Costly Cures:

The Broken Generic Drug Market and the Urgent Need for the Affordable Drug Manufacturing Act

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December 2019

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Executive Summary

Prescription drug manufacturers have relentlessly raised prices on U.S. consumers. In the first six months of 2019, pharmaceutical corporations increased prices by over 10%.[1] In the past 10 years, spending on retail prescription drugs in the U.S. increased by nearly $100 billion—from $240 billion in 2008 to $335 billion in 2018.[2]

As drug companies increase prices, patients bear the costs. Americans spend an average of over $1,200 a year on prescription drugs[3]—with some patients forced to shell out tens and even hundreds of thousands of dollars to obtain the lifesaving treatments they need. Stuck between financial hardship and medical need, patients are forced into dangerous choices. According to a recent Kaiser Family Foundation poll, at least three in ten adults reported skipping drug doses, delaying prescriptions, or taking less of a drug than prescribed to save money.[4]

The federal government awards patents and exclusivities—essentially giving companies monopoly power over parts of the drug market—in an effort to incentivize new biopharmaceutical development. Once these patents and exclusivities on brand-name drugs expire, patients and providers have traditionally relied on generic drug companies to enter the market and create competition, driving down costs and ensuring a reliable supply of affordable drugs. The average cost of a generic drug is 80% to 85% lower than its brand-name equivalent,[5] and generic drugs saved the U.S. nearly $300 billion in 2018 alone.[6] The generic drug market, however, is plagued by market failures that harm patients and keep the costs of drugs high:

- **Generic drug markets often lack competition, resulting in higher prices.** When only a few companies make a generic drug, competition is insufficient to drive down prices. A study of 1,120 generic drugs from 2008 to 2013, for example, found that drugs with two manufacturers experienced price increases of 29%—and drugs with just one manufacturer experienced price increases of 116%—compared to drugs in markets with more competitors.[7] Unfortunately, the U.S. generic drug industry is concentrated. Today, 40% of generic drugs are made by a single manufacturer, and the majority are manufactured by only one or two companies.[8] Meanwhile, generic drug companies are merging at higher rates,[9] and two-thirds of FDA-approved generic drugs are not being actively marketed by their manufacturers—further limiting competition.[10]

- **Uncompetitive generic drug markets allow for market manipulation, causing rapid increases in generic drug prices.** Generic drug manufacturers can—and do—take advantage of uncompetitive markets by rapidly increasing their drugs' prices. In 2010, for example, drug maker Valeant acquired the rights to be the sole generic manufacturer of Syprine, a drug to treat Wilson's disease—and jacked up its price by 3,000% over five years.[11] A 2016 U.S. Senate Aging Committee investigation of generic price spikes revealed a "monopoly business model" that allows manufacturers "to identify and acquire off-patent sole-source drugs over which they [can] exercise de facto monopoly pricing power, and then impose and protect astronomical price increases."[12]

- **Pharmaceutical companies have been accused of engaging in illegal activity to keep generic drug prices high.** In addition to manipulating markets, some pharmaceutical companies have been accused of engaging in illegal behavior. Today, for example, 47 states have ongoing investigations into top generic drug makers for allegedly conspiring to fix the prices of hundreds of generic drugs in what one investigator called "the largest cartel in the history of the United States."[13]

- **Uncompetitive generic drug markets increase the risk of drug shortages, leaving patients without critical treatments in times of need.** Drug shortages are an ongoing nationwide problem that drive up costs and put patients' health at risk: there have been more than 100 drug shortages per year since 2007, and in

2018, there were 186 drug shortages, the second highest total in more than a decade.[14] There are multiple causes of these shortages—but the reliance on one or two suppliers for generic drugs is a key risk factor. Researchers have concluded that "a lack of healthy competition in the generic drug market…is likely contributing to price hikes and shortages."[15]

To address these market failures, Congress should pass the *Affordable Drug Manufacturing Act* (the Act), legislation introduced by Senator Elizabeth Warren and Representative Jan Schakowsky. The bill would allow the Department of Health and Human Services (HHS) to manufacture generic drugs at low costs in cases where the market has failed—increasing competition and lowering prices for consumers. The bill would give the HHS Secretary the authority to manufacture generic drugs in cases where: (1) no company is marketing the drug in the United States; (2) only one or two companies are marketing the drug, and the price has spiked; (3) only one or two companies are marketing the drug, and the drug is in shortage; or (4) if only one or two companies are marketing the drug, the price is a barrier to patient access, and the drug is listed as an "essential medicine" by the World Health Organization (WHO).[16] The legislation also authorizes the federal government to contract for the manufacture of these products, similar to the way that federal agencies already work with the private sector to produce medications essential to our national security.[17]

The *Affordable Drug Manufacturing Act* would increase competition and lower prices for consumers. Under the bill, the federal government—at the discretion of the HHS Secretary, could manufacture hundreds of drugs and would be required to manufacture:

- **Insulin.** Insulin, a hormone produced in the pancreas, helps the body process glucose derived from food. Glucose is the body's "main source of energy"; without glucose (and the insulin necessary to process it), the human body cannot function properly.[18] Diabetes is a disease that prevents the body from producing or adequately processing insulin. For many of the more than 30 million Americans living with diabetes, insulin is an essential medicine. The cost of insulin has increased by over 1,200% since the 1990s.[19] Researchers have estimated that a 10-ml vial for certain types of insulin could be profitably produced for $7 to $11 per patient per month.[20] The *Affordable Drug Manufacturing Act* would require the federal government to begin manufacturing insulin within one year of passage of the bill.

- **Naloxone.** Naloxone is a critically important drug that can reverse the effects of an opioid overdose. As the opioid crisis has escalated in the United States, consumers and advocates have raised concerns about the lifesaving drug's affordability and accessibility. The *Affordable Drug Manufacturing Act* would require the federal government to manufacture generic naloxone to help combat the opioid epidemic.

