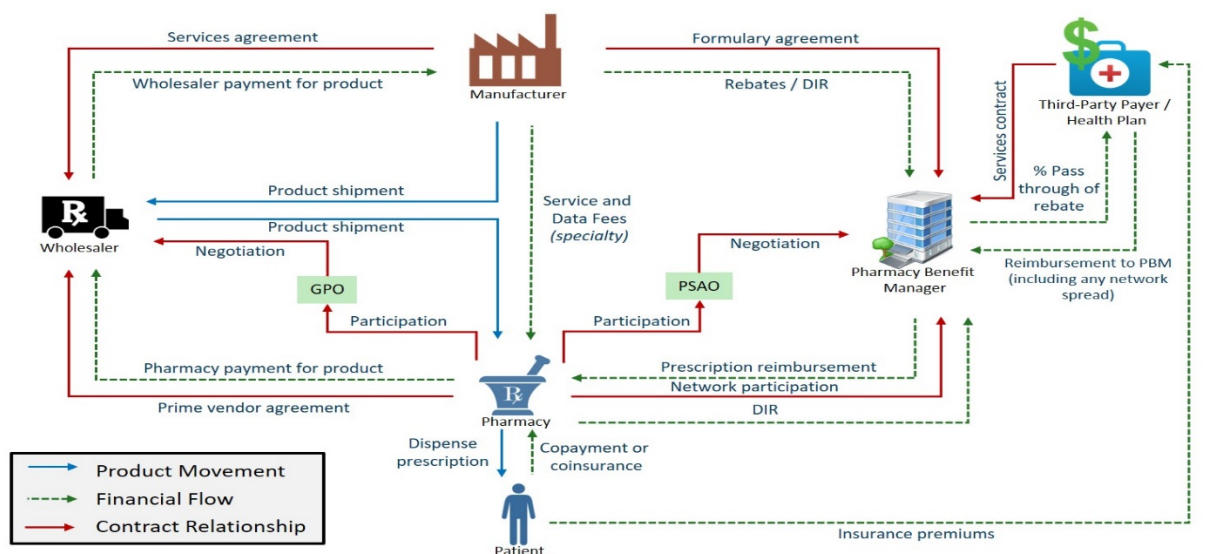
Different patients can pay different amounts for the same drug depending on the policies of their respective insurance plans. The non-transparent nature of prescription drug costs allows for opaque pricing tactics and different financial incentives for the various actors in the pharmaceutical distribution chain (drug manufacturers, wholesalers, pharmacy benefit managers, pharmacies, health plans, etc.). Some of these tactics benefit patients, and some do not.

¹⁶ I-MAK, *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices* (Aug. 2018) (<https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>).

¹⁷ Ernst R. Berndt, et al., *A Primer on the Economics of Prescription Pharmaceutical Pricing in Health Insurance Markets*, National Bureau of Economic Research (Mar. 2011).

¹⁸ Erin Fox and Linda Tyler, *Potential Association between Drug Shortages and High-Cost Medications*, Pharmacotherapy Publications, Inc. (2016).

U.S. Distribution and Reimbursement System: Patient-Administered, Outpatient Drugs



GPO = Group Purchasing Organization; PSAO = Pharmacy Services Administrative Organization; DIR = Direct and Indirect Remuneration
Source: Drug Channels Institute. Chart illustrates flows for Patient-Administered, Outpatient Drugs. Please note that this chart is illustrative. It is not intended to be a complete representation of every type of product movement, financial flow, or contractual relationship in the marketplace.

DRUG CHANNELS
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Figure 1: Flow of Money in Pharmaceutical Supply Chain¹⁹

Price Transparency: The list price of a drug, commonly referred to as the wholesale acquisition cost (WAC), is the manufacturer's published price for a drug product.²⁰ The net price of a drug is the final price paid for the product after rebates, discounts, and coupons.²¹ Consumers are only able to see global financial statements from pharmaceutical companies and do not have access to the net price that was actually paid for a drug by individual buyers.²² The only public drug price consistently available in the U.S. is the list price.

To date, companies have successfully argued that the net price of a drug is a trade secret, and as such, is immune from regulatory disclosure.²³ Courts have not definitively ruled on these claims and, according to Robin Feldman, Distinguished Professor of Law at the University of California Hastings, the argument is faulty:

This sort of information hardly sounds like intellectual property. It is not an idea, and it certainly is not the product of innovation. The pricing in a PBM agreement is not information developed by a

¹⁹ *Profits in 2019 Fortune 500: Manufacturers vs. Managed Care vs. Pharmacies, PBMs, and Wholesalers*, Drug Channels (Jun. 5, 2019) (<https://www.drugchannels.net/2019/06/profits-in-2019-fortune-500.html>).

²⁰ Congressional Research Service, *Drug Price Disclosure to Consumers: Current Legal Authority and Considerations for Congress* (LSB10323) (Jul. 9, 2019).

²¹ A discount is a reduction in price at the point of sale. A rebate is a price reduction after the point of sale.

²² Dr. Shereef Elnahal, President and CEO of University Hospital in Newark, New Jersey, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Jul. 31, 2019) (hereinafter "Interview with Dr. Shereef Elnahal").

²³ Robin Feldman and Charles Graves, *Naked Price and Pharmaceutical Trade Secret Overreach*, Yale Journal of Law & Technology (forthcoming).

company to operate its business. Rather, it is a mere deal point negotiated between two entities ... [T]he very targets of regulation – artificially inflated prices – are claimed as intellectual property to avoid disclosure. Thus, trade secret law is being asserted as an offensive weapon to avoid regulation, and to avoid responsibility for the public harm created by the supposed “trade secret” itself Certainly, litigants claim financial information as a trade secret, and companies submit information to state and federal regulators under seal. But price competition is quite often open, not hidden – not something traditionally seen as “property” that is off-limits to competitors.²⁴

Due to lack of transparency in the net price of the drug, analyzing drug pricing practices is complicated. As Dr. Walid Gellad, a University of Pittsburgh professor who specializes in drug pricing, noted “most of us can’t see what’s happening inside this black hole ... It’s impossible to understand what people are really paying.”²⁵ Based on recent analyses, the net price for certain drugs can be substantially less than the list price. One analysis of gross and net prices for three pharmaceutical firms revealed average discounts from the list prices by 42% to 51%.²⁶ List prices are also increasing at a faster rate than net prices, with the average list price for brand name drugs growing by 11.3% in 2013 and 6.9% in 2017, compared to the average net price increase of 1.5% in 2013 and 2.1% in 2017.²⁷ Given the complex pharmaceutical distribution chain, a variety of factors can impact the net price of a drug.

Pharmacy Benefit Managers: Pharmacy benefit managers (PBMs) are intermediaries between health plans (insurers), pharmacies, drug manufacturers, and drug wholesalers. PBMs’ primary responsibilities are negotiating price on behalf of health insurers and setting formularies (a list of drugs covered by a health plan). The largest PBMs, which control the majority of the market, are owned by health insurers or retail pharmacy chains.

²⁴ *Id.* But see Federal Trade Commission, *Price transparency or TMI?* (Jul. 2, 2015) (<https://www.ftc.gov/news-events/blogs/competition-matters/2015/07/price-transparency-or-tmi>) (noting that transparency can go too far and harm competition).

²⁵ *Inside the impossibly byzantine world of prescription drug prices*, STAT News (Dec. 21, 2015) (<https://www.statnews.com/2015/12/21/prescription-drug-prices-confusion/>).

²⁶ *Payer Power: Why Eli Lilly, Janssen, and Merck Deeply Discount Their Drug Prices*, Drug Channels (Apr. 5, 2018) (<https://www.drugchannels.net/2018/04/payer-power-why-eli-lilly-janssen-and.html>).

²⁷ IQVIA, *Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022* (Apr. 2018) (<https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf>).

Vertical Business Relationships Among Insurers, PBMs, and Specialty Pharmacies, 2019



Source: Drug Channels Institute research. AllianceRx Walgreens Prime is jointly owned by Prime Therapeutics and Walgreens Boots Alliance.

This chart appears as Exhibit 77 in *The 2019 Economic Report on U.S. Pharmacies and Pharmacy Benefit Managers*, Drug Channels Institute. Available at <http://drugch.nl/pharmacy>



Figure 2: Vertical Business Relationships among PBMs, Insurers, and Specialty Pharmacies, 2019²⁸

With no insight into the closed-door contractual negotiations between drug manufacturers and PBMs, Erin Taylor, a health economist at the RAND Corporation, noted that “concern has arisen that PBMs are getting too big a piece of the pie and contributing to high [drug] prices.”²⁹ Currently, there is no comprehensive information on PBMs and their negotiations, though there have been some specific studies from state audits. As one example, the Ohio Auditor of State found that PBM fees for generic drugs amounted to over \$208 million in one year, or 31.4% of the \$662.7 million paid by managed care plans for generic drugs.³⁰

One concern related to PBMs’ role and the resulting impact on prices is a practice known as spread pricing. This occurs when the PBM retains the difference between what it paid to the pharmacy and what it billed to the payer, also known as the “spread.”³¹ A 2018 U.S. Senate Finance Committee Minority Staff Report found that “PBMs conceal the payment terms and

²⁸ CVS, Express Scripts, and the Evolution of the PBM Business Model, Drug Channels (May 29, 2019). (<https://www.drugchannels.net/2019/06/profits-in-2019-fortune-500.html>).

²⁹ Pew Charitable Trusts, *Drug-Price Debate Targets Pharmacy Benefit Managers* (Feb. 12, 2019) (<https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2019/02/12/drug-price-debate-targets-pharmacy-benefit-managers>).

³⁰ Ohio Auditor of State, *Auditor’s Report: Pharmacy Benefit Managers Take Fees of 31% on Generic Drugs Worth \$208M in One-Year Period* (Aug. 16, 2018) (<https://ohioauditor.gov/news/pressreleases/Details/5042>). Auditors found that PBMs took 1.1% (\$617.6 million) of the overall cost for specialty drugs and 0.8% (\$9.8 million) of the overall cost for brand name drugs.

³¹ Massachusetts Health Policy Commission, *HPC DataPoints, Issue 12: Cracking Open the Black Box of Pharmacy Benefit Managers* (Jun. 5, 2019) (<https://www.mass.gov/info-details/hpc-datapoints-issue-12-cracking-open-the-black-box-of-pharmacy-benefit-managers>). See also *The Secret Drug Pricing System Middlemen Use to Rake in Millions*, Bloomberg (Sept. 11, 2018) (<https://www.bloomberg.com/graphics/2018-drug-spread-pricing/>).

rebates they negotiate so that their plan sponsor clients do not know the extent to which the savings secured by a PBM are – or are not – passed on...PBMs do not disclose the fees they may be receiving from manufacturers for other services ... [and] [t]his lack of transparency extends to PBMs' relationships with other entities in the drug supply chain.”³² A Bloomberg analysis of 90 of the best selling drugs in Medicaid managed-care plans found that “PBMs and pharmacies siphoned off \$1.3 billion of the \$4.2 billion Medicaid insurers spent on the drugs in 2017.”³³

The net income of PBMs, however, is publicly available. In 2016, the net income for one standalone PBM, Express Scripts, was \$3.4 billion. This was higher than the net income for a number of leading health insurers, including Anthem (\$2.5 billion), Aetna (\$2.3 billion), Cigna (\$1.9 billion), and Humana (\$1.2 billion).³⁴ A 2017 study by the Centers for Medicare and Medicaid Services (CMS) noted that PBM rebates are “estimated to have contributed to lower net prices for many prescription drugs.”³⁵ However, because insurers pay PBMs based on the discount the PBM is able to negotiate, PBMs may gravitate toward higher priced drugs to realize higher rebates.³⁶ According to Dr. Gerard Anderson, a professor of health policy and management with Johns Hopkins Bloomberg School of Public Health, “PBMs put drugs on the formulary that are not useful, simply for the high rebate and it is affecting medical practice in a way it should not.”³⁷

A 2019 report by Pew Charitable Trusts found that manufacturer rebates increased from \$39.7 billion in 2012 to \$89.5 billion in 2016.³⁸ According to the health plans and PBMs surveyed, 78% of these rebates were passed down to health plans in 2012 and 91% in 2016.³⁹ However, in some instances, PBMs may be earning profits through volume discounts or agreements to prioritize certain more expensive brand name drugs. With no publically available data regarding negotiations between PBMs and drug companies, it is impossible to fully evaluate the impact PBMs have on drug pricing.

³² U.S. Senate Committee on Finance, Minority Staff, *A Tangled Web: An Examination of the Drug Supply and Payment Chains* (Jun. 2018).

³³ *The Secret Drug Pricing System Middlemen Use to Rake in Millions*, Bloomberg (Sept. 11, 2018) (<https://www.bloomberg.com/graphics/2018-drug-spread-pricing/>).

³⁴ *Understanding high drug costs and the role of pharmacy benefit managers*, Stanford Medicine Scope (Mar. 5, 2019) (<https://scopeblog.stanford.edu/2019/03/05/understanding-high-drug-costs-and-the-role-of-pharmacy-benefit-managers/>).

³⁵ Gigi A. Cuckler et al., *National Health Expenditure Projections, 2017-26: Despite Uncertainty, Fundamentals Primarily Drive Spending Growth*, Health Affairs (Feb. 14, 2018).

³⁶ The Commonwealth Fund, *Pharmacy Benefit Managers and Their Role in Drug Spending* (Apr. 22, 2019) (<https://www.commonwealthfund.org/publications/explainer/2019/apr/pharmacy-benefit-managers-and-their-role-drug-spending>).

³⁷ Dr. Gerard Anderson, Professor of Health Policy and Management with Johns Hopkins Bloomberg School of Public Health, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Aug. 7, 2019) (hereinafter “Interview with Dr. Gerard Anderson”).

³⁸ Pew Charitable Trusts, *The Prescription Drug Landscape Explored* (Mar. 8, 2019) (<https://www.pewtrusts.org/en/research-and-analysis/reports/2019/03/08/the-prescription-drug-landscape-explored>).

³⁹ *Id.*

2. Patent Abuses

Brand name drug companies are able to maintain high prices, in part, by obtaining longer exclusivity periods – legally protected limits on introducing competitor generic drugs. When a brand name drug’s exclusivity period ends and generics with interchangeable therapeutic benefits enter the market, the brand name drug traditionally loses more than 80% to 90% of the market within six months.⁴⁰ The incentive, therefore, to maintain exclusive control over a given market is high. A recent study estimated that an additional two years of market exclusivity for branded drugs cost the U.S. health care system an additional \$31.7 billion in drug expenses.⁴¹

A separate study examining 10 years of market activity from 2005 to 2015 found that “[r]ather than creating new medicines, pharmaceutical companies are largely recycling and repurposing old ones” with 78% of new drug patents relating to existing drugs. Of the 100 best-selling drugs examined during this 10 year period, more than 70% had their exclusivity period extended at least once.⁴² Moreover, since 2017, 36% of generic drugs that received approval to enter the market (and would therefore be the first to compete against a branded drug) are not yet on the market because of litigation, patent related challenges, or other factors delaying entry.⁴³ Of the top 12 grossing drugs in 2017, manufacturers filed an average of 125 patent applications per drug, with an average of 71 patents granted per drug, resulting in an additional 31-38 years in exclusivity. AbbVie, the maker of Humira, the number one selling branded drug in the U.S., has filed a total of 247 patent applications related to that single drug. Of those applications, more than 100 were approved, many “as the expiration of Humira’s main patent grew closer.”⁴⁴

Patent protection for pharmaceutical products, like for other inventions that qualify as new and useful under U.S. patent law, generally provides 20 years of exclusivity from the date of the application. However, because it takes time to develop medications and receive FDA approval, new drugs usually have patent protection for an average period of approximately twelve to fourteen years.⁴⁵ Pharmaceutical companies can exploit protections under current patent law in two ways. One practice is known as “patent thickening,” where a company obtains as many additional patents on a drug as possible. This requires future generic competitors to challenge a “thicket” of patents before entering the market. A second practice is known as “evergreening” (also referred to as product hopping), in which pharmaceutical companies

⁴⁰ *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638, 647 (2015).

⁴¹ Matrix Global Advisors, *Gamesmanship and Other Barriers to Drug Competition* (Jul. 2019) (http://www.affordableprescriptiondrugs.org/app/uploads/2019/07/brand_gamesmanship_july_2019.pdf).

⁴² Robin Feldman, *May your drug price be evergreen*, Oxford Journal of Law and the Biosciences (Dec. 7, 2018).

⁴³ *Trump Administration Salutes Parade Of Generic Drug Approvals, But Hundreds Aren’t For Sale*, Kaiser Health News (Feb. 7, 2019) (<https://khn.org/news/trump-administration-salutes-parade-of-generic-drug-approvals-but-hundreds-arent-for-sale/>).

⁴⁴ I-MAK, *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices* (Aug. 2018) (<https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>). See also *This Shield of Patents Protects the World’s Best-Selling Drug*, Bloomberg Businessweek (Sept. 7, 2017) (<https://www.bloomberg.com/news/articles/2017-09-07/this-shield-of-patents-protects-the-world-s-best-selling-drug>).

⁴⁵ Robin Feldman, *Drugs, Money, & Secret Handshakes: The Unstoppable Growth of Prescription Drug Prices* (2019). See also Congressional Research Service, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress* (R45666) (Apr. 4, 2019).

introduce a slightly modified version of a drug product covered by the new patent, switching the market over to the new product before generic competition can successfully take hold.⁴⁶

Secondary patents are not used for inventing new drugs. For example, they can cover modified forms of an already existing drug's active ingredients and new combinations of old chemical compounds that have long been on the market (e.g. sinus and headache medicine that combines a decongestant with ibuprofen). They can also cover devices that administer drugs.⁴⁷ Michael Carrier, Distinguished Professor of Law at Rutgers Law School, explained the harm of evergreening:

Every time that the brand company switches from one version of a drug to another, from a capsule to a tablet or 150 milligram dose to 140 milligram dose, the generic has to go back to the drawing board, reformulate the drug, get FDA approval [and] be subject to patent litigation, so every single time it's kept off the market for years and this has significant effects on consumers.⁴⁸

Some patents covering modified versions of drugs can have benefits, such as convenience, fewer side effects, or less invasive treatments (e.g., taking a medication once instead of twice a day). State drug product selection laws allow or require pharmacists to substitute generic equivalents to a branded drug. However, a drug cannot be automatically substituted if the FDA has not recognized a generic equivalent. Product hopping can negatively impact generic competition by delaying the substitution of an otherwise suitable generic product. For example, by changing the form of the drug (e.g. capsule to tablet) or the dosage of the active ingredient (e.g. 20-mg to 23-mg), a pharmacist is unable to substitute the generic product because there is no FDA approved equivalent for the new slightly modified branded drug.⁴⁹ This can effectively delay market transition from brand name drug exclusivity to more widespread availability of lower-cost generics.

Professor Feldman has emphasized how pharmaceutical companies use these practices to maintain market exclusivity and fend off competition. In her statement before the House Ways and Means Health Subcommittee in March 2019, she explained:

Consider the cancer drug Imbruvica. The company extended the drug's protection cliff from 2018 to 2031, using 24 additions to its protection. Or consider the cholesterol drug Crestor. The company extended the protection cliff from 2008 to 2022, piling on 32

⁴⁶ Congressional Research Service, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress* (R45666) (Apr. 4, 2019).

⁴⁷ Reed F. Beall and Aaron S. Kesselheim, *Tertiary patenting on drug-device combination products in the United States*, *Nature Biotechnology* (Feb. 6, 2019).

⁴⁸ House Committee on Energy and Commerce, Consumer Protection and Commerce Subcommittee, Opening Statement of Michael Carrier, *Hearing on Profits over Consumers: Exposing How Pharmaceutical Companies Game the System*, 116th Cong. (Sept. 19, 2019).

⁴⁹ Annabelle C. Fowler, *Pharmaceutical Line Extensions in the United States: A Primer on Definitions and Incentives*, Harvard University (Oct. 6, 2019).

additions. Or consider the drug Lyrica—used to treat nerve pain from diabetes and other conditions. The company extended the protection cliff from 2009 to 2018 with 16 additions. These are not outliers; this is the normal business practice for the industry.⁵⁰

Prof. Feldman described the piling on of these exclusivity rights as “market distortions.”⁵¹ The top eight grossing pharmaceutical products in the U.S. – Humira, Rituxan, Revlimid, Enbrel, Herceptin, Eliquis, Remicade, and Avastin – are protected by a total of 650 patents.⁵²

3. Restrictive Practices

Litigation Strategies: Branded drug companies engage in an array of litigation strategies to prevent competition and maintain market exclusivity. In one example, when faced with multiple patent challenges, in 2017 pharmaceutical company Allergan transferred its patents for Restasis, the dry-eye drug, to the Saint Regis Mohawk Tribe for \$13.75 million and \$15 million in annual royalties in exchange for an agreement for the tribe to grant Allergan exclusive license for Restasis so that the tribe could claim sovereign immunity as grounds to dismiss a patent challenge. Ultimately, the U.S. Court of Appeals for the Federal Circuit ruled that sovereign immunity cannot be invoked in *inter partes* review, an administrative proceeding for patent challenges.⁵³

Patent infringement lawsuits against generic manufacturers are common at the point in time when generics seek FDA approval to enter the market. Under the Hatch-Waxman Act, pharmaceutical companies can further extend market exclusivity so long as they file a patent infringement lawsuit within 45 days of the generic drug application.⁵⁴ Once filed, the generic applicant is prohibited from entering the market until it receives FDA approval, which the FDA cannot grant for 30 months. If the FDA grants approval upon the conclusion of the 30-month stay, generic applicants may still find themselves in “limbo” if the patent litigation is still pending, because launching a new product could create risk in the event of an adverse court ruling.⁵⁵

⁵⁰ House Ways and Means Health Subcommittee, Testimony Submitted for the Record of Robin Feldman, University of California Hastings, *Hearing on Promoting Competition to Lower Medicare Drug Prices* 116th Cong. (Mar. 7, 2019).

⁵¹ Prof. Robin Feldman, Distinguished Professor of Law at the University of California Hastings, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Sept. 4, 2019) (hereinafter “Interview with Robin Feldman”).

⁵² I-MAK, *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices* (Aug. 2018) (<https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>).

⁵³ *How to Protect a Drug Patent? Give it to a Native American Tribe*, New York Times (Sept. 8, 2017) (<https://www.nytimes.com/2017/09/08/health/allergan-patent-tribe.html>).

⁵⁴ Congressional Research Service, *Drug Pricing and the Law: Pharmaceutical Patent Disputes: In Focus* (IF11214) (May 17, 2019).

⁵⁵ Matrix Global Advisors, *Gamesmanship and Other Barriers to Drug Competition* (Jul. 2019) (http://www.affordableprescriptiondrugs.org/app/uploads/2019/07/brand_gamesmanship_july_2019.pdf).

Parties often decide to settle these patent infringement lawsuits. One tactic, commonly referred to as “pay-for-delay settlements,” occurs when branded companies pay generic manufacturers to keep their product off the market. The parties enter into a settlement where the generic manufacturer agrees to refrain from market entry for a certain period of time in exchange for not contesting the branded manufacturer’s patent(s). According to the FTC, “‘pay-for-delay’ agreements are a ‘win-win’ for the companies: brand name pharmaceutical prices stay high, and the brand and generic share the benefits of the brand’s monopoly profits. Consumers lose, however: they miss out on generic prices that can be as much as 90 percent less than brand prices. For example, brand-name medication that costs \$300 per month might be sold as a generic for as little as \$30 per month.”⁵⁶ The FTC has estimated that this practice can cost consumers and taxpayers \$3.5 billion per year in higher drug costs.⁵⁷

According to Dr. Shereef Elnahal, President and CEO of University Hospital in Newark, New Jersey, strategic manipulation by pharmaceutical companies for market control is a “big problem and there are no therapeutic advantages brought about by these practices.”⁵⁸ Enforcement is one solution, but these lawsuits are expensive, time consuming, and have had limited impact in this market.

In 2014, the FTC filed an antitrust lawsuit against pharmaceutical companies AbbVie and Besins alleging that they filed meritless patent infringement lawsuits against generic competitors seeking market entry as a generic to AbbVie’s AndroGel, a testosterone replacement drug. After multiple years of litigation, in June 2018, a judge ordered AbbVie to pay \$448 million, which amounted to the company’s profits during the period it fended off generic competitors.⁵⁹ This decision is currently on appeal before the Third Circuit.⁶⁰

During the height of the national opioid epidemic, the drug manufacturer for Suboxone, which is used to treat opioid withdrawal symptoms, was indicted and alleged to have engaged in a scheme to increase prescriptions.⁶¹ The company, Indivior PLC (formerly part of Reckitt Benckiser Pharmaceuticals), took its older drug off the market in 2012 and was alleged to have falsely claimed that the drug raised “concerns regarding pediatric exposure.” However, The Department of Justice alleges that the company removed the drug from the market to delay entry of generic competitors.⁶² Indivior then introduced another version of Suboxone and was alleged

⁵⁶ Federal Trade Commission, *Pay for Delay: How Drug Company Pay-Offs Cost Consumers Billions* (Jan. 2010) (<https://www.ftc.gov/sites/default/files/documents/reports/pay-delay-how-drug-company-pay-offs-cost-consumers-billions-federal-trade-commission-staff-study/100112payfordelayrpt.pdf>).

⁵⁷ *Id.*

⁵⁸ Interview with Dr. Shereef Elnahal.

⁵⁹ *Federal Trade Commission v. AbbVie Inc., et al.*, No. 14-5151 (E.D. Pa. Jun. 29, 2018). *See also* *AbbVie, AndroGel partner owe \$448 million in antitrust case: U.S. judge*, Thomson Reuters (Jun. 29, 2018) (<https://www.reuters.com/article/us-abbvie-lawsuit/abbvie-androgel-partner-owe-488-million-in-antitrust-case-u-s-judge-idUSKBN1JP3A8>).

⁶⁰ *Federal Trade Commission v. AbbVie Inc., et al.*, (3d Cir. 2019).

⁶¹ *United States v. Indivior, Inc. (a/k/a Reckitt Benckiser Pharmaceuticals Inc.) and Indivior PLC*, 1:19-CR-16 (W.D. Va. 2019). The criminal case is still pending.

⁶² *Id.* *See also* Department of Justice, Office of Public Affairs, *Indivior Inc. Indicted for Fraudulently Marketing Prescription Opioid*, (Apr. 9, 2019).

to have used false and misleading marketing tactics – claiming the drug was safer and less susceptible to abuse than the older version, despite a lack of any support for these claims.⁶³ In October 2019, the company settled a civil suit with Michigan and 32 other states.⁶⁴

Regulatory Strategies: Exclusivity is also granted by law upon FDA approval, regardless of whether a drug is patented or can run concurrently to patent exclusivity. This exclusivity generally prevents other qualified applicants from entering the market.⁶⁵ These types of protections can come in several forms. Data exclusivity precludes other potential drug makers from relying on FDA safety and effectiveness findings in new drug applications. Market exclusivity prevents other qualified applicants from entering the market for a period of time. For example, The Orphan Drug Act provides seven years of exclusivity upon FDA approval for drugs that treat fewer than 200,000 people.⁶⁶ This protection was originally designed to encourage manufacturers to develop treatments for rare diseases that may lack patent protection.⁶⁷ Despite this, branded drug manufacturers have been able to obtain orphan drug exclusivity for drug treatments that don't address the intent of the protection. According to Dr. Martin Makary, professor and surgical oncologist at Johns Hopkins University, "[t]he industry has been gaming the system by slicing and dicing indications so that drugs qualify for lucrative orphan status benefits . . . As a result, funding support intended for rare disease medicine is diverted to fund the development of blockbuster drugs."⁶⁸

When a drug patent eventually expires, pharmaceutical companies can engage in other tactics intended to prevent generics from reaching the market. These can include refusing to provide generic entrants with the drug samples necessary for generic manufacturers to demonstrate bioequivalence and obtain premarket approval from the FDA to bring new drugs to market.⁶⁹ According to Dr. Kesselheim, "even just one day of additional exclusivity can pay for a lot of lawyers."⁷⁰ In May 2018, the FDA published a list of brand name manufacturers that were alleged to have blocked access to samples needed by generic manufacturers.⁷¹ Despite the FDA's

⁶³ *Id.*

⁶⁴ *Michigan to receive \$2.6 Million in Settlement with Suboxone Drug Manufacture*, Michigan Department of Attorney General (Oct. 4, 2019) (<https://www.michigan.gov/som/0,4669,7-192-47796-509201--,00.html>).

⁶⁵ Congressional Research Service, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress* (R45666) (Apr. 4, 2019).

⁶⁶ Pub. L. No. 97-414. Orphan drug status can also be awarded for a drug that may affect more than 200,000 people if the pharmaceutical company does not expect to recover its investment costs. *See FDA to Revoke Orphan Designation for Opioid Addiction Drug Sublocade*, Regulatory Affairs Professional Society (Nov. 8, 2019) (<https://www.raps.org/news-and-articles/news-articles/2019/11/fda-revokes-orphan-designation-for-opioid-addictio>).

⁶⁷ Matrix Global Advisors, *Gamesmanship and Other Barriers to Drug Competition* (Jul. 2019) (http://www.affordableprescriptiondrugs.org/app/uploads/2019/07/brand_gamesmanship_july_2019.pdf).

⁶⁸ 'Orphan Drug' Loophole Needs Closing, *Johns Hopkins Researchers Say*, Johns Hopkins Medicine (Nov. 19, 2015) (https://www.hopkinsmedicine.org/news/media/releases/orphan_drug_loophole_needs_closing_johns_hopkins_researchers_say).

⁶⁹ Congressional Research Service, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development* (R44810) (Mar. 16, 2018).

⁷⁰ Interview with Dr. Aaron Kesselheim.

⁷¹ Food and Drug Administration, *Reference Listed Drug (RLD) Access Inquiries* (Sept. 24, 2019) (<https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/reference-listed-drug-rld-access-inquiries>).

public “shaming” list, generic manufacturers continue to experience harm from lack of access to drug samples necessary to file new drug applications with the FDA.

4. Research and Development

One common misconception is that pharmaceutical companies discover all of the drugs they are currently manufacturing. This is often not the case. According to Dr. Anderson, “most research and development is already accounted for before a pharmaceutical company gets their hands on it.”⁷² For transformative drugs in particular, research and development usually begins at an academic institution or another federally funded organization. Of the 210 new drugs approved by the FDA from 2010-2016, funding from the National Institute of Health contributed to published research associated with every drug.⁷³ A 2015 study found that of the most transformative drugs throughout the past twenty-five years, more than half of the products originated as part of publicly funded research.⁷⁴

Pharmaceutical companies have explained that only a small percentage of drug therapies that enter clinical trials are ever approved and the average cost of development can exceed \$2.5 billion, with large setbacks and high failure rates of clinical trials.⁷⁵ However, pharmaceutical companies consider research and development information to be proprietary and confidential, so it is difficult to say with any certainty how much a drug actually costs to develop.⁷⁶ A 2014 study found that investment expenditures in research and development for the ten largest pharmaceutical companies amounted to anywhere from 7% to 21% of pharmaceutical companies’ overall revenue.⁷⁷

C. Generic Drugs

The contrast in pricing between brand name and generic drugs is stark. Branded drug prices continue to rise at rates greater than 100 times the rate of inflation while generic drug prices have declined.⁷⁸ In 2018, generic drug competition created about \$293 billion in overall

⁷² Interview with Dr. Gerard Anderson.

⁷³ Ekaterina Galkina Cleary, et al., *Contribution of NIH funding to new drug approvals 2010–2016*, Proceedings of the National Academy of Sciences of the United States of America (Feb. 12, 2018).

⁷⁴ Aaron S. Kesselheim, et al., *The Roles Of Academia, Rare Diseases, And Repurposing In The Development Of The Most Transformative Drugs*, Health Affairs (Feb. 2015).

⁷⁵ Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, *Innovation in the pharmaceutical industry: New estimates of R&D costs*, Journal of Health Economics (May 2016). See also Chi Heem Wong, Kien Wei Siah, and Andrew W. Lo, *Estimation of clinical trial success rates and related parameters*, Biostatistics (Jan. 31, 2018).

⁷⁶ *With drug costs rising, it’s time for pharma companies to open their books*, STAT News (Jan. 16, 2016) (<https://www.statnews.com/pharmalot/2016/02/16/drug-cost-transparency/>).

⁷⁷ Aaron S. Kesselheim, Jerry Avorn, and Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, Journal of American Medicine Association (Aug. 2016).

⁷⁸ AARP Public Policy Institute, *Brand Name Prescription Drug Prices Increase Four Times Faster than Inflation in 2017* (Sept. 2018) (<https://www.aarp.org/content/dam/aarp/ppi/2018/09/brand-name-prescription-drug-prices-increase-four-times-faster-than-inflation.pdf>). See also Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Understanding Recent Trends in Generic Drug Prices* (Jan. 27, 2016) (<https://aspe.hhs.gov/system/files/pdf/175071/GenericsDrugpaperr.pdf>).

savings.⁷⁹ Statewide savings in 2018 through using generic prescriptions drugs range from an annual average of approximately \$399 million in Alaska to \$26.1 billion in California. The state of Michigan saves an average of \$9.5 billion dollars on prescription drugs through its use of generic products.⁸⁰

Currently, 90% of prescription drugs sold in the U.S. are generic medications. Despite this, generic drug sales account for less than 25% of prescription drug spending.⁸¹ Drug prices drop substantially after generic manufacturers enter the market. Generic retail prices are an average of 75 to 90% lower than retail prices of brand name counterparts.⁸² Of the generic prescriptions filled at pharmacies throughout the U.S., 93% cost twenty dollars or less and the average generic copay is approximately \$6.06.⁸³

Figure 1: The expanding role of generics in the U.S. drug market

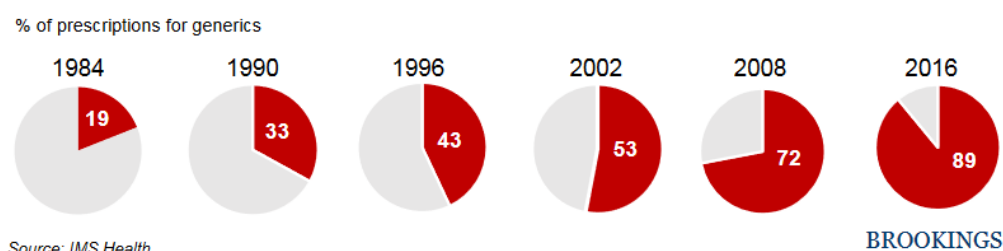


Figure 3: Expanding Role of Generics in US Drug Market⁸⁴

Though generics present significant potential savings, those savings do not come without costs. Generic drug manufacturers have been the subject of multiple recent lawsuits alleging price fixing. Generic manufacturers have also engaged in periodic price spikes for key medications. In addition, as discussed below, the bulk of generic drugs sold in the U.S. are produced by manufacturers with facilities in other countries. Today, the FDA inspects or samples less than 1% of all regulated drug products before allowing them into the U.S.⁸⁵ While the

⁷⁹ Association for Accessible Medicines, *The Case for Competition: 2019 Generic Drug & Biosimilars Access & Savings in the U.S. Report* (2019) (<https://accessiblemeds.org/sites/default/files/2019-09/AAM-2019-Generic-Biosimilars-Access-and-Savings-US-Report-WEB.pdf>). See also Acting Commissioner Norman E. Sharpless, Food and Drug Administration, *Statement on continued progress enhancing patient access to high-quality, low-cost generic drugs* (Oct. 16, 2019) (<https://www.fda.gov/news-events/press-announcements/statement-continued-progress-enhancing-patient-access-high-quality-low-cost-generic-drugs>).

⁸⁰ Association for Accessible Medicines, *Generic Drug Access & Savings in the U.S.: Access in Jeopardy* (2018) (https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf).

⁸¹ *Id.*

⁸² Government Accountability Office, *Generic Drug Applications: FDA Should Take Additional Steps to Address Factors that May Affect Approval Rates in the First Review Cycle* (GAO-19-565) (Aug. 2019).

⁸³ Association for Accessible Medicines, *Generic Drug Access & Savings in the U.S.: Access in Jeopardy* (2018) (https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf).

⁸⁴ Thomas J. Bollyky and Aaron S. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* Center for Health Policy and Hutchins Center of Fiscal & Monetary Policy at Brookings (May 2, 2017).

⁸⁵ FDA Consumer Health Information, *Ensuring the Safety of Imported Products, Q&A with David Elder* (Oct. 2010) (<https://www.fda.gov/consumer>). See also *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*,

United States. drug market remains among the safest in the world, shifts in domestic production and reliance on active pharmaceutical ingredients for production require sufficiently resourced and prioritized oversight.⁸⁶ In addition, the economic model of the U.S. drug market for generic manufacturers has, at times, perpetuated unsustainable profit margins and an increased dependence on foreign countries with cheaper production costs. The cumulative effects of these concerns often lead to manufacturers exiting the market, potential drug shortages, and price increases.

1. Abbreviated New Drug Approval Process

Generic manufacturers experience three significant roadblocks when trying to enter the market. First, they must successfully obtain samples of the brand name drug from the manufacturer and demonstrates bioequivalence. Second, like all new drugs, generics must receive approval from the FDA through the abbreviated new drug application (ANDA) process.⁸⁷ Third, they must navigate patents and exclusivities that oftentimes are used to shield brand name drugs from competition.