- **Antibiotics.** Antibiotics are drugs that fight bacterial infections. The misuse of antibiotics can lead to antimicrobial resistance, which kills over 35,000 Americans a year.[21] Due to the unique economics of the antibiotic market, many companies often elect not to manufacture antibiotics—contributing to antibiotic shortages and inhibiting development of new antibiotics that could combat resistant infections.[22] The *Affordable Drug Manufacturing Act* would require the HHS Secretary to manufacture antibiotics with limited generic competition in order to ensure affordability and stable supplies and help fight antimicrobial resistance.

The appendix of this report also lists over 400 examples of drugs approved by FDA to be marketed in the United States that are experiencing limited competition and are potential candidates for public manufacturing under the *Affordable Drug Manufacturing Act*.

Introduction

Prescription drug manufacturers have relentlessly raised prices on U.S. consumers. In the first six months of 2019 alone, pharmaceutical corporations raised prices by over 10%—matching a decades-long trend in price increases.[23] In the past 10 years, spending on retail prescription drugs in the U.S. increased by nearly $100 billion—from $240 billion in 2008 to $335 billion in 2018.[24]

When drug companies hike prices, patients bear the costs. Americans spend, on average, over $1,200 a year on prescription drugs,[25] with some patients forced to shell out tens and even hundreds of thousands of dollars to obtain the lifesaving treatments they need. Nearly one in four Americans taking prescription drugs "report[s] difficulties affording their medications."[26] Stuck between financial hardship and medical need, patients sometimes are unable to take medications as prescribed: according to a recent Kaiser Family Foundation poll, at least three in ten adults reported skipping drug doses, delaying prescriptions, or taking less of a drug than prescribed to save money.[27]

The federal government awards patents and exclusivities in an effort to incentivize new biopharmaceutical development with the price-setting powers of a monopoly. This system is designed to ensure that brand-name drug companies, after investing capital to develop a new drug, will recoup their investment during a period of patent-protected exclusivity. After patents and exclusivities for brand-name drugs expire, patients, health care providers and policymakers can rely on generic drugs to drive down costs and ensure a reliable supply of affordable drugs. To spur the development of generic drugs, Congress passed the *Drug Price Competition and Patent Term Restoration Act of 1984* (Hatch-Waxman Act; P.L. 98-417). The law created an expedited pathway for generic manufacturers to gain approval from the U.S. Food and Drug Administration (FDA)—making it easier for drug companies to produce generic drugs affordably and sell cheap, effective drugs to patients at a fraction of the cost of brand-name counterparts.

Federal efforts to spur generic competition have largely been successful. On average, the cost of a generic drug is 80% to 85% lower than the brand-name product.[28] Generic drugs represent 90% of prescription drugs sold, but only 23% of prescription drug costs.[29] In 2018 alone, generic drugs saved the U.S. over $292 billion in health care spending, including $90.3 billion in Medicare savings and $46.8 billion in Medicaid savings.[30]

The benefits to the health care system from generic drugs, however, are only available if generic drug markets operate as intended. In recent years, the generic drug market has become more concentrated, and there is increasingly disturbing evidence of illegal collusion among generic drug companies—raising questions about whether the generic drug marketplace is functioning efficiently and effectively. In response, Senator Warren and Representative Schakowsky introduced the *Affordable Drug Manufacturing Act*. The bill would permit the federal government to manufacture generic drugs at low costs in cases where the market has failed—increasing competition and lowering prices for consumers.

Findings

This report, prepared by the staff of Senator Warren and Representative Schakowsky, provides an overview of some of the ways in which the generic drug market has failed.[31] It describes how the *Affordable Drug Manufacturing Act* would address certain market failures in the generic drug market, lowering drug prices for millions while improving competition. Its key findings reveal that the generic drug market is plagued by market failures that harm patients and keep the costs of drugs high.

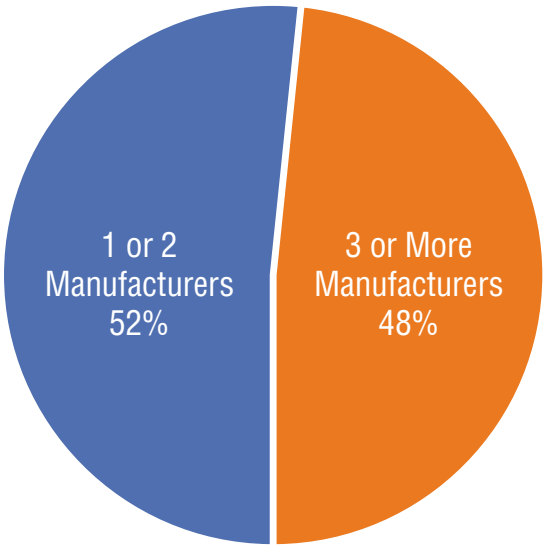
- **U.S. generic drug markets often lack competition, resulting in higher prices.**

Uncompetitive generic drug markets are associated with significant price increases. A study of 1,120 generic drugs from 2008 to 2013, for example, found that generic drugs with a duopoly experienced price increases of 29%, generic drugs with a near-monopoly experienced price increases of 59%, and generic drugs with a monopoly experienced price

increases of 116%, as compared to drugs with high levels of competition.[32]

Unfortunately, the generic drug market has trended toward increased concentration and decreased competition. Today, 40% of generic drugs are made by a single manufacturer, and the majority are manufactured by only one or two companies.[33] On average, the median number of manufacturers in each drug market is about two.[34]

More than Half of Drugs Have Limited or No Competition



Some of this concentration stems from the low-revenue nature of generic drug markets. Because generic drug manufacturers are able to enter already-established markets without having to conduct extensive research or the full array of clinical trials required to demonstrate safety and efficacy for new drugs, generic drugs in a functioning market are sold at prices closer to the marginal cost of production. The markets are also often small: on average, the annual inflation adjusted sales revenues of a particular generic drug-dosage form are typically less than $10 million.[35] Over time, the small market size and low profit margins can squeeze out competition. Generic drug manufacturers may choose to exit markets once markets have bottomed out or may be hesitant to enter markets with existing competition—leaving only a few manufacturers responsible for the entire market supply. According to FDA, less than a third of approved generics are being actively marketed, more than half are not being sold, and 14% are of "unknown marketing status."[36] Some drug markets, like those for orphan disease treatments, do not attract generic competition at all because of the size of the market.[37] Potential market entrants may determine that a sufficient market does not exist to justify the capital investments needed to gain regulatory approval and to develop the capacity to produce a drug.