In the early 1980's, only 35% of top selling drugs had generic competitors.⁸⁸ In response, to help increase generics' ability to enter the market while maintaining incentives for brand name companies to continue developing new drugs, Congress enacted the Drug Price Competition and Patent Term Restoration Act, known as the "Hatch-Waxman Act." The law, in part, provides a pathway for generic drugs – those that can prove "bioequivalence" and "pharmaceutical equivalence" – to enter the market by being the first to file an ANDA with the FDA in exchange for six months' of market exclusivity in certain cases. The Hatch-Waxman Act paved the way for generics to more efficiently enter the market.⁸⁹

The ANDA process is estimated to take anywhere from ten months to several years depending on whether the process requires more than one review cycle. Passage and reauthorization of the Generic Drug User Fee Amendments (GDUFA) and other steps taken by the FDA, such as its 2017 Drug Competition Action Plan, have helped reduce the backlog of

Bloomberg Businessweek (Sept. 12, 2019); Judith Alphonse, et al., *The FDA Funding Crisis*, Journal of Pharmacy Technology (Apr. 30, 2014).

⁸⁶ Jasenko Karamelic et al., *Financial Aspects and the Future of the Pharmaceutical Industry in the United States of America*, Mater Sociomed (Nov. 24, 2013). See also U.S.-China Economic and Security Review Commission, *2019 Annual Report to Congress* (Nov. 2019) (<https://www.uscc.gov/sites/default/files/2019-11/2019%20Annual%20Report%20to%20Congress.pdf>) (hereinafter "USCC 2019 Annual Report"). See also Janet Woodcock, *Safety, Efficacy, and Quality Remain Top Priorities as We Continue Our Work to Expand Access to Cost-Saving Generic Drugs for the American Public*, Food and Drug Administration (May 13, 2019) (<https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/safety-efficacy-and-quality-remain-top-priorities-we-continue-our-work-expand-access-cost-saving>).

⁸⁷ The Biologics Price Competition and Innovation Act of 2009 created a similar pathway for the approval of a biologic product that can demonstrate it is biosimilar or interchangeable with the original biologic. See Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148.

⁸⁸ Congressional Research Service, *The Hatch-Waxman Act: A Quarter Century Later* (R41114) (Mar. 13, 2012).

⁸⁹ The Drug Price Competition and Patent Term Restoration Act, Pub. L. 98-417 (1984) (commonly referred to as the "Hatch-Waxman Act"). See also Congressional Research Service, *The Hatch-Waxman Act: A Quarter Century Later* (R41114) (Mar. 13, 2012).

ANDAs and provide the FDA with needed resources to ensure timely ANDA review. However, delays still exist. Critics argue that the FDA’s review process is too subjective. The process has led to an average approval of only 12% for first review cycle drug applications.⁹⁰

2. Economic Model

Race to the bottom: While the generic drug industry has helped to provide inexpensive and needed medications for patients, the economic model of the industry has created risks as well. In some instances, generic manufacturers have made business decisions not to maintain production of certain drugs with high production costs, resulting in consolidation (with fewer and sometimes only a single supplier), higher drug prices, and market fragility that makes the drug product susceptible to shortage.⁹¹

This pricing model has also led firms to look for inexpensive supply chain strategies. Raw materials and API are usually single sourced and bought in bulk. In 2011, former FDA Commissioner Dr. Scott Gottlieb described the problem in testimony before Congress:

[t]ake the example of more glass lamellae being found in solution. Through 2010, firms typically recalled no more than a single product for this kind of deficiency. By the end of the second quarter in 2011, there had been 21 products recalled for glass lamellae being found in drug solutions. This surge in recalls was primarily due to a single decision by a number of different firms to simultaneously switch to packaging their drugs in lower-cost vials that degraded under certain conditions.⁹²

Price Spikes: A 2016 bipartisan report by the Senate Special Committee on Aging found that price spikes among older off-patent drugs usually occurred in sole source “gold standard” drug products in small markets with closed distribution channels.⁹³ As one example, Martin Shkreli, the former hedge fund manager who acquired Turing Pharmaceuticals, increased the

⁹⁰ Pew Charitable Trusts, *FDA Approves More Generic Drugs, but Competition Still Lags* (Feb. 25, 2019) (https://www.pewtrusts.org/-/media/assets/2019/02/fda_approves_more_generic_drugs_but_competition_still_lags.pdf). See also Government Accountability Office, *Generic Drug Applications: FDA Should Take Additional Steps to Address Factors that May Affect Approval Rates in the First Review Cycle* (GAO-19-565) (Aug. 2019); FDA News Release, *FDA Tackles Drug Competition to Improve Patient Access* (Jun. 27, 2017) (<https://www.fda.gov/news-events/press-announcements/fda-tackles-drug-competition-improve-patient-access>); Food and Drug Administration, *List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic* (undated) (<https://www.fda.gov/media/105829/download>); FDA Reauthorization Act of 2017, Pub. L. No. 115-52.

⁹¹ *The generic drug industry has brought huge cost savings. That may be changing*, Washington Post (Aug. 1, 2017) (https://www.washingtonpost.com/business/economy/the-generic-drug-industry-has-brought-huge-cost-savings-that-may-be-changing/2017/08/01/ee128d0a-68cf-11e7-8eb5-cbccc2e7bfbf_story.html).

⁹² House Committee on Oversight and Government Reform, Subcommittee on Healthcare, Testimony Submitted for the Record of Dr. Scott Gottlieb, American Enterprise Institute, *Hearing on The Causes of Drug Shortages and Proposals for Repairing these Markets*, 116th Cong. (Nov. 30, 2011).

⁹³ Senate Special Committee on Aging, *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (2016) (S. Rept. 114-429).

price of pyrimethamine (Daraprim), a 62 year-old drug used to treat life threatening parasitic infections, from \$13.50 a tablet to \$750 a tablet.⁹⁴ There was no generic competitor for this drug. Another drug, alteplase/tPA (Activase), used to treat heart attacks by breaking up blood clots, has been on the market since it received FDA approval in 1987. Without any competition, Genentech tripled the price for a 100 mg vial from \$2,867 in 2005 to \$9,197 in 2019.⁹⁵

While in general, generic drug prices have been decreasing, certain exceptions exist. For example, a 2016 GAO study analyzing generic drug prices under Medicare Part D found that while prices declined overall under Medicare Part D, more than 300 generic drugs experienced “extraordinary” price hikes. The four main factors associated with generic price spikes are niche drug markets, mergers and acquisitions, drug shortages, and regulatory policy (e.g. FDA’s Unapproved Drug Initiative).⁹⁶

3. Competition

Competition in the generic marketplace is often distorted. There are two different types of generics: authorized generics and true generics.⁹⁷ Authorized generics are a branded drug company’s relabeling of its branded drug as a generic. True generics are an independent generic manufacturer’s version of the branded drug. Authorized generics are either marketed by the branded drug company or another company with the branded company’s permission. This market allocation often allows the branded drug company to control a significant portion of the market when there are only a small number of competitors. It also contributes to market barriers, making it difficult for true generics to obtain a strong market position.⁹⁸

Less competition in the branded marketplace can impact innovation, new drug approvals, and numerous other factors throughout the industry. From 1995 to 2015, 60 pharmaceutical companies merged into ten.⁹⁹ A 2017 GAO report found that mergers and acquisitions by the largest 25 pharmaceutical and biotechnology companies doubled from 29 transactions in 2006 to 61 transactions in 2015, indicating increased consolidation at the top. GAO found that “drug company mergers can have varied impacts on innovation as measured by research and development spending, patent approvals, and drug approvals.” GAO concluded, based on a

⁹⁴ Andrew Pollack, *Drug Goes From \$13.50 a Tablet to \$750, Overnight*, New York Times (Sept. 20, 2015) (<https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>).

⁹⁵ Dawn Kleindorfer, et al., *Cost of Alteplase Has More Than Doubled Over the Past Decade*, Journal of the American Heart Association (Apr. 5, 2017). See also *Activase Prices, Coupons and Patient Assistance Programs*, Drugs.com (undated) (<https://www.drugs.com/price-guide/activase>) (accessed Nov. 27, 2019).

⁹⁶ Government Accountability Office, *Part D Generic Drug Prices Declined Overall but Some had Extraordinary Price Increases* (GAO-16-706) (Aug. 2016). See also Frazer A. Tessema, et al., *Generic But Expensive: Why Prices Can Remain High for Off-Patent Drugs*, Hastings Law Journal (Aug. 21, 2019).

⁹⁷ Food and Drug Administration, *FDA List of Authorized Generic Drugs* (Oct. 1, 2019) (<https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/fda-list-authorized-generic-drugs>).

⁹⁸ Interview with Robin Feldman.

⁹⁹ *Pharmaceutical mergers and megamergers stifle innovation*, STAT News First Opinion (Jul. 10, 2019) (citing Open Markets Institute, *High Drug Prices & Monopoly* (undated)).

review of relevant studies, that “less competition—that is, a more highly concentrated market—is associated with higher drug prices, particularly for generic drugs.”¹⁰⁰

Market consolidation of purchasers creates an additional barrier for generic manufacturers. Three purchasing companies; Red Oak Sourcing (CVS Health and Cardinal Health), Express Scripts, and ClarusOne Sourcing Services, LLP (McKesson and Walmart), comprise 90% of the market.¹⁰¹ This structure makes it difficult for more than three generic manufacturers to be profitable and can lead to market withdrawal among manufacturers of low-cost generic drugs.¹⁰² The FDA has no insight into the market capacity of each approved manufacturer, so it may appear as though more manufacturers are producing a certain drug than actually are.¹⁰³ According to Erin Fox, Senior Director of Drug Information and Support Services at the University of Utah, many companies may own the rights to manufacture generics and other product, but that does not mean they are actually manufacturing these products. When the FDA approves a company to manufacture a product, there is no guarantee that the company will actually follow through and make it.¹⁰⁴ According to one report, over 155 injectable generic drugs approved by the FDA between 2016 and 2018 have not yet been brought to market.¹⁰⁵

A recent study found that the number of entrants to the generic market has decreased since 2013 while the number of exits from the market is generally increasing.¹⁰⁶ Additionally, the study found evidence to suggest that the prices of generic drugs are increasing over time, which “positively correlated with reduced manufacturer counts and alternative measures of increased supplier concentration.”¹⁰⁷ From 2008-2014, prices of generic medications with three or fewer manufacturers were “considerably higher” than those with a greater number of competitors.¹⁰⁸

¹⁰⁰ Government Accountability Office, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals* (GAO-18-40) (Nov. 2017).

¹⁰¹ *The Big Three Generic Drug Mega-Buyers Drove Double-Digit Deflation in 2018. Stability ahead?*, Drug Channels (Jan. 8, 2019) (<https://www.drugchannels.net/2019/01/the-big-three-generic-drug-mega-buyers.html>).

¹⁰² *The generic drug industry has brought huge cost savings. That may be changing*, Washington Post (Aug. 1, 2017) (https://www.washingtonpost.com/business/economy/the-generic-drug-industry-has-brought-huge-cost-savings-that-may-be-changing/2017/08/01/ee128d0a-68cf-11e7-8eb5-cbccc2e7bfbf_story.html).

¹⁰³ House Committee Energy and Commerce, Subcommittee on Health, *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, 116th Cong. (Oct. 30, 2019) (hereinafter “*Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*”). See also *Trump Administration Salutes Parade of Generic Drug Approvals, But Hundreds Aren’t For Sale*, Kaiser Health News (Feb. 7, 2019) (<https://khn.org/news/trump-administration-salutes-parade-of-generic-drug-approvals-but-hundreds-arent-for-sale/>).

¹⁰⁴ Erin Fox, Senior Director of Drug Information and Support Services at the University of Utah, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Aug. 1, 2019) (hereinafter “Interview with Erin Fox”).

¹⁰⁵ *Trump Administration Salutes Parade of Generic Drug Approvals, But Hundreds Aren’t For Sale*, Kaiser Health News (Feb. 7, 2019).

¹⁰⁶ Ernst R. Berndt, Rena M. Conti, and Stephen J. Murphy, *The Landscape of the US Generic Prescription Drug Markets, 2004-2016*, National Bureau of Economic Research (Jul. 2017).

¹⁰⁷ *Id.*

¹⁰⁸ Chintan V. Dave, Abraham Hartzema, and Aaron S. Kesselheim, *Prices of Generic Drugs Associated with Numbers of Manufacturers*, New England Journal of Medicine (2017).

Currently, there is ongoing antitrust litigation alleging price fixing among approximately twenty generic drug manufacturers.¹⁰⁹

D. Impacts

The issues identified with brand name and generic drug prices carry significant consequences for patients, consumers, and hospitals.

1. Hospitals

From 2015-2017, prescription drug spending at community hospitals throughout the U.S. increased by 18.5% , more than double the rate of overall medical inflation.¹¹⁰ Rising drug costs have forced hospitals to restructure their budgets to ensure they can afford critical care medications and scale back supply. According to a survey conducted by the American Hospital Association, 65% of hospitals indicated that drug prices had “moderate or severe impact on their budgets.”¹¹¹ As a result of rising drug costs, hospitals have had to find alternative drug treatments, perform more in-house compounding of drug products, delay investments in equipment, reduce staffing, and reduce services offered to patients.¹¹²

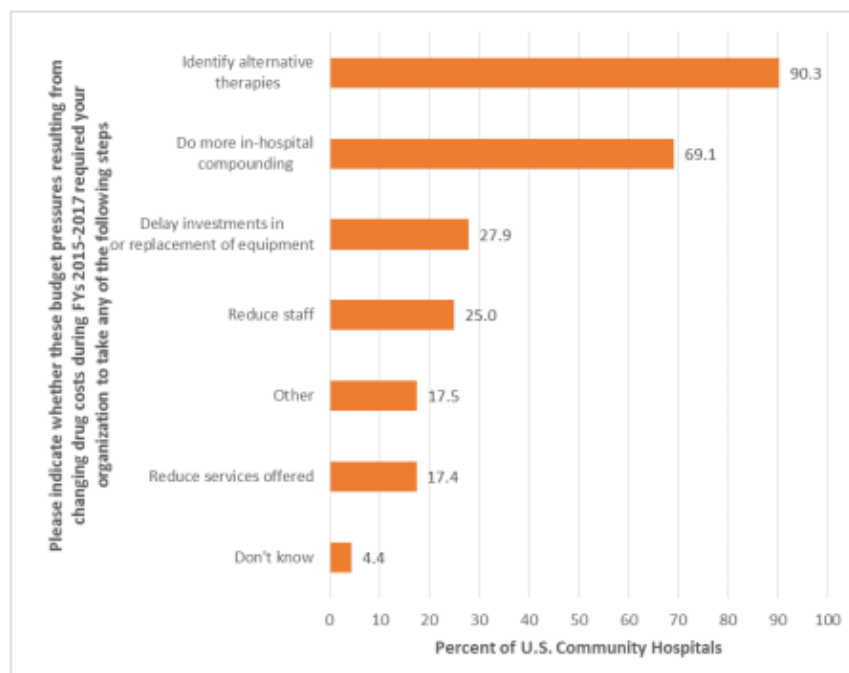


Figure 4: Measures Taken by Hospitals to Mitigate Budget Pressures Associated with Changing Drug Prices¹¹³

¹⁰⁹ *In re: Generic Pharmaceuticals Pricing Antitrust Litigation*, No. 2:16-md-02724-CMR (E.D. Pa. 2016).

¹¹⁰ NORC at the University of Chicago, *Recent Trends in Hospital Drug Spending and Manufacturer Shortages* (Jan. 15, 2019) (<https://www.aha.org/system/files/2019-01/aha-drug-pricing-study-report-01152019.pdf>).

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.*

2. Patients & Consumers

David Mitchell, President and Founder of Patients for Affordable Drugs, testified before Congress that “right now, there's a fundamental question drug companies want us to ask about drug prices, what are we willing to pay to save a life? And I can tell you, that's easy. When it's your child's ability breathe, when it's your cancer, the answer is anything. But that is the wrong question. We should be asking, what is the right amount of money the drug companies should make on these drugs?”¹¹⁴ With rising prescription drug costs, many patients are unable to afford their medication. Medication non-adherence has devastating effects for patients and places a significant burden on health care systems.¹¹⁵ A 2018 report by the Association for Accessible Medicines found that patients who were prescribed brand name prescription drugs were 2-3 times more likely to stop taking their prescriptions.¹¹⁶ Brett Gingrich, Director of Pharmacy for Cherry Health, a non-profit Federally Qualified Health Center (FQHC) in Michigan, often sees patients who are unable to afford their prescription medication. According to Gingrich, “people have to choose between food or medicine and many times, they choose food because they’re hungry.”¹¹⁷

Many people throughout the country have had difficulty affording needed medication because of the high cost of prescription drugs in the United States. Jenni Bramble, from Lincoln Park, Michigan, has lived with rheumatoid arthritis since 1999. She explained that she has at times had to resort to rationing and applying for supplemental assistance to afford the cost of her medication. Ms. Bramble, who makes below the median income in Michigan, estimates that even with the additional assistance she receives, her medical expenses for 2019 have already exceeded \$5,000. “It’s scary for me because I’m not even 50 years old and I have to ask myself how much longer am I going to be able to afford living.”¹¹⁸ In 2019, there has been an influx in the number of patients and their families that have resorted to traveling across the border to Canada to obtain affordable lifesaving drugs, such as insulin.¹¹⁹ In worst case scenarios, individuals have resorted to rationing or taking a different form of insulin, which in some cases has led to death.¹²⁰

¹¹⁴ House Committee on Education and Labor, Subcommittee on Health, Employment, Labor, and Pensions, *Hearing on Making Health Care More Affordable: Lowering Drug Prices and Increasing Transparency*, 116th Cong. (Sept. 26, 2019).

¹¹⁵ Rachelle Louise Cutler, et al. *Economic impact of medication non-adherence by disease groups: a systematic review*, BMJ Open (Jan. 21, 2018).

¹¹⁶ Association for Accessible Medicines, *Generic Drug Access & Savings in the U.S.: Access in Jeopardy* (2018) (https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf).

¹¹⁷ Brett Gingrich, Director of Pharmacy for Cherry Health, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Oct. 22, 2019).

¹¹⁸ Jenni Bramble, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Nov. 25, 2019).

¹¹⁹ *As price of insulin soars, Americans caravan to Canada for lifesaving medicine*, Washington Post (Jul. 31, 2019) (https://www.washingtonpost.com/world/the_americas/as-price-of-insulin-soars-americans-caravan-to-canada-for-lifesaving-medicine/2019/06/14/0a272fb6-8217-11e9-9a67-a687ca99fb3d_story.html). See also *American caravan arrives in Canadian 'birthplace of insulin' for cheaper medicine*, Reuters (Jun. 29, 2019) (<https://www.reuters.com/article/us-canada-health-insulin/american-caravan-arrives-in-canadian-birthplace-of-insulin-for-cheaper-medicine-idUSKCN1TU0T4>).