Increased merger and acquisitions activity has also contributed to generic drug market consolidation. A recent study found that "in 2014 there were 22 [merger and acquisition] deals worth $1.86 billion, in 2015 there were 34 deals totaling $33.5 billion, and in 2016 there were 42 deals worth [] $44 billion"—revealing a troubling trend toward consolidation in the generic market.[38] Significant mergers in this period included Teva's acquisitions of Allergan, Barr, and IVAX Corp; Mylan's acquisition of Merck Generics, and Takeda's acquisition of Nycomed.[39] Continuing this trend of anticompetitive consolidation, earlier this year, pharmaceutical giant Pfizer announced plans to merge its off-patent unit with one of the largest generic drug makers, Mylan.[40]

Most merger and acquisition activity in the generic market goes either undetected or unpenalized by antitrust authorities at the Federal Trade Commission (FTC) and the Department of Justice (DOJ).[41] Under current law, companies must report mergers to the FTC and DOJ that are valued at over $90 million.[42] Researchers have found, however, that "the U.S. generic drug industry is populated by numerous relatively small firms, with each of their small product portfolios capturing modest annual revenues"[43]—meaning that mergers, when they happen, likely do not trigger an antitrust review. The four largest generic pharmaceutical manufacturers in the U.S., for example, only accounted for one-quarter of the total generic drug market revenue in 2015.[44] Small generic drug manufacturers are spread across different generic drug markets, leaving only a few or no competitors in each market with small total revenues.

- **Uncompetitive generic drug markets allow for market manipulation, causing rapid increases in generic drug prices.**

When there is little competition, generic drug makers can increase prices and squeeze consumers in a captive market—just as is the case when the product is a brand-name drug protected by a legal monopoly.

Valeant Pharmaceuticals' strategy of purchasing off-patent drugs and jacking up prices was a notorious example of this approach.[45] In 2010, Valeant acquired the rights to Syprine (trientine hydrochloride), a nearly-50-year old drug to treat Wilson's disease, a rare genetic disorder that affects less than 10,000 people in the U.S. In the five years after acquiring Syprine, Valeant ramped its price up from $652 per month to $21,267 per month—an increase of more than 3,000%.[46]

Turing Pharmaceuticals provides another example of price gouging. In September 2015, Turing acquired the rights for pyrimethamine, a 62-year old drug used to treat a common parasite infection, toxoplasmosis. With the acquisition of the drug, Turing became its only manufacturer and immediately marked up the price from $13.50 per tablet to $750 per tablet,[47] a 5,000% increase.[48] Even after 62 years on the market, no other manufacturers had entered the market given pyrimethamine's low profit margins and relatively small market.

In 2015, the U.S. Senate Special Committee on Aging launched a bipartisan investigation into abrupt generic price hikes by Valeant, Turing, and other pharmaceutical companies. The subsequent report produced by the Committee revealed a "monopoly business model" designed to exploit market loopholes. This business model "enabled [manufacturers] to identify and acquire off-patent sole-source drugs over which they could exercise de facto monopoly pricing power, and then impose and protect astronomical price increases."[49] By pursuing the best drug available for treatment and produced by only one manufacturer, companies bet that their acquisition would not face immediate competition and that providers would continue to prescribe the drug despite high prices. After capturing the market, companies—without even investing in research and development—could rapidly increase prices to maximize profits.

A 2016 Government Accountability Office (GAO) report on generic drugs in the Medicare program found that more than 20% of generic drugs analyzed "had at least one extraordinary price increase of 100 percent or more" during the study period.[50] Despite generics typically capturing 80-90% of a brand-name drug's sales within a year following market entry, and promises that generics would significantly reduce costs, a 2015 analysis found the prices of half of all generic drugs had increased in the past two years.[51] At the same time, prescription drug costs are crushing families and putting millions of Americans' health at risk because people are unable to afford their prescriptions.

- **Pharmaceutical companies have been accused of engaging in illegal activity to keep generic drug prices high.**

In addition to manipulating captive markets, some generic pharmaceutical companies have been accused of engaging in illegal activity to keep generic drug prices high.

Today, 47 states have ongoing investigations into top generic drug makers for allegedly conspiring to fix the prices of hundreds of generic drugs in what one investigator called "the largest cartel in the history of the United States."[52] Antitrust authorities began investigating generic drug manufacturers for egregious price hikes and illegal collusion in December 2016, and the investigation has since "exploded into an investigation of alleged price-fixing involving at least 16 companies and 300 [new] drugs."[53] The investigations have targeted instances of alleged collusion related to coordinating price increases. In November 2018, a federal judge ruled that "more than 1 million emails, cellphone texts and other documents cited as evidence" are allowable evidence in the investigation, which allegedly provide "voluminous documentation" of illegal collusion and coordination.[54]

On May 10, 2019, 44 states filed another lawsuit in federal court against Teva, Sandoz, Mylan, Pfizer and 16 other drug manufacturers, alleging that these pharmaceutical companies schemed to increase drug prices. As outlined in the lawsuit, "during a 19-month period beginning in July 2013 and

continuing through January 2015, Teva significantly raised prices on approximately 112 generic drugs. … The size of the price increases varied, but a number of them were well over 1,000%."[55] One report found that between July 2013 and July 2014, the prices of more than 1,200 generic drugs sold by these companies increased an average of 448%.[56] The lawsuit alleges that generic manufacturers agreed to divide market share and forego competition, eventually escalating the conspiracy by gouging consumers and insurers with high drug prices.