¹²⁰ *He lost his insurance and turned to a cheaper form of insulin. It was a fatal decision*, Washington Post (Aug. 3, 2019) (https://www.washingtonpost.com/local/he-lost-his-insurance-and-turned-to-cheaper-form-of-insulin-it-was-a-fatal-decision/2019/08/02/106ee79a-b24d-11e9-8f6c-7828e68cb15f_story.html). See also *Insulin's High Cost*

Kathy Pawlicki, President of the American Society of Health-System Pharmacists and Vice President and Chief Pharmacist at Beaumont Health, explained how her hospital pharmacy spent hours with patients navigating unaffordable prescription drug costs. One patient on a monthly fixed income of \$1,700 was unable to pay for her approximately \$500 in medication costs each month. Beaumont Health’s pharmacists assisted the patient in enrolling in Medicare Parts B and D, utilizing patient assistance programs, and substituting alternative therapies. Eventually, they were able to lower the monthly cost of the medication from \$500 to \$50. Pawlicki explained that this level of involvement meant that “[a] patient would not be able to navigate this complex system independently to find a method of affording their medications.”¹²¹

III. DRUG SHORTAGES

The continued rise in drug shortages constitutes a serious public health concern. Drug shortages increased by 300% from 2005 to 2014.¹²² In the second quarter of 2019, the number of active shortages – 282 – already exceeded the number of shortages at any point in 2018 according to the American Society of Health-System Pharmacists (ASHP).¹²³ Active drug shortages in the U.S. are at their highest levels since 2015, and shortages are lasting longer. As Robert Ripley, Vice President and Chief Pharmacy Officer for Trinity Health, stated “25 years ago a bad year would be marked by a maximum of 10 to 15 drug shortages.” Today, the number of drug shortages is well over 100 per year, and oftentimes upward of 150.¹²⁴

The FDA defines a drug shortage as “a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply of the drug.”¹²⁵ ASHP takes a more practitioner focused approach to shortages, which they define as “a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.”¹²⁶ The FDA did not begin collecting data until the drug shortage crisis in 2011.¹²⁷ ASHP data on drug shortages has been in existence since 2001. Because ASHP

Leads To Lethal Rationing, National Public Radio (Sept. 1, 2018) (<https://www.npr.org/sections/health-shots/2018/09/01/641615877/insulins-high-cost-leads-to-lethal-rationing>).

¹²¹ Kathy Pawlicki, President of the American Society of Health-System Pharmacists and Vice President and Chief Pharmacist at Beaumont Health, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Sept. 11, 2019).

¹²² Judith Alphonse, et al., *The FDA Funding Crisis*, Journal of Pharmacy Technology (Apr. 30, 2014).

¹²³ University of Utah Drug Information Service, *National Drug Shortages: Active Shortages by Quarter* (<https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics>) (accessed Dec. 4, 2019).

¹²⁴ Interview with Robert Ripley. See also Food and Drug Administration, *Drug Shortages Root Causes and Potential Solutions* (2019) (<https://www.fda.gov/media/132058/download>) (hereinafter “FDA 2019 Drug Shortages Task Force Report”).

¹²⁵ 21 U.S.C. § 356c(h)(2).

¹²⁶ *Drug Shortages FAQs*, American Society of Health-System Pharmacists (undated) (<https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-FAQs>) (accessed Nov. 27, 2019).

¹²⁷ Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge*, Appendix I (GAO-16-595) (Jul. 2016) (noting FDA data “did not lend itself to analysis [as] it was not easily retrievable, routinely recorded, or sufficiently reliable”).

is regarded as the most comprehensive and reliable source of drug shortage data, this report refers predominately to ASHP's data.¹²⁸

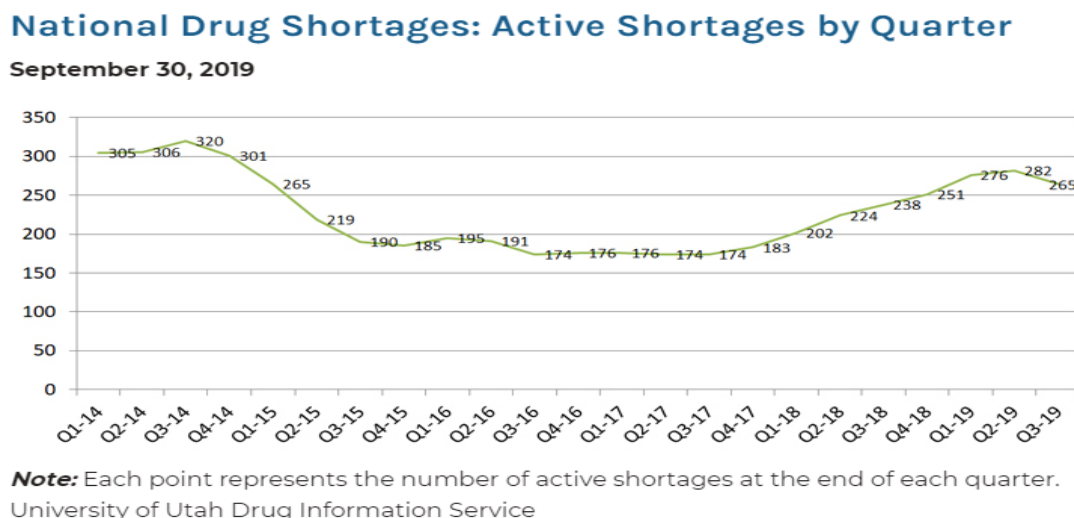


Figure 5: National Drug Shortages: Active Shortages by Quarter¹²⁹

A. Causes

The causes of drug shortages are different based on the type of drug. Generally, there are two ways to administer a drug, each with different implications as they relate to shortages. A non-parenteral drug is often administered orally, for example, by pill. Parenteral drugs are administered by injection and are often referred to as sterile injectables. Both non-parenteral and parenteral drugs can be brand name or generic.

Drug shortages disproportionately affect generic medications, such as antibiotics, central nervous system agents, electrolytes/fluids, cardiovascular drugs, and chemotherapies.¹³⁰ Of these generic medications, shortages affect sterile injectable drugs at a much higher rate than non-injectable drugs. The complex and costly production process required for sterile injectable drugs is one major reason that sterile injectable drugs make up the largest percentage of drugs in shortage.¹³¹ In 2018, 64% of drug shortages involved generic sterile injectable drugs, such as IV saline, sodium bicarbonate, chemotherapy agents, and other critical care drugs.¹³²

¹²⁸ Erin R. Fox, et al., *Drug Shortages: A Complex Health Care Crisis*, Mayo Clinic Proceedings (Mar. 2014). See also Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge*, Appendix I (GAO-16-595) (Jul. 2016).

¹²⁹ University of Utah Drug Information Service, *National Drug Shortages: Active Shortages by Quarter* (<https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics>) (accessed Dec. 4, 2019).

¹³⁰ *Id.*

¹³¹ House Committee on Oversight and Government Reform, Subcommittee on Healthcare, Testimony Submitted for the Record of Dr. Scott Gottlieb, American Enterprise Institute, *Hearing on The Causes of Drug Shortages and Proposals for Repairing these Markets*, 116th Cong. (Nov. 30, 2011).

¹³² Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, *Report on the State of Pharmaceutical Quality* (2018) (<https://www.fda.gov/media/125001/download>).

To begin to address these concerns, in 1997 Congress began requiring manufacturers to notify the FDA of certain changes to the manufacture and supply of drugs.¹³³ Nevertheless, drug shortages began to rise steadily from 2007 (129 new shortages) until a peak in 2011. That year, 11% of all FDA approved and marketed drugs, vaccines, and biologics and nearly 25% of all generic injectable drugs were in shortage.¹³⁴ In response to the 2011 shortage crisis, President Obama issued an Executive Order that directed the FDA to use all appropriate administrative tools “to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of [certain life sustaining] drugs” and to expedite review of new drug suppliers and manufacturing sites.¹³⁵

Between 2010 and 2012, the FDA issued warning letters to seven sterile injectable drug manufacturing facilities, all of whom had difficulty meeting required manufacturing standards prior to receiving warning letters.¹³⁶ Left unaddressed, these and other FDA inspections and findings identifying safety and other concerns could risk exposing patients to injury or death. However, in many instances, a particular drug’s absence as a result of these findings led to shortages that impacted hospitals and patients.

From 2013-2017, the FDA reported that 62% of drugs shortages were due to a quality control issue.¹³⁷ In 2012, Congress expanded manufacturer notification requirements to help combat shortages.¹³⁸ The law now requires drug manufacturers to notify the FDA of “a permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply of that drug. . . and the reason for such discontinuance or interruption”¹³⁹ The FDA has said it is not aware of “any situation where a manufacturer has refused to provide requested information, but some companies may not be as forthcoming with detailed information.”¹⁴⁰ However, according to Erin

¹³³ The FDA Modernization Act of 1997 (FDAMA) required sole source manufacturers of a drug that is life-supporting, life-sustaining, or “intended for use in the prevention or treatment of a debilitating disease or condition,” to notify the FDA of a discontinuance in manufacturing at least six months prior to the date of the discontinuance, Pub. L. 105-115, Sec. 131. *See also* 21 U.S.C. § 356c. Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, expanded these reporting requirements.

¹³⁴ Erin R. Fox, et al., *Drug Shortages: A Complex Health Care Crisis*, Mayo Clinic Proceedings (Mar. 2014). *See also* University of Utah Drug Information Service, *National Drug Shortages: New Drug Shortages by Year* (<https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics>) (accessed Dec. 4, 2019).

¹³⁵ Executive Order No. 13588.

¹³⁶ Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge*, Appendix I (GAO-16-595) (Jul. 2016).

¹³⁷ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

¹³⁸ The Food Drug Administration Safety Innovation Act (FDASIA), Pub. L. No. 112-144, 126 Stat. 993 (2012). FDASIA also authorized the FDA to extend reporting requirements to biological product manufacturers.

¹³⁹ 21 U.S.C. § 356c(a)(2). FDA Regulations, 21 C.F.R. § 314.81(c), also require that manufacturers disclose the name of the drug or biologic product in question; the national drug code (or alternative identifier); the name of the applicant approved for manufacturing the drug or biologic; the reason for the interruption or discontinuance; the estimated duration of the interruption; and whether it is an interruption in or discontinuation of the manufacture of the drug. Information not required under the FDASIA includes: the percentage of the market held by the manufacturer; whether a manufacturer is experiencing a lack of available product due to an increase in demand; the inventory on hand and in distribution channels; or shortage risk management plans.

¹⁴⁰ Response from the Food and Drug Administration to the Homeland Security and Governmental Affairs Committee Minority Staff (Received Oct. 3, 2019).

Fox, manufacturers often refuse to provide the reason for a discontinuance, claiming that the information is a trade secret.¹⁴¹

In response to requests from Senator Peters and thirty-one other Senators in a 2018 bipartisan letter seeking answers on the root causes of shortages, former FDA Commissioner Gottlieb announced the creation of a new Drug Shortages Task Force in July 2018.¹⁴² The Task Force’s efforts included listening sessions and roundtables with experts, think tanks, advocacy groups, physicians, pharmaceutical companies, pharmacies, group purchasing organizations, among others affected by shortages. In November 2018, the Drug Shortages Task Force held a public meeting and subsequently opened a public docket for comments on the issue. It published the results of its findings in October 2019.

The FDA’s Drug Shortages Task Force identified three root causes of drug shortages: (1) a lack of incentives for manufacturers to produce less profitable drugs; (2) related disincentives for manufacturers to build and maintain mature quality management systems; and (3) logistical and regulatory challenges that hinder the market’s ability to recover after a disruption in supply.”¹⁴³ Issues underlying the FDA’s findings (disruption in supply chain, increased demand, and business decisions) are discussed below.

1. Disruption in Supply Chain

The pharmaceutical supply chain operates on a “just in time” delivery model, which means a hospital will only purchase on an as needed basis. As a result, only a limited amount of inventory is procured and stored.¹⁴⁴ Hospitals have little ability to deviate from this delivery model due to a general lack of storage space in most facilities. Manufacturers have little incentive to engage in redundant manufacturing due to the costs associated with storing certain drugs.¹⁴⁵ In addition, 80% of the active pharmaceutical ingredients in drugs sold in the U.S. come from overseas. The more complex the supply chain, the greater the opportunity for error. Increased globalization of the supply chain often makes it difficult for manufacturers to quickly obtain an active pharmaceutical ingredient needed for manufacturing during a shortage. According to the Task Force, “nearly all shortages are preceded by supply disruptions,” and the majority of supply disruptions were caused by quality issues.¹⁴⁶

¹⁴¹ Interview with Erin Fox.

¹⁴² Letter from U.S. Senators to former Commissioner Scott Gottlieb, MD, Food and Drug Administration (Jun. 15, 2018). *See also* Food and Drug Administration, *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* (Jul. 12, 2018) (<https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-formation-new-drug-shortages-task-force-and-fdas>).

¹⁴³ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

¹⁴⁴ Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge* (GAO-16-595) (Jul. 2016).

¹⁴⁵ Martin Van Trieste, President and CEO of Civica Rx, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Aug. 15, 2019) (hereinafter “Interview with Martin Van Trieste”).

¹⁴⁶ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

a. Drug Characteristics

The characteristics of a drug play a large role in whether and the extent to which a drug may be susceptible to a shortage. Generic drugs, as opposed to branded drugs, have less incentive to increase production in response to a shortage.¹⁴⁷ As Martin Van Trieste, pharmaceutical expert and CEO of Civica Rx, noted, “[i]t is not unusual for proprietary branded companies to keep a strategic stockpile on hand due to the amount of revenue generated from a branded product.” According to Van Trieste, for generic drugs “the cost to carry additional inventory often amounts to more than the cost of the drug itself.”¹⁴⁸

Sterile generic injectable drugs, while essential and oftentimes made of basic and widely available ingredients, are difficult and costly to make in a form that can be safely administered. Shortages disproportionately affect emergency medicine, anesthesiology, oncology, and parenteral nutritional therapies. The following are examples of low margin cost drugs critical for care yet often susceptible to shortages.

- **Sodium Bicarbonate Injection:** Sodium bicarbonate generally costs around 26 cents for a bag of 7.5% sodium bicarbonate intravenous solution.¹⁴⁹ Commercial production of this injectable drug began over half a century ago. It is a lifesaving drug for patients experiencing kidney failure and cardiac arrest. However, it is also a low margin drug used by all hospitals. Despite the demand for the drug, only a few manufacturers produce it. It is essentially a sterilized version of the same baking soda that can be found on every supermarket shelf in America. Sodium Bicarbonate is currently in shortage.¹⁵⁰
- **Sodium Chloride Injections, Bags, Vials, and Syringes “IV Saline”:** IV saline, which is almost entirely a combination of sterile water and sodium chloride (salt), has relatively low costs associated with the raw materials. Yet, the manufacturing process to make this highly critical emergency room product is complex. As former FDA Commissioner Dr. Scott Gottlieb described, “[y]ou have cumbersome costs such as shipping the water, paired with difficult manufacturing conditions, such as maintaining sterile facilities and proper equipment – all of these factors contribute to a high cost of production.”¹⁵¹ It also affects the care provided to patients. Erin Fox explained how the University of Utah hospital had to use syringes to give medication

¹⁴⁷ Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge* (GAO-16-595) (Jul. 2016).

¹⁴⁸ Interview with Martin Van Trieste.

¹⁴⁹ *Sodium bicarbonate Prices, Coupons and Patient Assistance Programs*, Drugs.com (undated) (<https://www.drugs.com/price-guide/sodium-bicarbonate>) (accessed Nov. 1, 2019).

¹⁵⁰ FDA Drug Shortages Database (<https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>) (accessed Dec. 4, 2019).

¹⁵¹ Dr. Scott Gottlieb, Former Commissioner of the Food and Drug Administration, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Jul. 17, 2019).

previously administered in small volume saline bags.¹⁵² Sodium Chloride is currently in shortage.¹⁵³

- **Vincristine:** Vincristine is a critical pediatric chemotherapy drug that has been in use since the 1960's. It went into shortage in October 2019. Pfizer became the sole distributor for the entire market after Teva Pharmaceuticals discontinued production in July 2019.¹⁵⁴ According to Teva, however, at the time it made a business decision to discontinue the product, the company only supplied 3% of the market.¹⁵⁵ Pfizer's orders for Vincristine increased from approximately 41,000 per month to approximately 75,000 per month in August 2019.¹⁵⁶ Dr. Yoram Unguru, a pediatric blood and cancer physician at the Children's Hospital at Sinai and bioethicist at Johns Hopkins Berman Institute of Bioethics, described Vincristine, which has experienced its second shortage in less than two years, as a "lifesaving drug for which there is no alternative." He noted, "nearly every child with cancer relies upon vincristine... [and such a] shortage has far reaching implications for children with cancer."¹⁵⁷ Vincristine is currently in shortage.¹⁵⁸ In November 2019, Teva announced it would resume manufacturing its Vincristine drug product.¹⁵⁹
- **Parenteral Nutrition Therapy:** Parenteral nutrition (PN), a critical therapy for patients with nonfunctioning or inaccessible gastrointestinal tracts, is a complex medication that can contain upward of 40 individual ingredients.¹⁶⁰ Oftentimes the therapy's components, most of which are low margin generic drugs are regularly in shortage.¹⁶¹ In 2011, during a shortage of intravenous amino acid products, nine patients died from the use of a substitute PN that was later found to be contaminated.

¹⁵² Interview with Erin Fox.

¹⁵³ FDA Drug Shortages Database (<https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>) (accessed Dec. 4, 2019).

¹⁵⁴ *Faced With a Drug Shortfall, Doctors Scramble to Treat Children With Cancer*, New York Times (Oct. 14, 2019) (www.nytimes.com/2019/10/14/health/cancer-drug-shortage.html).

¹⁵⁵ *Teva to restart production of cancer drug after shortages stressed treatment*, BioPharma Dive (Nov. 14, 2019) (www.biopharmadive.com/news/teva-vincristine-restart-production-shortage-pfizer/567284/). According to the FDA, Teva's departure from the marketplace was not the cause of the shortage. *See also Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

¹⁵⁶ Homeland Security and Governmental Affairs Committee Minority Staff correspondence with Pfizer (Dec. 4, 2019).

¹⁵⁷ Dr. Yoram Unguru, Pediatric Hematologist/Oncologist at The Herman and Walter Samuelson Children's Hospital at Sinai and Core Faculty Member at The Johns Hopkins Berman Institute of Bioethics, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Aug. 5, 2019) (hereinafter "Interview with Dr. Yoram Unguru").

¹⁵⁸ FDA Drug Shortages Database (www.accessdata.fda.gov/scripts/drugshortages/default.cfm) (accessed Dec. 4, 2019).

¹⁵⁹ *Teva Pharmaceuticals To Resume Production Of Scarce Childhood Cancer Drug Vincristine*, Forbes (Nov. 13, 2019) (<https://www.forbes.com/sites/victoriaforster/2019/11/13/teva-pharma-resumes-vincristine/#41d88df1e6a1>).

¹⁶⁰ Erin M. Nystrom, et al., *Parenteral Nutrition Drug Shortages: A Single-Center Experience with Rapid Process Change*, Journal of Parenteral and Enteral Nutrition (Jul. 2019). *See also* Beverly Holcombe, Todd W. Mattox, and Steve Plogsted, *Drug Shortages: Effect on Parenteral Nutrition Therapy*, Nutrition in Clinical Practice (Feb. 2018).