- **Uncompetitive generic drug markets increase the risk of drug shortages, leaving patients without critical treatments in times of need.**

Generic drug industry consolidation and lack of competition has also increased the frequency and persistence of drug shortages.[57]

When there is a limited number of manufacturers in the supply chain, the risks of a supply disruption increase and the factors contributing to drug shortages, such as quality production issues, become more acute.[58] According to experts from FDA's Center for Drug Evaluation and Research, "drug shortages are first and foremost driven by the inability of various firms to maintain production because of the failure of quality management in facilities."[59] In 2011, the majority of sterile injectable drug shortages—one of the types of drugs most vulnerable to shortages[60]—were directly attributable to facility failures. This problem is exacerbated by the low revenues from the production of generics, which do not properly incentivize companies to maintain investment in high-quality production facilities.[61]

Permanent product discontinuations are another cause of drug shortages. These are particularly problematic in concentrated generic drug markets, where one or two suppliers may be responsible for all production and the discontinuation of a drug by a single manufacturer may have an outsized impact on the availability of that drug. A 2014 GAO report found that 12% of shortages reported to FDA from June 1, 2011, to June 30, 2013, were the result of product discontinuations—the highest reason for drug shortages after manufacturing problems such as quality issues or manufacturing delays.[62]

Finally, concentration in the active pharmaceutical ingredient (API) market has sometimes constrained manufacturers' access to raw materials, making it more difficult to manufacture generic drugs. GAO found that, regardless of the level of manufacturer competition, the "dependency on a sole API source can lead to shortages."[63]

According to the American Society of Health-System Pharmacists, there have been more than 100 drug shortages per year since 2007. In 2018, the number of drug shortages reached 186, the second highest since the peak of 267 drug shortages in 2011.[64] Generic drug shortages can have devastating consequences for patients, who may experience delays in treatment, receive unproven or less effective replacement drugs, or even have to completely forgo treatment.[65] Sometimes, these alternatives may prolong treatment or even result in death. For example, one study assessing the shortage of norepinephrine, a drug used to treat low blood pressure and heart failure, in the U.S. in 2011 found the shortage "was significantly associated with increased mortality among patients with septic shock."[66]

Shortages also impose severe financial burdens for hospitals. A recent survey of 700 hospital pharmacy managers found that all of them experienced a drug shortage in the previous year—forcing 81% of the pharmacy managers to hoard medications and 66% to ration them.[67] Every year, drug shortages cost hospitals $216 million in labor costs and an additional $200 million to substitute drugs.[68]

Given that decreased generic competition exacerbates the most common causes of drug shortages, additional manufacturing of generic drugs could alleviate supply chain disruptions.[69] Additionally, due to generic drug manufacturer dependency on a consolidating active pharmaceutical ingredient market, increased capacity to manufacture raw materials could decrease the prevalence and lessen the intensity of drug shortages.

The Affordable Drug Manufacturing Act

Ultimately, the primary driver of lower drug prices is increased market competition.[70] Research indicates that when drugs face competition from enough market entrants, prices drop: "drug prices decline to approximately 55% of brand-name drug prices with 2 generic manufacturers making the product, 33% with 5 manufacturers, and 13% with 15 manufacturers."[71] In addition to reducing costs, increased competition can also help address drug shortages and ensure a steady and reliable supply of drugs.

Senator Elizabeth Warren and Representative Jan Schakowsky's *Affordable Drug Manufacturing Act* would reduce drug prices and address drug shortages for millions while improving competition by tasking the Department of Health and Human Services (HHS) with the public manufacturing of generic drugs in cases where the market has failed. Public manufacturing of pharmaceuticals would strengthen the generic market by jump-starting competition.

To do this, the *Affordable Drug Manufacturing Act* would establish an Office of Drug Manufacturing (the Office) within HHS charged with lowering prices, increasing competition, and addressing shortages in the market for prescription drugs. The Act provides the Secretary of HHS with the discretion to choose which drugs the Office would manufacture, assuming that the drugs chosen meet certain conditions outlined in the Act. The *Affordable Drug Manufacturing Act* defines an "applicable drug" for public manufacturing as one for which all exclusivities and patents on the drug have expired—in other words, a drug that is a candidate for generic development. To qualify for public manufacturing, a drug would also have to meet one of the following conditions:

1. No company is marketing the drug in the United States;
2. Only one or two companies are marketing the drug and the price has spiked;
3. Only one or two companies are marketing the drug and the drug is in shortage; or
4. Only one or two companies are marketing the drug, the price is a barrier to patient access, and the drug is listed as an "essential medicine" by the World Health Organization.

Additionally, the Office can manufacture or contract for the manufacture of drugs if the government exercises a statutory licensing authority with respect to a patented drug such as "march-in rights" or government use under 28 U.S.C. 1498.

In turn, the government would be able to sell publicly-manufactured drugs at a fair price that covers manufacturing costs, while ensuring patients have access to these drugs. The Office would be required to offer to sell the rights to publicly-manufactured drugs to manufacturers who commit to keep the drug on the market at a fair price. This would ensure that public manufacturing spurs competition. In addition, the bill would improve the ability of new companies to enter the generic drug market and reduce the risk of drug shortages by authorizing the public manufacturing of active pharmaceutical ingredients.

The *Affordable Drug Manufacturing Act* also requires the Office to begin public production of certain drugs, including:

- **Insulin.** Insulin, a hormone produced in the pancreas, helps the body process glucose derived from food. Glucose is the body's "main source of energy"; without glucose (and the insulin necessary to process it), the human body cannot function properly.[72] Diabetes is a disease that prevents the body from producing or adequately processing insulin—resulting in high blood-glucose levels and associated health problems. For many of the more than 30 million Americans living with diabetes, insulin is an essential medicine. The cost of insulin has increased by over 1,200% since the 1990s,[73] and patient spending on insulin nearly tripled from 2002 to 2013[74]—then doubled again between 2012 and 2016.[75] Little generic competition exists in the insulin market, further contributing to increased prices. At least twelve Americans have died due to high insulin prices, with many more rationing access.[76] Researchers have

estimated that a 10-ml vial for certain types of insulin could be profitably produced for $7 to $11 per patient per month.[77] Production under the *Affordable Drug Manufacturing Act* would allow for significant cost savings for patients and medical providers. The *Affordable Drug Manufacturing Act* would require the federal government to begin manufacturing insulin within one year of enactment of the bill.

- **Naloxone.** Naloxone is a critically important drug that can reverse the effects of an opioid overdose. As the opioid crisis has escalated in the United States, consumers and advocates have raised concerns about the lifesaving drug's affordability and accessibility. Naloxone can be delivered via an injection, a nasal spray, or an auto-injector. FDA has approved naloxone, including the nasal spray and the auto-injector, for community use, meaning that individuals without medical training can use them outside of a medical setting to halt an overdose.[78] In April 2019, FDA approved the first generic naloxone nasal spray, but the generic has not yet been launched.[79] Production of naloxone under the *Affordable Drug Manufacturing Act* would introduce additional competition into the market—driving down costs and increasing accessibility for those most critically in need. The bill would require the Office of Drug Manufacturing to begin manufacturing naloxone, including naloxone indicated for community use, within one year of enactment of the *Affordable Drug Manufacturing Act.*
- **Antibiotics.** Antibiotics are types of drugs that fight bacterial infections. The misuse of antibiotics can lead to antimicrobial resistance, which kills over 35,000 Americans a year.[80] Due to the unique economics of the antibiotic market, many companies often elect not to manufacture antibiotics. Antibiotics do not necessarily generate large profits because they are typically only taken for short courses. Thus, antibiotics typically see limited generic competition and face increased risks of drug shortages. The lack of a steady supply of targeted, new antibiotics contributes to antibiotic resistance.[81] The *Affordable Drug Manufacturing Act* would require the HHS Secretary to manufacture antibiotics in shortage or with limited generic competition in order to ensure affordability and stable supplies—including at least three different antibiotics within one year of enactment of the *Affordable Drug Manufacturing Act*.

Other drugs could be produced at the HHS Secretary's discretion if they meet the listed criteria for lack of competition outlined in the *Affordable Drug Manufacturing Act*. For example, the following drugs—which include examples of antibiotics—could qualify for public manufacturing (Table 1):[82]

Table 1: Potential Candidates for Production Under the Affordable Drug Manufacturing Act

Generic	Brand Name	# of Manufacturers	Average Medicare Part D Spending Per Dosage Unit (Weighted)					% Change in Average Spending Per Dosage Unit from 2013 to 2017
			2013	**2014**	**2015**	**2016**	**2017**	
Penicillamine	Depen	1	$6.29	$27.36	$52.81	$58.71	$60.65	864%
Chlorambucil	Leukeran	1	$9.21	$10.13	$11.64	$20.92	$23.92	160%
Nitazoxanide	Alinia	1	$24.88	$27.06	$36.12	$59.95	$83.89	237%
Lomustine	Gleostine	1			$141.16	$205.35	$350.14	N/A
Pyrimethamine	Daraprim	1				$754.98	$758.15	N/A
Zileuton	Zyflo	1	$14.61	$18.36	$24.51	$26.31	$29.87	104%
Praziquantel	Biltricide	2	$14.82	$16.14	$70.17	$83.59	$83.54	464%
Dicloxacillin	Dicloxacillin Sodium	2	$0.53	$0.54	$0.60	$0.56	$0.77	44%
Corticotropin	H.P. Acthar	1	$6,161.51	$6,497.74	$6,827.41	$6,938.32	$7,350.98	19%
Cycloserine	Seromycin	1		$11.07	$45.27	$30.65	$36.60	231%

- **Penicillamine (Depen).** Penicillamine is a treatment for Wilson's disease and severe rheumatoid arthritis.[83] Mylan sells the drug as a tablet (Depen), but there are no other generic competitors. Mylan has taken advantage of the monopoly by hiking prices. Mylan has increased the price per tablet from $6.29 to $60.65—an increase of 864%. Depen was listed on the FDA Drug Shortage List from January 4, 2018 to October 1, 2019.[84] Production of Depen under the *Affordable Drug Manufacturing Act* would allow for significant cost savings for patients and medical providers, and help address the drug shortage that persisted for nearly two years.

- **Chlorambucil (Leukeran).** Chlorambucil is a cancer treatment used to treat chronic lymphocytic leukemia (CLL), Hodgkin lymphoma, and non-Hodgkin lymphoma.[85] Aspen, the sole manufacturer, has increased its list price per dosage by 27% every year from 2013 to 2017, a total of 160%. Medicare Part D pays $23.92 for one tablet (and almost $900 for a full prescription) —but the same tablet is available from the same manufacturer in Canada for $1.17.[86] Production of this drug under the *Affordable Drug Manufacturing Act* would allow for significant cost savings for patients.