¹⁶¹ *Id.*

In 2012, a nationwide shortage of injectable zinc was associated with additional complications of premature infants.¹⁶²

- **Epinephrine:** Pre-divided single doses of epinephrine, a critical drug used to treat patients suffering from asthma attacks and cardiac arrests, have been regularly in shortage. Now, physicians, nurses, firefighters, and EMS responders have resorted to measuring their own dosages of this medication, adding critically precious minutes to treatments for life threatening emergencies, for example, when a patient’s heart has stopped. Bill Forbush, Fire Chief for the City of Alpena Fire Department in Michigan, explained that measuring the appropriate epinephrine dosage to administer could take five to ten minutes. “Depending on the situation and the drug, it could be quite involved ... [epinephrine] is one of those meds you need to use frequently and quickly. A dosage error could be fatal.”¹⁶³

b. Compliance with Manufacturing Standards

Manufacturers are required to adhere with FDA Current Good Manufacturing Practices (“CGMPs”) in order to manufacture drug products sold in the U.S.¹⁶⁴ CGMPs are the minimum threshold that companies must meet. They do not include more robust measures for quality management or redundancy. The generic market offers little resiliency for manufacturing problems. Manufacturing difficulties can include quality control issues from not properly maintaining a facility, deterioration of older equipment, and reallocation of resources. A review of prior FDA inspection reports revealed manufacturing facilities that had been in continuous operation since the 1960’s with certain manufacturing lines having undergone “only limited upgrades during that time while running [continuously].”¹⁶⁵ In addition, oftentimes, more than one drug is produced on the same manufacturing line. Disruption to a single line can therefore impact multiple drugs.¹⁶⁶

A 2017 survey by Pew Charitable Trusts and the International Society for Pharmaceutical Engineering found that 70% of manufacturers were discouraged from upgrading facilities and equipment due to the high costs, especially for low-margin, low-volume products and “legacy products developed 10 to 20 years ago.”¹⁶⁷ If a manufacturer makes changes or updates its

¹⁶² *Children Are Dying*, Washingtonian (May 22, 2013) (www.washingtonian.com/2013/05/22/children-are-dying/). See also Duke Ruktanonchai, et al., *Zinc Deficiency—Associated Dermatitis in Infants During a Nationwide Shortage of Injectable Zinc — Washington, DC, and Houston, Texas, 2012–2013*, Morbidity and Mortality Weekly Report (Jan. 17, 2014).

¹⁶³ Bill Forbush, Fire Chief for the City of Alpena Fire Department in Michigan, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Nov. 8, 2019).

¹⁶⁴ 21 U.S.C. § 351(a)(2)(B); 21 CFR §§ 210, 211.

¹⁶⁵ Janet Woodcock and Marta E. Wosinska, *Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages*, Clinical Pharmacology & Therapeutics (Feb. 2013) (hereinafter “Woodcock and Wosinska”).

¹⁶⁶ Erin R. Fox and Linda S. Tyler, *Potential Association between Drug Shortages and High-Cost Medications*, Pharmacotherapy (Nov. 1, 2017).

¹⁶⁷ Pew Charitable Trusts and the International Society for Pharmaceutical Engineering, *Drug Shortages: An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies* (Jan. 2017) (https://www.pewtrusts.org/~media/assets/2017/01/drug_shortages.pdf).

operations after initial market approval, it must obtain approval from the FDA and any other regulatory bodies depending on the manufacturers' location, a process that often takes years.¹⁶⁸

The FDA recently analyzed 163 drugs that went into shortage between 2013 and 2017 and had similar findings. 62% of the drugs analyzed went into shortage after supply disruptions related to manufacturing or quality issues.¹⁶⁹ When manufacturers experience a quality control problem and are forced to exit the market, it significantly affects the market because most other facilities do not have the capacity to ramp up production.¹⁷⁰

When manufacturers do not comply with requisite manufacturing standards, the risk of shortages and related public health impacts increases. A 2012 House Committee on Oversight and Government Reform report claimed that the FDA's regulatory activity "effectively shut down 30% of the total manufacturing capacity at four of American's largest producers of generic injectable medications."¹⁷¹ The underlying cause of drug shortages, however, is not overregulation, but a lack of investment in quality control by pharmaceutical manufacturers.

In response to questions from then House Oversight and Government Reform Committee Ranking Member Cummings about quality related issues that have led to drug shortages, the FDA wrote that when products or manufacturing conditions posed a threat to patient safety "such as glass shards or metal shavings in vials of injectable drug products or fungal contamination of the product" the manufacturers needed to stop production and resolve the problem. As one of several examples in its response letter, the FDA explained that in 2009, based on an inspection that confirmed the presence of endotoxins in Teva's propofol injectable, which, if injected, could cause "severe fever and even death," the FDA issued a Warning Letter to Teva citing violations affecting manufacture and quality of propofol and other drugs. Teva voluntarily closed its facility in response to address the identified problems. The FDA explained that contrary to the House report conclusions, the root cause of most shortages was beyond the FDA's control as in the last several years "more than half of all drug shortages were related to manufacturing production problems, including quality-related issues [and that remaining shortages were] caused by business decisions to discontinue certain products, difficulty obtaining raw materials, loss of manufacturing sites, increased demand, and component problems."¹⁷²

Decisions not to invest in quality can lead to supply disruptions. Drug product recalls have increased exponentially: from 248 prescription drug recalls in 2001 to 2,329 recalls in 2011.¹⁷³ In a recent announcement, the FDA noted that a "lack of information about which companies have mature quality management systems means that buyers of pharmaceuticals are

¹⁶⁸ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

¹⁶⁹ *Id.*

¹⁷⁰ Woodcock and Wosinska, *supra* note 165.

¹⁷¹ Majority Report, House Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis* (Jun. 15, 2012).

¹⁷² Letter from Jeanne Ireland, Food and Drug Administration, to Ranking Member Elijah E. Cummings, House Committee on Oversight and Government Reform (Jul. 23, 2012).

¹⁷³ *New Prescription For Drug Makers: Update the Plants*, Wall Street Journal (Sept. 3, 2003) (<https://www.wsj.com/articles/SB10625358403931000>). See also W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, Boston College Law Review (Mar. 28, 2014).

unable to reward drug manufacturers that [invest in these systems].”¹⁷⁴ The shift of manufacturing overseas and lack of adequate FDA oversight of foreign manufacturers poses growing concerns as the U.S. increases its reliance on China and India for raw materials and manufacturing (discussed in Section IV). Drug purchasers also do not have insight into a manufacturer’s mature quality management system, or lack thereof, and therefore have little information regarding where each drug product was manufactured.¹⁷⁵ The FDA Drug Shortages Task Force also found that private sector contracting practices contribute to this problem.¹⁷⁶

c. Natural Disasters

Pharmaceutical manufacturers’ production facilities are located in areas throughout the world that are increasingly susceptible to extreme weather events. From 2016 through 2018, a historic number of extreme weather and climate related disasters impacted the U.S. and other countries. Without mitigation efforts, the effects of climate change on the U.S. economy, human health, and the environment are expected to “impose substantial damages” in coming years.¹⁷⁷

In September 2017, Hurricane Maria, a deadly Category 5 hurricane, swept through Puerto Rico and destroyed a significant amount of infrastructure on the island. Immediately after Hurricane Maria, the U.S. experienced a shortage in IV saline bags, a common hospital product used for mixing medicines in intravenous infusions and treating dehydration. Baxter Pharmaceuticals, a manufacturer based in Puerto Rico supplied a large percentage of the U.S. market with IV saline.¹⁷⁸ All three of Baxter’s Puerto Rico plants temporarily shut down and two were still running on generators over a month later.¹⁷⁹

2. Demand

Increases in demand can also prompt a drug shortage. This occurs in both branded and generic products. The way an increase in demand is handled by the manufacturer often depends

¹⁷⁴ *To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality – Not Just Medicine*, FDA Voices: Perspectives from FDA Leadership and Experts (Oct. 24, 2019) (<https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/help-reduce-drug-shortages-we-need-manufacturers-sell-quality-not-just-medicine>).

¹⁷⁵ FDA 2019 Drug Shortages Task Force Report, *supra* note 124. The FDA defines mature quality management as “a foundational quality management system that conforms to CGMPs and builds in a performance and patient focus that utilizes technology, statistical process control, and planning activities to ensure a reliable supply of the drugs manufactured at the facility.”

¹⁷⁶ *Id.*

¹⁷⁷ Adam B. Smith, *2018’s Billion Dollar Disasters in Context*, Beyond the Data (blog), National Oceanic and Atmospheric Administration (Feb. 7, 2019) (www.climate.gov/news-features/blogs/beyond-data/2018s-billion-dollar-disasters-context). See also Majority Staff, House Committee on the Budget, *The Steep Costs of Climate Change Call for Congressional Action* (Aug. 5, 2019).

¹⁷⁸ *Hospitals scramble to avert saline shortage in wake of Puerto Rico disaster*, Washington Post (Oct. 11, 2017) (www.washingtonpost.com/news/to-your-health/wp/2017/10/09/hospitals-scramble-to-avert-saline-shortage-in-wake-of-puerto-rico-disaster/).

¹⁷⁹ *Hurricane Damage to Manufacturers in Puerto Rico Affects Mainland Hospitals, Too*, National Public Radio (Nov. 15, 2017) (www.npr.org/sections/health-shots/2017/11/15/564203110/hurricane-damage-to-manufacturers-in-puerto-rico-affects-mainland-hospitals-too).

on the profitability of the drug. For generic sterile injectable drugs, some manufacturers may exit the market, which can be more cost effective than making necessary investments to increase supply.

The complex nature of the composition and production of some biologics can also strain manufacturers' ability to meet increased demand. As one example, Intravenous Immunoglobulin "IVIG," a biologic used to treat patients with many conditions and diseases, including cancer and autoimmune disorders, began experiencing shortages in the late 1990's. Because it is used so widely across many disciplines within medicine and not always based upon the same level of evidence, shortages of IVIG are not uncommon. IVIG is a biologic made from plasma donations and has been on the market since the 1950's.¹⁸⁰ Manufacturers must purify the plasma to make IVIG and conduct additional quality testing, a process which can take upward of one year.¹⁸¹ Now, if an individual wishes to donate plasma, they must find a donation center and are compensated for their donation. Approximately 70% of individuals diagnosed with primary immunodeficiencies rely on IVIG.¹⁸²

Dr. Yoram Unguru explained that "IVIG is used pretty much by every doctor as an immune product."¹⁸³ Dr. Andrew Shuman, a surgical oncologist and ethicist at the University of Michigan, explained that "IVIG is an expensive product for which there remains a strong financial incentive... so it's a supply issue due to increased demand – manufacturers and the FDA are doing as much as they can." The lack of product interchangeability further complicates shortages, often eliminating the option to switch from one drug manufacturer to another.¹⁸⁴ A reliable and routine supply of plasma donations ensures drug companies' ability to manufacture the drug. A reduction in plasma donations limits manufacturers' ability to increase production in a period where there is overwhelming demand. In November 2019, the Washington Post reported that the shortage worsened to a point where doctors had to cancel lifesaving infusions for patients and treatment centers had to ration the product.¹⁸⁵

Shingrix (Recombinant Zoster Vaccine), a new drug recently introduced by GlaxoSmithKline, is another biologic where the demand has exceeded supply. Shingrix is currently in shortage. The FDA approved Shingrix in 2017. Unlike certain generic sterile injectable drugs that have not yielded substantial profits, Shingrix has been extremely profitable

¹⁸⁰ Interview with Dr. Yoram Unguru.

¹⁸¹ Interview with Erin Fox.

¹⁸² Stephanie Albin and Charlotte Cunningham-Rundles, *An update on the use of immunoglobulin for the treatment of immunodeficiency disorders*, Immunotherapy (Aug. 1, 2015).

¹⁸³ Interview with Dr. Yoram Unguru.

¹⁸⁴ Dr. Andrew Shuman, Assistant Professor and Surgical Oncologist and Ethicist at University of Michigan, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Jul. 24, 2019) (hereinafter "Interview with Dr. Andrew Shuman").

¹⁸⁵ *A severe shortage hits a drug used for cancer, immune disorders, epilepsy, causing canceled treatments and rationing*, Washington Post (Nov. 4, 2019) (www.washingtonpost.com/health/a-severe-shortage-hits-a-drug-used-for-cancer-immune-disorders-epilepsy-causing-cancelled-treatments-and-rationing/2019/11/01/f2be3c4e-e93a-11e9-9c6d-436a0df4f31d_story.html).

for the company, with \$7.5 billion in sales in 2018. As such, GlaxoSmithKline has made significant investments to increase supply and capacity and is currently building a new facility.¹⁸⁶

3. Business Decisions

Manufacturers of critical generic drugs are, in some instances, unable to sustain sufficient margins to keep supplying those drugs once in the final multisource generic stage. As such, these drugs are more and more often in short supply when a drug maker exits the market, despite their critical importance. A key factor related to generic drug shortages, as explained by Martin Van Trieste, is a “broken economic model . . . when costs go down, companies exit the marketplace . . . and when there are one or two companies left in the market, there is no incentive to make investments to improve facilities or increase capacity because of the low prices.” Branded drugs, on the other hand, make a profitable return, so pharmaceutical companies have incentives to invest in infrastructure, equipment, and manufacturing. A disruption in the supply chain of a branded drug equates to significant loss in profits. For a generic drug, a disruption in supply equates to a very small percentage of loss in profits for each affected drug product.¹⁸⁷

From 2004-2016, 40% of the market for generic drugs was supplied by one manufacturer and an average of one competitor per generic drug.¹⁸⁸ This economic model leads to fewer suppliers in the market. For generic injectable products, there are even fewer companies. A 2011 FDA report found that the top three generic injectable manufacturers hold 71% of the market and the majority of sterile injectables (both branded and generic combined) “have one manufacturer that produces at least 90% of the drug.”¹⁸⁹ Unlike other well-functioning markets, a recent FDA analysis revealed that the marketplace for drug shortages does not self-correct. The analysis found that most drug products could not sustain a price increase of at least 50% or withstand significant production increases of up to 50% or more.¹⁹⁰

B. Approval Process / Contracting Practices

According to a recent FDA analysis, “generic companies are often approved to market drugs that are in shortage but make business decisions not to market them.” The FDA found that, on average, “three companies per drug in shortage” had been approved by the FDA to manufacture and market shortage drugs, but chose not to do so.¹⁹¹

¹⁸⁶ *New shingles vaccine is highly effective, long-lasting — and in short supply*, Washington Post (Jun. 20, 2018) (<https://www.washingtonpost.com/news/to-your-health/wp/2018/06/20/new-shingles-vaccine-is-highly-effective-long-lasting-and-in-short-supply/>). See also *UPDATE 1-GSK sees breakthrough in shingles vaccine output in 2024*, Reuters (Nov. 15, 2019) (<https://fr.reuters.com/article/allBreakingNews/idUKL8N27V2NN>); FDA Center for Biologics Evaluation and Research Regulated Products: Current Shortages (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages>) (accessed Dec. 4, 2019).

¹⁸⁷ Interview with Martin Van Trieste.

¹⁸⁸ Ernst R. Berndt, et al., *The Landscape of US Generic Prescription Drug Markets, 2004-2016*, National Bureau of Economic Research (Jul. 2017). See also Rena M. Conti and Ernst R. Berndt, *Four Facts Concerning Competition in the U.S. Generic Prescription Drug Markets*, National Bureau of Economic Research (Aug. 2019).

¹⁸⁹ Food and Drug Administration, *A Review of FDA’s Approach to Medical Product Shortages* (Oct. 31, 2011) (https://www.ipqpubs.com/wp-content/uploads/2012/02/FDA_drug_shortages_report.pdf).

¹⁹⁰ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

¹⁹¹ *Id.*



Figure 6: Number of Companies Approved to Market Shortage Drugs compared to Number of Companies Actually Marketing Shortage Drugs¹⁹²

As discussed above, the majority of drug shortages involve generic drugs that are administered by injection or IV. Market consolidation and decisions by manufacturers not to invest in new and advanced manufacturing techniques and to produce drugs overseas have also exacerbated shortages. While the FDA is responsible for ensuring the safety, efficacy, and security of drug products, its attempts to increase generic market entry have been hindered. The median time to complete the review process for generic manufacturers to receive approval is now almost three years. Efforts necessary to address economic and other contributing factors exacerbating shortages will likely require both short and long-term solutions.

Expedited ANDA approval process and fee incentives: As one potential solution, the FDA has proposed shortening the application wait time for generics to eight months.¹⁹³ In the short-term, an expedited ANDA approval process, especially for a limited number of drugs most often in shortage (sterile injectables commonly used in hospital settings), could help address the lack of manufacturers actively marketing products in shortage. In addition, FDA waiver of generic application filing fees for this limited population of drugs could encourage market entry. To address both affordability and sustainability concerns, however, fee waivers and expedited approvals would have to be tied to commitments from manufacturers to bring the drugs to market (as opposed to obtaining approval and holding the drug) and to do so in a way that ensures affordability, in line with pre-shortage prices.

Strategic Contracting Practices: In the FDA's 2019 Drug Shortages Task Force Report, it found that current private sector contracting practices may contribute to drug shortages and

¹⁹² *Id.*

¹⁹³ House Committee Energy and Commerce, Subcommittee on Health, *Hearing on Examining FDA's Generic Drug and Biosimilar User Fee Programs* (Mar. 2, 2017).

proposed several reforms.¹⁹⁴ As one potential longer term solution, when purchasers have been able to contract directly with manufacturers and enter long-term, high volume contracts, they have generally succeeded in securing supplies of sustainable and affordable drugs. Such efforts, targeted at key drugs in shortage, could have a similar impact. One potential model is Civica Rx, a first of its kind non-profit generic drug company, founded in 2018. Civica Rx contracts directly with health systems and offers long-term contracts to eliminate uncertainty in supply and provide affordable and sustainable prices. Within its first year on the market, Civica Rx obtained agreements to contract directly with over 45 health systems, representing 1,100 hospitals in 46 states, including Trinity Health, based in Michigan, which is one of the seven governing health system members on Civica's board of directors.¹⁹⁵ Civica Rx's contract agreements cover over one-third of the licensed hospital beds in the United States. In September, Civica Rx delivered its first of over a dozen drugs expected to come to market this year – vancomycin, a critical generic injectable antibiotic for treating resistant infections.¹⁹⁶ The U.S. Department of Veterans Affairs (VA) has also joined Civica Rx as a partner and will look to pass on lower cost drugs and to address shortages impacting veterans as well as the general population. In the past, the VA has been successful in obtaining lower drug prices by eliminating middlemen and directly negotiating with manufacturers.¹⁹⁷

Another model could involve authority for HHS to negotiate longer-term contracts directly with drug manufacturers for a specific subset of sterile injectable generic drugs most commonly in shortage to ensure a sufficient supply of safe and affordable medicine. A similar effort was undertaken to launch the Vaccines for Children Program (VFC) through the Centers for Disease Control and Prevention (CDC), which purchases vaccines at a discount from suppliers and provides vaccines to children who are uninsured or Medicaid-eligible.¹⁹⁸

C. Impacts

The FDA has said that while the clinical and financial effects of shortages on healthcare providers and patients is substantial, there is a lack of comprehensive data that accurately captures the effects.¹⁹⁹ Dr. Yoram Unguru highlighted this concern, emphasizing that “we are only as good as the data we have.” On August 21, 2019, Senator Peters wrote to the FDA requesting additional information on drug shortages and expressing concern that the “FDA may

¹⁹⁴ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

¹⁹⁵ Homeland Security and Governmental Affairs Committee Minority Staff correspondence with Civica Rx (Dec. 4, 2019). *See also Hospitals Prepare to Launch Their Own Drug Company to Fight High Prices and Shortages*, National Public Radio (Sept. 6, 2019) (<https://www.npr.org/sections/health-shots/2018/09/06/644935958/hospitals-prepare-to-launch-their-own-drug-company-to-fight-high-prices-and-shor>).

¹⁹⁶ Heather Wall, Chief Commercial Officer for Civica Rx, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Oct. 21, 2019). *See also Patients Are Now Being Treated with a Civica Rx Medication*, BusinessWire (Oct. 2, 2019) (<https://www.businesswire.com/news/home/20191002005196/en/Patients-Treated-Civica-Rx-Medication>).

¹⁹⁷ Health Affairs, *Prescription Drug Pricing: Veterans Health Administration*, Health Policy Brief Series (Aug. 2017).

¹⁹⁸ *Vaccines for Children Program*, Centers for Disease Control and Prevention (undated) (<https://www.cdc.gov/vaccines/programs/vfc/about/index.html>).

¹⁹⁹ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

not have the data it needs to adequately assess and mitigate drug shortages.”²⁰⁰ In response, the FDA provided information and briefed Committee staff. However, the FDA did not provide the Committee with the specific data it requested regarding the FDA’s inspections, the effects of any changes made to FDA inspections on drug shortages, or compliance with CGMPs. The FDA’s unwillingness or inability to provide this information raises questions about the comprehensiveness and reliability of the FDA’s data.

1. Hospitals

The costs of shortages for hospitals continue to increase. Estimated costs incurred by hospitals due to the higher costs of substitute drugs because of shortages amount to almost \$230 million per year.²⁰¹ Additional labor costs account for an estimated \$359 million per year for hospitals to manage the impacts of shortages.²⁰² According to Martin Van Trieste, “shortages create immense inefficiencies” as valuable time that should be dedicated to patient care must be diverted to weekly clinician meetings to discuss shortages. While visiting a member hospital and observing the process of acquiring a critical drug in shortage, Van Trieste added “I’ve seen pharmacy technicians just staring at computers looking for where they can purchase critical drugs in short supply.” This process involves looking at multiple wholesalers and other ordering systems and then waiting for inventory to become available, so pharmacists and purchasers can place the order before another institution acquires limited inventory.²⁰³

A 2019 report by the National Opinion Research Center (NORC) at the University of Chicago found that drug shortages had a multitude of consequences for hospitals including disruptions in patient care; reductions in budgets resulting in reduced staffing or delayed investments; the use alternative therapies; additional in-house compounding of drugs; and a reduction in the number of services offered.²⁰⁴

As Dr. Unguru pointed out, “[t]he amount of money directly linked to coping with the shortages is astronomical.”²⁰⁵ A 2011 shortage of norepinephrine caused an additional \$13.7 billion in healthcare costs and was associated with an almost 4% increase in in-patient deaths.²⁰⁶

²⁰⁰ Letter from Senator Gary Peters, Ranking Member of the Senate Committee on Homeland Security and Governmental Affairs, to Acting Commissioner Norman Sharpless, Food and Drug Administration (Aug. 21, 2019).

²⁰¹ Pew Charitable Trusts and the International Society for Pharmaceutical Engineering, *Drug Shortages: An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies* (Jan. 2017) (https://www.pewtrusts.org/~media/assets/2017/01/drug_shortages.pdf).

²⁰² Vizient, *Drug Shortages and Labor Costs: Measuring the hidden costs of drug shortages on U.S. hospitals* (Jun. 2019) (https://newsroom.vizientinc.com/sites/vha.newshq.businesswire.com/files/doc_library/file/Drug_Shortages_Labor_Cost_Report_Vizient.pdf).

²⁰³ Interview with Martin Van Trieste.

²⁰⁴ NORC at the University of Chicago, *Recent Trends in Hospital Drug Spending and Manufacturer Shortages* (Jan. 15, 2019) (<https://www.aha.org/system/files/2019-01/aha-drug-pricing-study-report-01152019.pdf>).

²⁰⁵ Interview with Dr. Yoram Unguru.

²⁰⁶ Emily Vail, et al., *Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock*, *Journal of the American Medical Association* (Mar. 21, 2017). See also FDA and Duke Margolis Center for Health Policy Presentation Slides, *Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions*

When generic drugs go into shortage, such as Tacrolimus, an organ transplant anti-rejection medication, hospitals are forced to purchase the brand name version at a higher cost. In some cases, these costs, or a portion of them, can be passed down to patients.²⁰⁷ Tacrolimus is currently in shortage.²⁰⁸

Different hospitals have different policies for procuring drugs during a shortage. In some cases, hospitals resort to what has been described as panic buying or hoarding, where they purchase excess amounts of the drug needed due to market volatility. These business decisions can further aggravate an already aggrieved market. Another potential buying source is what is called the gray market, an unfortunate and unintended consequence of drug shortages. The gray market is comprised of intermediary distribution companies that purchase large quantities of medications and substantially inflate those prices during a shortage.²⁰⁹ It is not unusual for gray market participants to contact hospitals and pharmacies during shortages. According to Dr. Unguru, “it’s a tough decision to make: on one hand, you don’t have a drug your patient needs, but on the other, you don’t want to reward the offender as the gray market is partially responsible for shortages.”²¹⁰

The University Hospital at the University of Michigan now has multiple full-time pharmacists dedicated solely to dealing with shortages, and it is estimated that the hospital spends “hundreds of thousands of dollars to anticipate, mitigate, and react to shortages each year.” Dr. Andrew Shuman deals with drug shortages on a “daily basis, especially in times of crisis like right now.”²¹¹ Christine Collins, Vice President and Chief Pharmacy Officer at Lifespan, a multi-hospital health system, has daily calls regarding drug shortages that are currently impacting the hospitals she oversees. She mentioned that these calls began around mid-2017, with the opioid shortage.²¹²

Unfortunately, hospital physicians encounter medical ethics decisions on a regular basis as they deal with the impacts of drug shortages. They must determine whether a drug should be given on a first-come first-serve basis, prioritized for children or other patient populations, how much of a drug a hospital needs to save for future patients, and other difficult considerations. Dr. Shuman, who spearheads institutional rationing approaches explained how “clinicians are

(Nov. 27, 2018) (https://healthpolicy.duke.edu/sites/default/files/atoms/files/duke-fda_drug_shortages_presentation_slides__0.pdf); Shelley Lyford, *A Civic Duty To Improve Access To Generic Pharmaceuticals*, Health Affairs (blog) (Sept. 26, 2019) (<https://www.healthaffairs.org/doi/10.1377/hblog20190924.303385/full/>).

²⁰⁷ Christine Collins, Vice President and Chief Pharmacy Officer at Lifespan, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Jul. 31, 2019).

²⁰⁸ FDA Drug Shortages Database (www.accessdata.fda.gov/scripts/drugshortages/default.cfm) (accessed Dec. 4, 2019).

²⁰⁹ Staff Report prepared for Senate Committee on Commerce, Science and Transportation; Senate Committee on Health, Education, Labor, and Pensions; House Committee on Oversight and Government Reform, *Shining Light on the “Gray Market”* (Jul. 25, 2012).

²¹⁰ Interview with Dr. Yorum Unguru.

²¹¹ Interview with Dr. Andrew Shuman.

²¹² Christine Collins, Vice President and Chief Pharmacy Officer at Lifespan, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Jul. 31, 2019).

rightfully in angst when they have to tell a patient that their preferred drug is unavailable. The most important thing is that the process remains transparent, objective, and fair.”²¹³

Dr. Yoram Unguru explained the devastating consequences when chemotherapy agents are in shortage: “Each one of us [referring to oncologists] has to meet with patients and their parents and tell them about the shortage. This is one of the hardest conversations to have – to tell a patient and parent that a lifesaving medication for which there exists no alternative is unavailable and we’re not sure when it will be available. Cancer is hard enough without unnecessary scarcity of medications. Although cancer is not preventable, drug shortages are.”²¹⁴

2. Patients & Consumers

“Patients have died because of shortages and mostly because of medication errors.”²¹⁵ This statement by pharmaceutical expert and CEO of Civica Rx, Martin Van Trieste, sets out the consequences of failing to remedy shortages. In a 2017 national survey of nearly 300 health care practitioners conducted by the Institute for Safe Medication Practices, 71% indicated that they were unable to provide patients with the recommended drug or treatment due to shortages.²¹⁶ Almost one quarter of practitioners stated that they were aware of at least one medication error related to a drug shortage in the past six months.

Therapeutic substitutions may also not be as effective as practitioners may predict. In 2010, there was a shortage of mechlorethamine, a cancer drug used to treat Hodgkin’s lymphoma in children. Practitioners thought another drug would be equally as effective and since mechlorethamine was in shortage, many children received the alternative therapy. The children who received the alternative therapy due to the shortage had a 12% higher return rate of symptoms and had to undergo additional treatments.²¹⁷ Dr. Shuman recalls this tragedy and noted, “every institution across the country is facing these dilemmas.”²¹⁸ In pediatric oncology, it is rare to find drugs that have a comparable substitute. Chemotherapy agents frequently utilized in childhood cancer that have experienced shortages and affect the ability to treat children, include vincristine, asparaginase, methotrexate, doxorubicin, cytarabine, and nelarabine: none of which have alternatives or adequate substitutions.²¹⁹

In addition to medication errors, patients also experience delays in treatment due to drug shortages. When there is not a therapeutic alternative or interchangeable medication, patients have no choice but to wait until the drug they need becomes available. For example, many individuals with primary immunodeficiencies, such as Severe Combined Immune Deficiency

²¹³ Interview with Dr. Andrew Shuman.

²¹⁴ Interview with Dr. Yoram Unguru.

²¹⁵ Interview with Martin Van Trieste.

²¹⁶ *Drug Shortages Continue to Compromise Patient Care*, Institute for Safe Medication Practices (Jan. 11, 2018) (www.ismp.org/resources/drug-shortages-continue-compromise-patient-care).

²¹⁷ Monika L. Metzger, Amy Billett, and Michael P. Link, *The Impact of Drug Shortages on Children with Cancer – The Example of Mechlorethamine*, *New England Journal of Medicine* (Dec. 27, 2012).

²¹⁸ Interview with Dr. Andrew Shuman.

²¹⁹ Interview with Dr Yoram Unguru.

(SCID), may not know when they will be able to receive their next treatment due to the current shortage of IVIG.²²⁰ When there is a therapeutic alternative, that drug may come in other formats, making it difficult for health care professionals to quickly administer medication.

Though shortages are not as prevalent for prescription medications, usually because pills and tablets are easier to produce than sterile injectable drugs, consumers are also affected if a medication they rely on is in shortage. Low cost generic medication treatments for depression, anxiety, and obsessive compulsive disorder have all experienced shortages.²²¹ Lifesaving drugs, including epinephrine, atropine (used to treat cardiac arrest), and dextrose (used to raise low blood pressure for people with diabetes) that have long been required by the Federal Aviation Administration to be stocked on all flight are now exempt from medical kits due to shortages.²²²

As discussed above, Civica Rx, a non-profit generic drug company founded in September 2018 aims to address drug shortages by stabilizing the supply of generic drugs and reduce predatory pricing through transparent prices their innovative structure. As CEO Martin Van Trieste describes, Civica Rx's manufacturing strategy focuses on quality: "we will always source and manufacture at the same time and keep a six month safety stock." The underlying factor in Civica Rx's model is transparency in pricing and manufacturing: its pricing is based on a cost-plus model and not on what the market will bear and the names and locations of all Civica Rx's manufacturing locations are available to the public. Civica Rx member health system advisory committees, comprised of pharmacy executives and clinicians, prioritized critical drugs that often experience shortages and in September 2019, Civica Rx delivered its first batch of medicine to hospitals. It expects to bring over a dozen drug products to the market in 2019 and 100 in the next five years. Its goal is to increase capacity and promote competition in the market place for generics to stabilize the market.²²³

IV. GLOBALIZATION OF PHARMACEUTICAL SUPPLY CHAIN AND NATIONAL SECURITY IMPLICATIONS

The pharmaceutical supply chain includes suppliers, manufacturers, repackagers, distributors, and dispensers located all over the world. The FDA is responsible for regulating the approval, production, distribution, and advertising of prescription drug products sold in the U.S. The U.S. drug supply is among the safest in the world. However, increased U.S. dependence on foreign sources for prescription drugs and medical supplies present both safety and national security risks for Americans.²²⁴ To ensure the continued safety, efficacy, and security of drugs in

²²⁰ *Drug Shortage Leaves Patients Without Immune-Disorder Treatment*, Wall Street Journal (Aug. 9, 2019) (<https://www.wsj.com/articles/drug-shortage-leaves-patients-without-immune-disorder-treatment-11565343023>).

²²¹ FDA Drug Shortages Database (www.accessdata.fda.gov/scripts/drugshortages/default.cfm) (accessed Dec. 4, 2019). These drugs include Isocarboxazid Tablets, Buspirone HCl Tablets, and Fluvoxamine ER Capsules.

²²² *Why Lifesaving Drugs May Be Missing on Your Next Flight*, New York Times (Oct. 3, 2019) (www.nytimes.com/2019/10/03/health/drugs-airplanes-faa.html).

²²³ Heather Wall, Chief Commercial Officer for Civica Rx, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Oct. 21, 2019).

²²⁴ Jasenko Karamelic, et al., *Financial Aspects and the Future of the Pharmaceutical Industry in the United States of America*, Mater Sociomed (Nov. 24, 2013). See also USCC 2019 Annual Report, *supra* note 86; *Safety, Efficacy,*

the U.S. market, the FDA, Assistant Secretary for Preparedness and Response (ASPR), and potentially DHS and other necessary actors must have sufficient resources and authority to protect U.S. interests as the supply chain for both branded and generic drugs evolves.

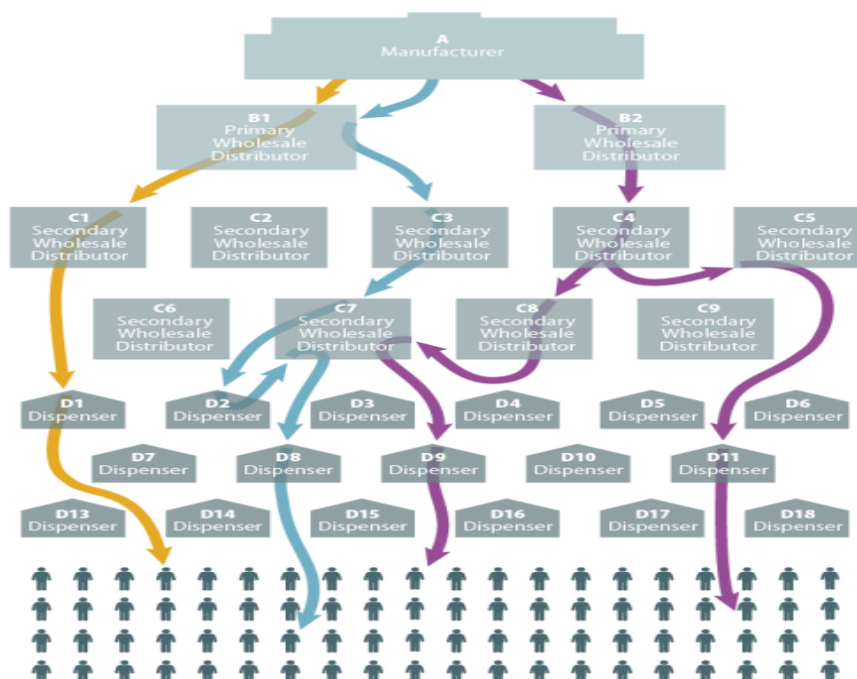


Figure 7: CRS Diagram, Downstream Pharmaceutical Supply Chain²²⁵

A. Dependence on Foreign Sources

Ensuring the quality and safety of U.S. drug products is an issue that applies to both branded and generic drugs. According to the FDA, approximately 80% of the manufacturing facilities that produce active pharmaceutical ingredients (API) – the key ingredients that give a drug its intended effect – are located outside of the U.S.; however, the FDA does not have the real-time data to determine the percentages of APIs produced at each facilities.²²⁶ Other reports indicate that over 80% of the API itself, for those drugs sold throughout the U.S., comes from overseas, primarily China and India.²²⁷ India is the largest producer of generic medications in the

and Quality Remain Top Priorities as We Continue Our Work to Expand Access to Cost-Saving Generic Drugs for the American Public, Food and Drug Administration (May 13, 2019).

²²⁵ Congressional Research Service, *Pharmaceutical Supply Chain Security* (R43106) (Oct. 31, 2013).

²²⁶ Food and Drug Administration, *FDA at a Glance: Regulated Products and Facilities* (Oct. 2019) (<https://www.fda.gov/media/131874/download>). See also House Committee on Energy and Commerce, Subcommittee on Health, Testimony Submitted for the Record of Janet Woodcock, M.D., Food and Drug Administration, *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, 116th Cong. (Oct. 30, 2019) (hereinafter “Testimony of Dr. Janet Woodcock (Oct. 30, 2019)”). Dr. Woodcock’s testimony also indicated that as of Aug. 2019, “72% of the API manufacturers supplying the U.S. market were overseas, and 13% are in China.”

²²⁷ Katherine Eban, Senior Advisor, The Hastings Center, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019). See also Rosemary Gibson and Janardan Prasad Singh, *ChinaRx*

world but is dependent on China for the vast majority of the API in drug products produced in India.²²⁸ Not only does China produce the critical medications that patients, hospitals, and consumers rely on throughout the U.S., but other countries also depend on China for the raw materials to make the medicines they distribute. China is currently the largest supplier of API in the world.²²⁹ According to FDA data, the number of registered API manufacturing facilities in China “more than doubled between 2010 and 2019.”²³⁰

The U.S. obtains approximately 40% of its finished product drugs from overseas, which leaves little, if any, room to ensure a national independent supply of critical drugs.²³¹ The risks are two-fold: first, the U.S. is more dependent upon China and India as it no longer has the domestic manufacturing capacity needed to produce certain critical drugs, such as penicillin and doxycycline; and second, many pharmaceutical manufacturing facilities abroad have significant quality control issues that increase risks for potential contamination, leading to recalls and ultimately drug shortages.²³²

The FDA still lacks insight into critical manufacturing information. Today, there are 4,159 registered foreign manufacturing facilities.²³³ However, the FDA does not have information on the real-time volume of products produced at each manufacturing facility and distributed throughout the U.S. market.²³⁴ In October 2019, Dr. Woodcock testified to Congress that “we know...where the facilities are that can produce [drugs] around the world but again we don’t know the percentage [that] is being sourced from China.” The FDA receives annual reports that retrospectively provide most of this information; however, in real time, the FDA is in the dark, for example, on which facilities produce the largest percentage of antibiotics distributed in the U.S. or which suppliers provide the bulk of material for heparin. Overdependence on any one country for these and other critical drugs puts Americans at risk.