- **Nitazoxanide (Alinia).** Nitazoxanide is an antimicrobial treatment used for diarrhea caused by some parasites.[87] Romark Laboratories sells the medicine as a solution (marketed by Lupin Pharameuticals[88]) for $7.34 per milliliter, and as tablets for $84.61 per tablet. In 2013, Romark sold each tablet for $24.88. In other words, Romark increased the price per dosage by 240% from 2013 to 2017. Increasing price competition by allowing production of this drug under the *Affordable Drug Manufacturing Act* has the potential to significantly reduce prices.

- **Lomustine (Gleostine).** Lomustine is a cancer treatment used to treat brain tumors and Hodgkin's lymphoma.[89] It was first approved in 1976. In 2015, an average prescription cost Medicare Part D $316. In 2017, the same prescription cost $594.[90] If the HHS Secretary chooses to produce this drug under the Affordable Drug Manufacturing Act, it would increase price competition and result in substantially reduced drug costs for patients.

- **Pyrimethamine (Daraprim).** Pyrimethamine is a 62-year-old medicine used to treat toxoplasmosis and other infections associated with HIV.[91] In 2015, the CEO of Turing Pharmaceuticals, Martin Shkreli, infamously gouged the price of Daraprim by 5,000% from $13.50 per pill to $750 per pill.[92] Medicare Part D spent $758 per pill in 2017. Pyrimethamine is available in the UK for under a dollar,[93] yet in 2017, Medicare Part D spent $758 per pill, $37,377 per prescription, and $198,289 per beneficiary—totaling $35.1 million in Medicare Part D spending on the drug. Although its price has not changed in the past three years, pyrimethamine is on the WHO List of Essential Medicines[94] and could thus be selected for production under the *Affordable Drug Manufacturing Act* if the HHS Secretary deemed the price a barrier to patient access.

- **Zileuton (Zyflo).** Zileuton is a drug for the prophylaxis and chronic treatment of asthma.[95] Chiesi USA is the only manufacturer of Zyflo. In 2013, Medicare Part D spent $14.61 for a pill of Zyflo. By 2017, Medicare Part D was spending $29.87—or more than double per pill. By choosing to publicly manufacture Zileuton under the authorities granted in the *Affordable Drug Manufacturing Act*, the HHS Secretary could introduce another competitor into the market, forcing down prices and benefitting consumers.

- **Praziquantel (Biltricide).** Praziquantel is an antiparasitic drug used to treat infections, including schistosomiasis.[96] Without any generic competition, Bayer was able to increase the price of the drug from $14.82 per pill in 2013 to $83.54 per pill in 2017. By 2017, one prescription of Praziquantel cost $987.11 in Medicare Part D spending. Over four years, Bayer increased the price on average by 54% every year, for a total increase of 464%. Par Pharmaceutical has since received approval to sell the generic

drug.[97] Praziquantel is on the WHO List of Essential Medicines,[98] and could thus be selected for production under the *Affordable Drug Manufacturing Act* if the HHS Secretary deemed the price a barrier to patient access even after introduction of a generic competitor into the market.

- **Dicloxacillin.** Dicloxacillin is a common antibiotic used to treat infections like bronchitis and pneumonia.[99] Teva and Sandoz are the two remaining manufacturers of the drug, after three manufacturers discontinued their production of the drug.[100] The drug is sold in three different dosage forms (i.e., 125 mg, 250 mg, 500 mg). Medicare Part D spending does not distinguish between the different dosage forms. From 2013 to 2017, Teva increased the price of dicloxacillin from around $0.53 per pill ($22.99 per prescription) to $0.77 per pill ($36.68 per prescription). On average, the price increased by nearly 10% each year, for a total 44% increase over five years. Sandoz has done something similar, leading to a price increase of 7.12% every year. Given these steady price increases despite generic competition, the HHS Secretary could decide to inject another competitor into the market through the authorities granted in the *Affordable Drug Manufacturing Act*—lowering prices for consumer and holding pharmaceutical companies accountable for proper pricing.

- **Corticotropin (H.P. Acthar Gel).** Corticotropin (Acthar gel) is used to treat a variety of conditions, including multiple sclerosis, lupus, and rheumatoid arthritis. In 2016, the New York Times reported that Acthar, sold by Mallinckrodt Pharmaceuticals, was "a 1950s vintage, off-patent drug whose cost has rocketed from $40 a vial in 2001 to $38,000 today."[101] In 2017, Medicare Part D spent over $680 million on the drug. From 2013 to 2017, Medicare Part D spending increased by nearly 20% to $7,350.98 per mL in 2017. On June 5, 2019, the Department of Justice filed charges against Mallinckrodt, accusing it of illegally subsidizing patient co-pays, which, in part, allowed it to raise prices exorbitantly despite questions about the drug's effectiveness compared to cheaper alternatives.[102] Under the *Affordable Drug Manufacturing Act*, the federal government would also be able to hold companies like Mallinckrodt accountable by creating competition.

- **Cycloserine (Seromycin).** Cycloserine is an antibiotic used to treat drug-resistant tuberculosis. Eli Lilly stopped manufacturing the drug in 2000 because of its low profit margins, leaving only one manufacturer producing the drug. In 2015, Rodelis Therapeutics acquired the drug and raised the price overnight from $500 for 30 capsules to $10,800—a total increase of over 2,000%.[103] Under this price, the total cost of a treatment would have been $500,000.[104] In response to public outrage, Rodelis returned the drug to its former owner, the Chao Center, which lowered the price to $1,050 per capsule.[105] Abroad, generic versions sell for $20 per 100 pills.[106] From 2014 to 2017, Medicare Part D spending per dosage unit amounted to a 230% increase. Cycloserine is a WHO Essential Medicine, and could thus qualify for public manufacturing under the *Affordable Drug Manufacturing Act* if the HHS Secretary deemed its price a barrier to access. Furthermore, Cycloserine was listed as an acute drug shortage on the FDA drug shortage list from December 20, 2018 to April 17, 2019.[107]

Conclusion

Generic drugs offer the potential to save patients and health care providers billions of dollars, improving health outcomes and helping to alleviate drug shortages. But in many cases, the generic drug market is failing, allowing pharmaceutical companies to exploit monopolies and engage in price gouging.

Senator Warren and Representative Schakowsky's *Affordable Drug Manufacturing Act* would restore market competition by allowing, under circumstances where the market has failed, public manufacturing of generic drugs. These reforms are urgently needed to restore the generic drug marketplace and cut patients' drug costs.

Appendix: Drugs Potentially Eligible for Office of Drug Manufacturing Production under the Affordable Drug Manufacturing Act

Under the *Affordable Drug Manufacturing Act*, drugs with no patents or exclusivities can qualify for public manufacturing if they meet one of the following criteria:

1. No company is marketing the drug in the United States;
2. Only one or two companies are marketing the drug, and the wholesale acquisition cost of at least one of the drugs has experienced an increase that is greater than the consumer price index for all urban consumers during at least 1 year in the previous 5-year period;
3. Only one or two companies are marketing the drug, and the drug is in shortage; or
4. Only one or two companies are marketing the drug, the price is a barrier to patient access, and the drug is listed as an "essential medicine" by the World Health Organization (WHO).

The Offices of Senator Warren and Representative Schakowsky sought to identify examples of drugs that could meet the criteria for public manufacturing under the *Affordable Drug Manufacturing Act*. To do so, staff analyzed data published in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" ("the Orange Book"), which identifies all drug products that have been approved by FDA for marketing in the United States under Section 505 of the Federal Food, Drug, and Cosmetic Act.[108] The Orange Book also lists all related patent and exclusivity information, and it is updated monthly. Staff did not analyze drugs that are not being marketed in the United States, instead focusing on drugs with FDA-approval to be marketed in the United States.

Staff accessed Orange Book data on November 26, 2019, to identify drugs without current patents or exclusivities that had received approval for marketing from two or fewer different companies. Of the 1,777 unique active pharmaceutical ingredients in the Orange Book, 978 were without patents or exclusivities on any form or strength of the drug. Of the 978 active pharmaceutical ingredients, 427 were manufactured by only one or two companies—295 active pharmaceutical ingredients made by one company and 132 made by two companies. Discontinued drugs were not included in the analysis. Staff then sought to identify which of the 427 active pharmaceutical ingredients identified could qualify for public manufacturing by nature of meeting one of the following additional criteria: (1) the drug is in shortage; (2) the drug is listed as an "essential medicine" by WHO; and/or (3) the wholesale acquisition price of the drug increased, for at least one year in the past five years, at a rate greater than the consumer price index.

- **Drugs in Shortage:** FDA updates a database of drug shortages, with information supplied by drug manufacturers. As outlined by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), drugs on the list could be in shortage for any number of reasons including, "requirements related to complying with good manufacturing practices, regulatory delay, shortage of an active ingredient, shortage of an inactive ingredient component, discontinuation of the manufacture of the drug, delay in shipping of the drug, [or] demand increase for the drug."[109] The FDA Drug Shortage list focuses on medically necessary products and does not typically include shortages that "are expected to be resolved quickly, shortages that involve only a particular strength or package size, and shortages where a substitute strength(s) or package size(s) is available."[110]

  Staff examined drugs on the FDA Drug Shortage list as of December 4, 2019. Of the 427 drugs with no patents or exclusivities and two or fewer approved manufacturers, 21 were included on the FDA shortage list. Many of these drugs have been on the FDA drug shortage list for over a year.

- **Drugs Listed as WHO "Essential Medicines":** WHO defines Essential Medicines as "those that satisfy the priority health care needs of the population."[111] Medicines are deemed essential by a WHO Expert Committee, which meets every two years to review the latest scientific evidence to select drugs "with due regard to disease

prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness."[112] WHO recommends that treatments on the Model List "be available within the context of functioning health systems at all times in adequate amounts… and at a price the individual and the community can afford."[113] Of the 427 drugs identified, at least 50 drugs are considered WHO Essential Medicines.

- **Drugs with Price Spikes:** Staff had limited access to data on the wholesale acquisition costs of the 427 drugs identified. However, though comprehensive and detailed pricing information on all drugs is not readily available to the public, the Centers for Medicare and Medicaid Services publishes a spending database for Medicare Part D drugs, which can be used as a proxy measure for price increases and drug spending. The most updated data for Medicare Part D spending is available through the end of 2017. The Medicare Part D spending database provides spending information for nearly 3,000 drugs—including average spending per dosage unit and change in average spending per dosage unit over time.

  Staff examined Medicare Part D spending data from 2013-2017 to find examples from the list of 427 drugs that had experienced price spikes during the 5-year period. For the purposes of this analysis, staff conservatively considered a price increase above the consumer price index to be an increase of 10% or more. Of the 427 drugs, staff compared pricing information from the Medicare Part D database for 175 in the Medicare Part D database.[114] Of those 175 drugs, staff identified 117 that had experienced a price increase over 10% from 2013-2017.

The table below lists 427 drugs identified in the Orange Book with no patents or exclusivities that are manufactured by one or two companies. The table indicates whether a drug was identified as being in shortage, a WHO essential medicine, or having experienced a price increase. Drugs that did not meet any of these three additional criteria were included for the purposes of demonstrating the high number of drugs with limited competition across all dosage forms and strengths that HHS could monitor and consider, with more complete pricing information, as candidates under the *Affordable Drug Manufacturing Act*.