(2018) (hereinafter “*ChinaRx 2018*”); Institute of Medicine of the National Academies, *Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad* (Apr. 2012) (http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2012/Ensuring-Safe-Foods-and-Medical-Products-Through-Stronger-Regulatory-Systems-Abroad/safefoodmeds_rb.pdf).

²²⁸ Benjamin A. Shobert, Senior Associate, National Bureau of Asian Research; Director, Healthcare Strategy, Microsoft, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019). See also *Culture of Bending Rules in India Challenges U.S. Drug Agency*, Bloomberg (Jan. 31, 2019) (www.bloomberg.com/news/features/2019-01-31/culture-of-bending-rules-in-india-challenges-u-s-drug-agency).

²²⁹ USCC 2019 Annual Report, *supra* note 86. See also Rosemary Gibson, Senior Advisor, The Hastings Center, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019).

²³⁰ Testimony of Dr. Janet Woodcock (Oct. 30, 2019), *supra* note 226.

²³¹ Erwin A. Blackstone, et al., *The Health and Economic Effects of Counterfeit Drugs*, American Health & Drug Benefits (Jun. 2014).

²³² USCC 2019 Annual Report, *supra* note 86.

²³³ Food and Drug Administration, *FDA at a Glance: Regulated Products and Facilities* (Oct. 2019) (<https://www.fda.gov/media/131874/download>).

²³⁴ 21 CFR 314.81(b)(2)(ii). See also *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

The Heparin Crisis: In 2008, contamination from materials produced in China for the finished drug product heparin – a critical emergency medication to help prevent potential blood clots during surgery – was associated with hundreds of deaths and severe allergic reactions in the U.S. and around the world.²³⁵ Two American companies, Baxter Healthcare Corp. (Baxter) and Scientific Protein Laboratories (SPL), had contact at points along the supply chain for heparin. In January 2008, Baxter, which manufactured and distributed the finished drug product, voluntarily recalled multiple units of heparin. The FDA issued a public health advisory in February 2008 and Baxter voluntarily recalled all remaining doses. Heparin was ultimately recalled for multiple products and suppliers in multiple countries. The FDA conducted a wide-ranging investigation and discovered a previously undetected contaminant associated with both the drug and certain medical devices. The FDA identified Changzhou SPL, a subsidiary of SPL based in China, as the source of the contamination.²³⁶ Additional reports identified other unrelated facilities in China that produced the product, indicating that the contamination may have originated farther back at other points in the supply chain. The FDA traced the contaminant to twelve different Chinese companies and identified at least eleven other countries where contamination was detected involving multiple suppliers.²³⁷

Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, testified to Congress that “some of the heparin product and heparin API manufactured by Baxter’s supplier, SPL, was contaminated by oversulfated chondroitin sulfate” a “heparin-like” product that comes from animal cartilage. The FDA acknowledged that it failed to inspect the Changzhou SPL China facility when Baxter first obtained approval to use that API manufacturer, but determined that any prior inspection would not have detected what the FDA viewed as potentially intentional contamination by unknown actors in China. The FDA found in a separate investigation that the materials used to make heparin, pig intestines, were made in dirty tanks. Investigators also found that the contaminated oversulfated chondroitin sulfate cost \$9 per pound whereas the heparin API cost \$900 per pound. Between January 1, 2007 and May 8, 2008, 246 deaths were reported after heparin was administered to patients, though it is not possible to determine whether all deaths were attributed to the contaminated heparin.²³⁸

²³⁵ Food and Drug Administration, *Information on Heparin* (undated) (<https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-heparin>); Food and Drug Administration, *Information on Adverse Event Reports and Heparin* (Jun. 18, 2009) (<http://wayback.archive-it.org/7993/20170113124004/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112669.htm>). Heparin is also commonly used in kidney dialyses and open heart surgeries.

²³⁶ House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, Testimony Submitted for the Record of Janet Woodcock, M.D., Food and Drug Administration, *Hearing on The Heparin Disaster: Chinese Counterfeits and American Failures*, 110th Cong. (April 29, 2008) (hereinafter “Testimony of Dr. Janet Woodcock (April 29, 2008)”).

²³⁷ Testimony of Dr. Janet Woodcock (April 29, 2008), *supra* note 236; *See also*, *Germans Seek China Tie to Blood Thinner Heparin*, New York Times (Mar. 8, 2008) (<https://www.nytimes.com/2008/03/08/world/europe/08heparin.html>).

²³⁸ Testimony of Dr. Janet Woodcock (April 29, 2008), *supra* note 236. *See also* Food and Drug Administration, *Information on Heparin* (undated) (<https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-heparin>); Food and Drug Administration, *Information on Adverse Event Reports and Heparin* (Jun. 18, 2009) (<http://wayback.archive-it.org/7993/20170113124004/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112669.htm>); *Heparin Contamination May Have Been Deliberate, F.D.A. Says*, New York Times (Apr. 30, 2008) (<https://www.nytimes.com/2008/04/30/health/policy/30heparin.html>); *Tainted Drug May Still be in*

Eighty percent of the world's heparin now originates in China and the U.S. continues to rely on China for heparin today.²³⁹ The U.S. is now facing a new heparin shortage. The FDA listed the reason for the current shortage as “other” and so the specific underlying causes are unknown.²⁴⁰ However, fear concerning the risk of this current shortage has been looming since a Chinese outbreak of African swine fever emerged in 2019. Dr. Thoralf Sundt, Chief of Cardiac Surgery at Massachusetts General Hospital explained in a recent news report that it is “simply not possible ... to do heart surgery without heparin.” At one point, Dr. Paul Biddinger, Chief of the Division of Emergency Preparedness, said the hospital was “as close as two weeks away from having to cancel lifesaving cardiac surgery.”²⁴¹

Heparin is just one example where contaminants have found their way into pharmaceuticals – both branded and generic – with foreign sources of raw material that are then sold throughout the United States. Problems with drug potency and contamination are on the rise.²⁴² Examples include:

- **Blood Pressure Medications:** Beginning in July 2018, several manufacturers voluntarily recalled certain angiotensin II receptor blocker (ARB) high blood pressure medications after a suspected carcinogen, previously used to make rocket fuel, was detected in certain drugs, including losartan, valsartan, and irbesartan.²⁴³ Bloomberg reported that some of the valsartan drug manufactured in China contained 17 micrograms of a nitrosamine referred to as NDMA, a suspected carcinogen, in a single pill, which is “equivalent to eating 48 pounds of bacon.” The FDA has stated that the risk to patients associated with the recalled ARB is low. However, as of September 2019, the industry-wide recall

U.S. Almost Decade After Deaths, Bloomberg Business (Mar. 30, 2016) (www.bloomberg.com/news/articles/2016-03-30/tainted-drugs-may-still-be-in-u-s-almost-a-decade-after-deaths).

²³⁹ *African Swine Fever: An Unexpected Threat to the Global Supply of Heparin*, Global Biodefense (Oct. 7, 2019) (<https://globalbiodefense.com/2019/10/07/african-swine-fever-an-unexpected-threat-to-the-global-supply-of-heparin/>).

²⁴⁰ FDA Drug Shortages Database (www.accessdata.fda.gov/scripts/drugshortages/default.cfm) (accessed Dec. 4, 2019).

²⁴¹ *U.S. hospitals, FDA grapple with shortages of lifesaving drugs*, NBC News (Oct. 31, 2019) (<https://www.nbcnews.com/health/health-news/u-s-hospitals-fda-grapple-shortages-life-saving-drugs-n1074821>).

²⁴² *The Generic Drugs You're Taking May Not be as Safe or Effective as you Think*, National Public Radio (May 16, 2019) (www.npr.org/sections/health-shots/2019/05/16/723545864/the-generic-drugs-youre-taking-may-not-be-as-safe-or-effective-as-you-think).

²⁴³ Food and Drug Administration, *Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)* (undated) (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan>). See also *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*, Bloomberg (Sept. 12, 2019) (www.bgov.com/core/news/#!/articles/PXPNP46TTDS1). Commissioner Larry M. Wortzel of the U.S.-China Economic and Security Review Commission noted in a July 31st hearing, “[i]n the past three months, I have had four blood pressure medications recalled. When I tracked down the sourcing, they all came out of India, but originally sourced in China, from four different U.S. manufacturers, supposed manufacturers or at least provider companies. In each case, that particular medication was contaminated with rocket fuel.” U.S.-China Economic and Security Review Commission, *Hearing Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products*, (July 31, 2019).

of these medications expanded 51 times and included ten different companies.²⁴⁴

A former FDA inspector, Dr. Massoud Motamed, identified two facilities in China and India as potentially problematic noting that the Zhejiang Huahai Pharmaceutical plant in Linhai, China had “facilities and equipment [that] were not maintained, anomalies in testing [were] not investigated, [] gaskets that were fraying, [and] white particulates and residue on the equipment.” He recommended that “official action” be taken. Despite these findings, according to Dr. Motamed, his recommendation was overruled and the FDA determined that “official action was not required.”²⁴⁵

- **Over-the-Counter Heartburn Medications:** In September 2019, the FDA announced that it detected low levels of NDMA, a probable human carcinogen, ranitidine, commonly sold under the brand name Zantac.²⁴⁶ A spokesperson for Sanofi, the manufacturer of Zantac said it did not plan to recall the drug and that “Sanofi takes patient safety seriously . . . [and Zantac] has been around for over a decade and meets all the specified safety requirements for use in the O.T.C. [over the counter] market.”²⁴⁷ Two weeks later, CVS suspended the sale of Zantac and other generic heartburn medications as a precautionary measure based on FDA’s September announcement. On October 18, Sanofi issued a recall of the product. The U.S. experienced multiple ranitidine drug product recalls.²⁴⁸

The recalls described above are all voluntary because unlike food products, the FDA does not have the authority to mandate a recall for drug products. In 2015, the FDA banned the importation of 29 products from a Chinese manufacturing company, Zhejiang Hisun Pharmaceutical, after it had received 61 complaints regarding impurities in the drug products, but

²⁴⁴ *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*, Bloomberg (Sept. 12, 2019) (www.bgov.com/core/news/#!/articles/PXPNP46TTDS1).

²⁴⁵ *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India*, NBC News (May 10, 2019) (www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971); Dr. Massoud Motamed, Former Consumer Safety Officer for FDA, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Nov. 12, 2019) (hereinafter “Interview with Dr. Massoud Motamed”).

²⁴⁶ *Statement alerting patients and health care professionals of NDMA found in samples of ranitidine*, Food and Drug Administration (Sept. 13, 2019) (<https://www.fda.gov/news-events/press-announcements/statement-alerting-patients-and-health-care-professionals-ndma-found-samples-ranitidine>).

²⁴⁷ *Zantac has low levels of a cancer-causing chemical, the F.D.A. says*, New York Times (Sept. 13, 2019) (www.nytimes.com/2019/09/13/health/zantac-cancer-ndma.html).

²⁴⁸ *CVS suspends sales of Zantac brand and generic heartburn drug during safety review*, Reuters (Sept. 28, 2019) (www.reuters.com/article/us-cvs-health-heartburn/cvs-suspends-sales-of-zantac-brand-and-generic-heartburn-drug-during-safety-review-idUSKBN1WD0P0). See also *Sanofi to pull heartburn drug Zantac in US, Canada*, Reuters (Oct. 18, 2019) (www.reuters.com/article/sanofi-heartburn-zantac/sanofi-to-pull-heartburn-drug-zantac-in-us-canada-idUSL3N2733IQ); CVS Customer Service Representative, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Nov. 8, 2019).

later made an exemption for 14 of the banned products, which included key ingredients for chemotherapies and antibiotics, out of fear for a shortage.²⁴⁹

Valisure, an analytical pharmacy that batch-tests drugs, explained that “all generics are not created equal.” As one example, the brand drug was “almost 100% consistent in dosage” whereas a generic version was “almost 10% both up and down from the intended 20 mg dosage.”²⁵⁰ A Harvard Medical School study found that the batch-to-batch variability of refilling antiepileptic medications (regardless of brand or generic) was associated with a 2.3-fold increased risk of having a seizure.²⁵¹ Dr. Woodcock testified before Congress that “[t]he lack of a reliable supply of critical medicines creates a significant risk for national security not just for our Military but for all our citizens.”²⁵²

National Security: As Christopher Priest, the Acting Deputy Assistant Director for Health Care Operations and Tricare for the Defense Health Agency, outlined in his testimony before the U.S.-China Economic and Security Review Commission, “[t]he national security risks of increased Chinese dominance of the global API market cannot be overstated.” Priest testified that key medications are crucial to protect servicemen and women “from nuclear, biological[,] and chemical threats . . . [s]hould China decide to limit or restrict the delivery of APIs to the United States, it would have a debilitating effect on U.S. domestic production and could result in severe shortages of pharmaceuticals for both domestic and military uses.”²⁵³ In its 2019 Annual Report, the U.S.-China Economic and Security Review Commission noted that although DOD contracts require pharmaceutical suppliers to disclose their manufacturing locations (including APIs), “since there is no national registry for API sources, Defense Logistics Agency has no means to independently determine the origin of APIs.”²⁵⁴

The U.S. military is as dependent on foreign manufacturing as the average American consumer since the Department of Defense is not authorized or funded to produce commercial pharmaceuticals. The Trade Agreements Act of 1979 (TAA) requires that certain products sold to federal agencies be manufactured in the U.S. or one of the “designated countries” with which the U.S. has a fair trade agreement.²⁵⁵ The Defense Logistics Agency, which procures pharmaceuticals and medical supplies for the Military, is bound by the TAA. The Defense Department is also dependent on the FDA’s inspection process to ensure the safety and quality of drugs for the military. These potential impacts obviously go beyond the military, with

²⁴⁹ USCC 2019 Annual Report, *supra* note 86. See also *Banned Chinese Supplier Given Exemption to Ship Chemotherapy Drug to U.S.*, BioPharmaDive (Feb. 25, 2016) (www.biopharmadive.com/news/banned-chinese-supplier-given-exemption-to-ship-chemotherapy-drug-to-us/414560/).

²⁵⁰ *All Generics are not created equal*, The Valisure Notebook (undated) (<https://www.valisure.com/blog/valisure-notebook/all-generics-are-not-created-equal/>).

²⁵¹ Joshua J. Gagne, et al., *Refilling and switching of antiepileptic drugs and seizure-related events*, Clinical Pharmacology and Therapeutics (Jul. 14, 2010).

²⁵² *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

²⁵³ Christopher Priest, Principal Deputy, Deputy Assistant Director of Healthcare Operations at the Defense Health Agency, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019).

²⁵⁴ USCC 2019 Annual Report, *supra* note 86.

²⁵⁵ Trade Agreements Act of 1979, Pub. L. No. 96-39.

implications for all Americans. According to Rosemary Gibson, “[i]f China shut the door on exports of medicines and their key ingredients and raw materials, U.S. hospitals and military hospitals and clinics would cease to function within months, if not days.”²⁵⁶

The FDA acknowledged it “has no formal means for quality surveillance, except through inspections, and lacks resources to comprehensively review annual reports and other data ... which may provide significant amounts of pharmaceutical quality information.”²⁵⁷ The FDA’s inability to identify in real time which suppliers are producing what percentage of drug products is potentially one of the greatest long-term safety and security risks for prescription drugs sold in the United States.²⁵⁸ As Rosemary Gibson explained, the U.S. government needs “market intelligence and a diversification of suppliers, just like we have for oil and wheat.”²⁵⁹ Trade, political, or security unrest with other countries all impact U.S. prescription drug safety and independence. Gaining a comprehensive understanding of current vulnerabilities and reliance is essential.

B. Inadequate Oversight of Foreign Manufacturing

The FDA has failed to sufficiently exercise its authority to conduct oversight at overseas manufacturing facilities. According to the FDA, this is due to staffing issues and not appropriations.²⁶⁰ Since 1998, the FDA’s foreign drug inspection program has been deficient. In 1998, GAO found that the FDA had serious problems managing foreign inspections, including “infrequent routine inspections.” GAO found that the FDA often allowed four to five years between inspections and couldn’t provide a complete list of foreign manufacturers who are delivering drugs to the United States.²⁶¹ A decade later, GAO identified similar deficiencies and concluded that the FDA had inaccurate data on the number of foreign drug establishments subject to inspection.²⁶² By 2016, GAO found that, while improved, the FDA lacked inspection history on one-third of foreign manufacturers and had a high number of vacancies in their foreign offices.²⁶³

In a 2018 report, FDA’s Office of Pharmaceutical Quality noted that its oversight of foreign manufacturers is conducted predominately through its surveillance inspections. In 2018,

²⁵⁶ Rosemary Gibson, Senior Advisor, The Hastings Center, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019).

²⁵⁷ Food and Drug Administration, Office of Pharmaceutical Quality, *FDA Pharmaceutical Quality Oversight: One Quality Voice* (2015) (<https://www.fda.gov/media/91721/download>).

²⁵⁸ *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

²⁵⁹ Rosemary Gibson, Senior Advisor at the Hastings Center, Interview with Senate Committee on Homeland Security and Governmental Affairs Minority Staff (Oct. 8, 2019).

²⁶⁰ *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

²⁶¹ Government Accountability Office, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program* (HEHS-98-21) (Mar. 17, 1998).

²⁶² Government Accountability Office, *Drug Safety: FDA Has Conducted more Foreign Inspections and Begun to Improve its Information on Foreign Establishments, but More Progress is Needed* (GAO-10-961) (Sept. 30, 2010).

²⁶³ Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge* (GAO-16-595) (Jul. 2016).

the FDA conducted 1,346 drug quality inspections, which represented only 29% of all pharmaceutical manufacturing sites importing drugs into the United States.²⁶⁴ For those foreign manufacturers the FDA does inspect, it has faced various challenges and barriers to performing complete inspections.

Author Katherine Eban has detailed the data manipulation and other obstacles, such as serving FDA inspectors contaminated water, pretesting samples, and purposefully crashing software, that manufacturers throughout India have employed to thwart legitimate investigations.²⁶⁵ Former FDA inspector Dr. Massoud Motamed highlighted the significant difference between FDA inspections in the U.S. and abroad: "Say I'm at a domestic facility and I tell my supervisors that I'm finding all these problems and I need more time to inspect. That happens — no issue . . . The same is not true of a foreign facility. I've had inspections where I really could have benefited from the extra time and I knew there were problems to be uncovered, but I had to leave the country."²⁶⁶

Inspection Process: The FDA's inspection process is bifurcated between its Center for Drug and Evaluation Research (CDER) and Office of Regulatory Affairs (ORA). CDER selects which sites to inspect using a risk-based assessment model. ORA then inspects the sites and issues its findings. CDER then determines the ultimate outcome (e.g. whether to confirm or overrule the inspector's findings).

FDA surveillance inspections in the U.S. are unannounced. However, despite evidence clearly articulating the many problems with announced inspections, including pervasive and outright fraud, the FDA still provides notice before conducting the majority of inspections at foreign facilities. This announcement period is often when companies actively engage in improper or fraudulent practices to hide data abnormalities and bad test results that would otherwise lead to lost revenue and a banned drug product by the FDA.²⁶⁷

After Indian pharmaceutical manufacturer Ranbaxy Laboratories Limited pleaded guilty to seven felony counts relating to product adulteration through data falsification in May 2013, the FDA recognized its need to address widespread data manipulation throughout Indian generic drug manufacturers.²⁶⁸ In 2014, the FDA instituted an inspection pilot program in India with unannounced inspections. The program revealed "widespread malfeasance," uncovered phantom manufacturing facilities, and gross unsanitary conditions, such as a bird infestation at a sterile manufacturing site. Katherine Eban noted, "[t]he pilot program uncovered a long-running

²⁶⁴ FDA Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, *Report on the State of Pharmaceutical Quality* (2018).

²⁶⁵ Katherine Eban, *Bottle of Lies* (2019).

²⁶⁶ Interview with Dr. Massoud Motamed.

²⁶⁷ Interview with Dr. Massoud Motamed. See also Katherine Eban, *Bottle of Lies* (2019).

²⁶⁸ *Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay \$500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to FDA*, Department of Justice (May 13, 2013) (<https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false>). See also Katherine Eban, *Bottle X: Exposing Impurities in the Generic Drug Business*, Newsweek Magazine (Jul. 2, 2019) (<https://www.newsweek.com/2019/07/19/bottle-x-exposing-impurities-generic-drug-business-1446934.html>).

machinery dedicated not to producing perfect drugs but to producing perfect data.” During this time, Eban found that the rate of inspections resulting in “official action indicated,” the FDA’s most serious finding, increased by nearly 60 percent.²⁶⁹ One year later, however, the FDA discontinued the program.

Dr. Massoud Motamed, a former consumer safety officer for the FDA, flagged numerous concerns about the inspection process. According to Dr. Motamed, “[t]here is very little managerial oversight abroad. Supervisors are in a different time zone and are not really present.” Dr. Motamed claimed that bribes are a problem, stating “[w]hen I was working in India, it was common knowledge as to which auditors to bribe and which to offer vacations.” The lack of a sufficient numbers of trained and qualified inspectors hampers effective oversight even in the United States. Dr. Motamed estimates that there are only a handful of FDA inspectors finding substantial problems among the approximately 200 staff with domestic and foreign investigation responsibilities.²⁷⁰

Ultimately, both foreign and domestic based companies present safety and efficacy concerns that require a sufficiently resourced and supported cadre of FDA inspectors able to carry out the agency’s mission. In July 2018, Zhejiang Huahai Pharmaceutical Co., Ltd, based in China, issued a voluntary recall of valsartan. Five months after its recall, in November 2018, the FDA issued a warning letter to Zhejiang Huahai Pharmaceutical.²⁷¹ In the U.S., FDA inspection of Mylan’s facility in Morgantown, West Virginia in November 2016 resulted in issuance of a warning letter to the company two years later in November 2018.²⁷² Mylan subsequently announced a voluntary recall of 15 lots of valsartan tablets after it detected a probable carcinogen, nitrosamine, NDEA, in certain batches.²⁷³

C. Diminished U.S. Manufacturing

According to the FDA, 88% of API manufacturing sites and 63% of finished dosage manufacturing sites for all drug products are located overseas.²⁷⁴

²⁶⁹ Katherine Eban, *Americans Need Generic Drugs. But Can They Trust Them?*, New York Times (May 11, 2019) (<https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html>).

²⁷⁰ Interview with Dr. Massoud Motamed.

²⁷¹ Warning Letter from Francis Godwin, Food and Drug Administration, to Mr. Jun Du, Zhejiang Huahai Pharmaceutical (Nov. 29, 2018).

²⁷² Warning Letter from Diana Amador-Toro, Food and Drug Administration, to Mylan Pharmaceuticals, Inc. (Nov. 9, 2018).

²⁷³ *Mylan Initiates Voluntary Nationwide Recall of 15 Lots of Valsartan Tablets, USP, Amlodipine and Valsartan Tablets, USP, and Valsartan and Hydrochlorothiazide Tablets, USP, Due to the Detection of Trace Amounts of NDEA (N-Nitrosodiethylamine) Impurity Found in the Active Pharmaceutical Ingredient*, Mylan (Nov. 20, 2018) (<http://newsroom.mylan.com/2018-11-20-Mylan-Initiates-Voluntary-Nationwide-Recall-of-15-Lots-of-Valsartan-Tablets-USP-Amlodipine-and-Valsartan-Tablets-USP-and-Valsartan-and-Hydrochlorothiazide-Tablets-USP-Due-to-the-Detection-of-Trace-Amounts-of-NDEA-N-Nitrosodiethylamine-Impurity->).

²⁷⁴ FDA 2019 Drug Shortages Task Force Report, *supra* note 124.

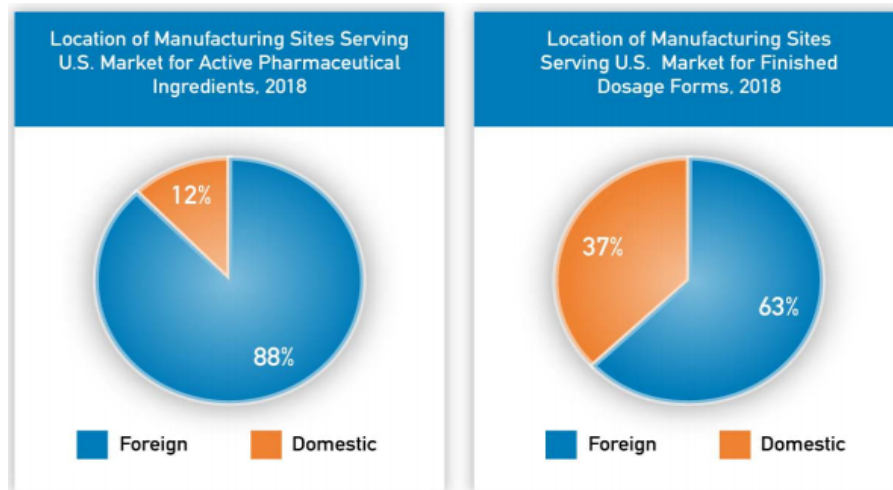


Figure 8: Percentage of Manufacturing Facilities Located in the U.S. v. Abroad²⁷⁵

As one example of the risks associated with this overdependence, despite the fact that global antibiotic use rose by 65% from 2000 through 2015, U.S. manufacturers have largely lost the ability to produce and manufacture certain antibiotics domestically.²⁷⁶ In Rosemary Gibson’s testimony before the U.S.-China Economic and Security Review Commission, she stated that “because the U.S. has allowed the industrial base to wither, the U.S. cannot produce generic antibiotics for children’s ear infections, strep throat, pneumonia, urinary tract infections, sexually-transmitted diseases, Lyme disease, superbugs and other infections that are threats to human life.”

By 2005, there were more drug manufacturing facilities abroad than in the U.S., and by 2015, the U.S. imported nearly \$86 billion in pharmaceutical products compared with \$47 billion in exports.²⁷⁷ The last U.S.-based manufacturing plant to produce key ingredients for antibiotics like penicillin closed in 2004.²⁷⁸ Now, U.S. imports from China include vitamins A, B, C, and D and other supplements, antibiotics, ibuprofen, hydrocortisone, contraceptives, hormones, chemotherapies, pain medications, and many medical supplies and devices.²⁷⁹ Dr. Tara J. O’Toole, Senior Fellow and Executive Vice President of In-Q-Tel recently testified before Congress that the U.S. is “critically dependent on China for a lot of drugs [and] have been shipping our manufacturing capacity to Asia for over a decade now ... We haven’t been paying

²⁷⁵ *Id.*

²⁷⁶ *Global antibiotic use rises, fueled by economic growth*, Center for Infectious Disease Research and Policy (Mar. 26, 2018) (www.cidrap.umn.edu/news-perspective/2018/03/global-antibiotic-use-rises-fueled-economic-growth). See also Rosemary Gibson, Senior Advisor, The Hastings Center, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing on Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019).

²⁷⁷ Department of Commerce, International Trade Association, *2016 Top Markets Report Pharmaceuticals* (2016) (https://www.trade.gov/topmarkets/pdf/Pharmaceuticals_Executive_Summary.pdf). See also *ChinaRx* 2018, *supra* note 227.

²⁷⁸ *Drug Making’s Move Abroad Stirs Concerns*, New York Times (Jan. 19, 2009) (<https://www.nytimes.com/2009/01/20/health/policy/20drug.html>).

²⁷⁹ *ChinaRx* 2018, *supra* note 227.

attention to biology as a national security asset or as a possible threat and that has to change. The fragility of our supply chain in terms of drugs is a real problem.” She explained, “[t]here is not a CEO of a major pharma company who hasn’t been recruited by China to build facilities there.”²⁸⁰

The U.S.-China Economic and Security Review Commission has found that “[t]he U.S. generic drug industry can no longer produce certain critical medicines such as penicillin and doxycycline, and [that] the APIs needed to make these antibiotics are sourced from China.”²⁸¹ Dr. O’Toole recently testified before Congress that the U.S. does not have the “surge capacity” it needs to produce a sufficient amount of doxycycline in the event of an epidemic.²⁸² The FDA has said there are currently two API manufacturing facilities for doxycycline located in the U.S. but it does not have the data it needs “to calculate the volume of APIs being used for U.S.-marketed drugs from China or India, and what percentage of U.S. drug consumption this represents.”²⁸³

The FDA maintains a list of drugs that are for use as antidotes in public health emergencies to counter biological, chemical, influenza, and radiation threats. According to the FDA, the majority of facilities that manufacture API for most critical medical countermeasures against these threats now originate in foreign countries. For example, 96% of facilities that manufacture API for ciprofloxacin and 82% of those for doxycycline, two critical antibiotics used to counteract anthrax and other biological threats, are now located in foreign countries.²⁸⁴

The U.S. still has the capacity to manufacture pharmaceuticals in the United States. However, many companies lack economic incentives to do so.²⁸⁵ In 2006, over 90% of large pharmaceutical companies’ revenue was from branded drugs that had been on the market for more than five years.²⁸⁶ Many of those patents were set to expire in a few years. When pharmaceutical companies lose their patents on blockbuster drugs, they begin to cut back on personnel. U.S. based layoffs in the pharmaceutical industry exceeded 43,000 in 2010; 19,000 in 2011; 10,000 in 2012; and 8,000 in 2013.²⁸⁷

Medical Products: In addition to its deficit in manufacturing capabilities for medicines, the U.S. has also become increasingly reliant on overseas production for medical products such as medical gloves, gowns, masks, and syringes. A 2011 report by the Department of Commerce found “a very high degree of foreign sourcing and dependency” for critical components and materials necessary to manufacture pharmaceuticals and medical devices/surgical equipment. The report also found that “there is no U.S.-based alternate source available” for these

²⁸⁰ Senate Committee on Armed Services, Subcommittee on Emerging Threats and Capabilities, *Hearing on Biological Threats to U.S. National Security*, 116th Cong. (Nov. 20, 2019).

²⁸¹ USCC 2019 Annual Report, *supra* note 86.

²⁸² Senate Committee on Armed Services, Subcommittee on Emerging Threats and Capabilities, *Hearing on Biological Threats to U.S. National Security*, 116th Cong. (Nov. 20, 2019).

²⁸³ Testimony of Dr. Janet Woodcock (Oct. 30, 2019), *supra* note 226.

²⁸⁴ *Id.*

²⁸⁵ *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy*, *supra* note 103.

²⁸⁶ PricewaterhouseCoopers, *The Changing Dynamics of Pharma Outsourcing in Asia: Are you Readjusting your sights?* (2008) (https://www.pwc.com.au/industry/healthcare/assets/pharmaoutsourcing_oct08.pdf).

²⁸⁷ *Still Waiting For Good Times*, Chemical & Engineering News Magazine (Nov. 4, 2013) (cen.acs.org/articles/91/i44/Still-Waiting-Times.html).

materials.²⁸⁸ Dr. O'Toole testified before Congress that today it would take four years' worth of [domestically manufactured] needles to vaccinate the entire U.S. population with the H1N1 flu vaccine.²⁸⁹

Currently, the U.S. does not have the capability to independently manufacture needles and syringes necessary for administering certain medication in the event of a pandemic influenza outbreak (and other infectious diseases would implicate similar challenges).²⁹⁰ Greg Burel, Director of HHS's Strategic National Stockpile, noted "[w]hile the [Strategic National Stockpile (SNS)] maintains ancillary supplies to administer countermeasures, the current manufacturing capability for licensed products cannot keep pace with predicted threats." As an example, Burel stated that "we know that demand will outpace commercial supply for just needles and syringes during a pandemic influenza outbreak. The [U.S. government] is working with domestic supply chain partners to identify alternatives to reduce reliance on foreign suppliers ... [and] toward potential development of innovative new drug delivery devices to decrease reliance on limited supply chain capability."²⁹¹

Advanced Manufacturing Technology and Potential for Domestic Production: In 2016, Congress passed the 21st Century Cures Act, which among other things provided funding to assist in medical product development and innovations. A provision of the Act awarded grants for the study of improvements to the process of continuous manufacturing of drugs and biologics. Continuous manufacturing is a form of advanced manufacturing that "transforms the traditional, stepwise manufacturing processes into a single system that's based on modern process monitoring and controls."²⁹² This advanced technology and continuous model allows for greater control over the manufacturing process to ensure consistency in and a reliable output of finished drug products. As former FDA Commissioner Margaret Hamburg stated in testimony before the U.S. Senate Committee on Health, Education, Labor and Pensions, "[a]dvances in pharmaceutical manufacturing technology provide new opportunities to lower costs, limit drug shortages, and reduce supply chain vulnerabilities—and reinvigorate U.S. pharmaceutical manufacturing."²⁹³

²⁸⁸ Department of Commerce, Bureau of Industry and Security and Office of Technology Evaluation, *Reliance on Foreign Sourcing in the Healthcare and Public Health (HPH) Sector: Pharmaceuticals, Medical Devices, and Surgical Equipment* (Dec. 2011) (https://www.hida.org/App_Themes/Member/docs/GA/Industry-Issues/Emergency-Pandemic/Dept-Commerce-Study_Healthcare-Foreign-Sourcing.pdf).

²⁸⁹ Senate Committee on Armed Services, Subcommittee on Emerging Threats and Capabilities, *Hearing on Biological Threats to U.S. National Security*, 116th Cong. (Nov. 20, 2019).

²⁹⁰ See Congressional Staff Tour and Exercise, *Discussion: Manufacturing of PPE and Ancillary Supplies*, Department of Health and Human Services, Assistant Secretary for Preparedness and Response (Oct. 3, 2019).

²⁹¹ Committee Correspondence from Department of Health and Human Services, Assistant Secretary for Preparedness and Response to Homeland Security and Governmental Affairs Committee Minority Staff (Received Nov. 27, 2019).

²⁹² Pub. L. No. 114-255 (2016); *FDA Statement on FDA's modern approach to advanced pharmaceutical manufacturing*, Food and Drug Administration (Feb. 26, 2019) (<https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-modern-approach-advanced-pharmaceutical-manufacturing>).

²⁹³ Senate Committee on Health, Education, Labor and Pensions, *Hearing on Continuing America's Leadership in Medical Innovation for Patients*, 114th Cong. (Mar. 10, 2015) (S. Hrg. 114-572).

In 2017, the FDA awarded the National Institute for Pharmaceutical Technology and Education (NIPTE), a non-profit academic organization, \$35 million in funding to improve pharmaceutical manufacturing throughout the United States. According to NIPTE's research, the generic drug sector currently operates at a 40% efficiency rate.²⁹⁴ However, pharmaceutical manufacturing continues to lag far behind its industry counterparts. Dr. Ajaz S. Hussain, President of the National Institute for Pharmaceutical Technology and Education and former Deputy Director of the FDA's Office of Pharmaceutical Science, noted "tide detergent granules are better controlled and more efficiently manufactured than many pharmaceuticals products."²⁹⁵

A transition to continuous manufacturing in the U.S. for the generic industry could aid in reducing shortages, decreasing drug costs, and stabilizing the market. However, there are multiple barriers to entry, including the cost of transitioning to this technology, especially for makers of those drugs most commonly in shortage. As discussed above, the FDA's Generic Drug User Fee Amendments include multiple fees. These include facility and program fees as well as ANDA application fees.²⁹⁶ One potential consideration for companies that decide to utilize continuous manufacturing is to waive or reduce those fees. To address the deficit in domestic manufacturing capabilities as well as drug shortages, waivers could also be applied for program and facility fees when producing critical generic sterile injectable drugs within the United States.

CONCLUSION

Drug pricing, shortages, and the source and supply of materials for drugs sold in the U.S. are contributing to a growing public health crisis. The reforms needed to address these issues are necessary to avoid a worsening spiral of consequences for patients, consumers, and hospital systems. The underlying national security concern these threats represent will only increase in likelihood and severity if no action is taken.

As Dr. Aaron Kesselheim has suggested, Congress should consider "a suite of different policy solutions for drug pricing and shortage issues because the factors contributing to these issues change during the different time points after a drug is approved."²⁹⁷ To curtail skyrocketing drug prices and address the harm patients, consumers, and hospitals have experienced as a direct consequence, Congress must improve transparency, hold pharmaceutical companies accountable for unsubstantiated price hikes and unfair competition tactics, and foster transition to a multisource generic drug market. To help prevent the continued increase in drug shortages and counter their impacts, Congress must address the need for increased transparency, decentralization, and utilization of advanced manufacturing technology in the United States.

²⁹⁴ Ajaz S. Hussain, Vadim J. Gurvich, and Kenneth Morris, *Pharmaceutical "New Prior Knowledge": Twenty-First Century Assurance of Therapeutic Equivalence*, Journal of the American Association of Pharmaceutical Scientists (Mar. 12, 2019). See also *FDA Awards NIPTE Potential \$35 Million in Grants to Reform Drug Manufacturing Process*, PR Newswire (Oct. 4, 2011) (<https://www.prnewswire.com/news-releases/fda-awards-nipte-potential-35-million-in-grants-to-reform-drug-manufacturing-process-131085843.html>).

²⁹⁵ Congressional Briefing, *Strengthening the Generic Drug Sector: New Approaches for Ensuring Availability and Affordability of Prescription Drugs on behalf of Long Island University* (Oct. 16, 2019).

²⁹⁶ *Generic Drug User Fee Amendments*, Food and Drug Administration (undated) (<https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments>).

²⁹⁷ Interview with Dr. Aaron Kesselheim.

Finally, to address national security implications, Congress must ensure that DHS and HHS have a robust understanding of the market intelligence behind our pharmaceutical supply chain and encourage U.S. pharmaceutical manufacturing independence for essential drugs products.