The example list provided below is a conservative analysis of drugs that could qualify for the *Affordable Drug Manufacturing Act*. Because we broadly grouped drugs for the purposes of this analysis by active ingredient—regardless of strength or dosage form—additional drugs could qualify for public manufacturing that are not listed below. For example, the Penicillamine Capsule (Depen) and Zileuton Capsule (Zyflo) are listed as examples in the report, but are not identified in the list below because although the two active pharmaceutical ingredients (Penicillamine and Zileuton) are manufactured by more than two companies, key dosage forms (Depen and Zyflo) have only one manufacturer. The list below provides a snapshot of the drugs that could qualify and highlights drugs that face the most limited competition across all of their possible forms and dosages.

Table 2: 427 Drugs with Two or Fewer Manufacturers and No Patents or Exclusivities

Ingredient	Number of Manufacturers	FDA Drug Shortage List? (12/4/19)	WHO Essential Medicines 2019 List?	Maximum Annual Change in Medicare Part D Spending Per Unit From 2013-2017
Abacavir Sulfate; Lamivudine; Zidovudine	2			
Acebutolol Hydrochloride	2			36%
Acetaminophen; Aspirin; Caffeine	2			
Acetaminophen; Caffeine; Dihydrocodeine Bitartrate	2			
Acetohydroxamic Acid	1			812%

Acetylcholine Chloride	1			
Acrivastine; Pseudoephedrine Hydrochloride	1			3%
Albumin Iodinated I-125 Serum	1			
Albumin Iodinated I-131 Serum	1			
Alcohol; Chlorhexidine Gluconate	1			
Alendronate Sodium; Cholecalciferol	1			14%
Alfentanil Hydrochloride	2			
Alitretinoin	1			2%
Allopurinol Sodium	2			
Alpha-Tocopherol Acetate; Ascorbic Acid; Biotin; Cholecalciferol; Cyanocobalamin; Dexpanthenol; Folic Acid; Niacinamide; Pyridoxine Hydrochloride; Riboflavin 5'-Phosphate Sodium; Thiamine Hydrochloride; Vitamin A Palmitate; Vitamin K	1			
Aluminum Hydroxide; Magnesium Trisilicate	1			
Amcinonide	2			12%
Amiloride Hydrochloride; Hydrochlorothiazide	2			24%
Amino Acids; Calcium Acetate; Glycerin; Magnesium Acetate; Phosphoric Acid; Potassium Chloride; Sodium Acetate; Sodium Chloride	1			
Amino Acids; Calcium Chloride; Dextrose; Magnesium Chloride; Potassium Phosphate, Dibasic; Sodium Acetate; Sodium Chloride	1			
Amino Acids; Calcium Chloride; Dextrose; Magnesium Sulfate; Potassium Chloride; Sodium Acetate; Sodium Glycerophosphate; Soybean Oil	1			
Amino Acids; Dextrose	1			
Amino Acids; Magnesium Acetate; Phosphoric Acid; Potassium Acetate; Potassium Chloride; Sodium Acetate	1			
Amino Acids; Magnesium Acetate; Phosphoric Acid; Potassium Chloride; Sodium Acetate; Sodium Chloride	1			
Aminophylline	1	Yes		
Aminosalicylic Acid	1		Yes	
Amitriptyline Hydrochloride; Chlordiazepoxide	1			17%
Amitriptyline Hydrochloride; Perphenazine	1			8%
Amlodipine Benzoate	1			
Ammonium Chloride	1			
Amoxapine	1			17%
Amoxicillin; Clarithromycin; Lansoprazole	2			
Amoxicillin; Clarithromycin; Omeprazole	1			19%
Ampicillin/Ampicillin Trihydrate	2			12%
Apomorphine Hydrochloride	1			3%
Apraclonidine Hydrochloride	2			
Arginine Hydrochloride	1			
Artemether; Lumefantrine	1		Yes	13%
Ascorbic Acid; Biotin; Cholecalciferol; Cyanocobalamin; Dexpanthenol; Folic Acid; Niacinamide; Pyridoxine; Riboflavin; Thiamine; Tocopherol Acetate; Vitamin A; Vitamin K	1			

Ascorbic Acid; Biotin; Cholecalciferol; Cyanocobalamin; Dexpanthenol; Folic Acid; Niacinamide; Pyridoxine; Riboflavin; Thiamine; Tocopherol Hydrochloride; Vitamin A; Vitamin K	1			
Ascorbic Acid; Biotin; Cyanocobalamin; Dexpanthenol; Ergocalciferol; Folic Acid; Niacinamide; Phytonadione; Pyridoxine Hydrochloride; Riboflavin 5'-Phosphate Sodium; Thiamine Hydrochloride; Vitamin A; Vitamin E	1			
Ascorbic Acid; Biotin; Cyanocobalamin; Dexpanthenol; Ergocalciferol; Folic Acid; Niacinamide; Pyridoxine Hydrochloride; Riboflavin 5'-Phosphate Sodium; Thiamine Hydrochloride; Vitamin A; Vitamin E; Vitamin K	1			
Aspirin; Caffeine; Orphenadrine Citrate	2			
Aspirin; Carisoprodol; Codeine Phosphate	2			10%
Aspirin; Methocarbamol	1			
Atorvastatin Calcium; Ezetimibe	1			
Atropine	1			
Atropine Sulfate; Difenoxin Hydrochloride	1			
Atropine; Pralidoxime Chloride	1			
Auranofin	1			15%
Avobenzone; Ecamsule; Octocrylene	1			
Avobenzone; Ecamsule; Octocrylene; Titanium Dioxide	1			
Azathioprine Sodium	1		Yes	
Bacitracin Zinc; Hydrocortisone Acetate; Neomycin Sulfate; Polymyxin B Sulfate	1			
Barium Sulfate	1		Yes	
Beclomethasone Dipropionate Monohydrate	1			
Bendroflumethiazide; Nadolol	2			
Benoxinate Hydrochloride; Fluorescein Sodium	1	Yes		
Bentoquatam	1			
Benzylpenicilloyl Polylysine	1			
Beractant	1			
Betaine	1			26%
Betamethasone Acetate; Betamethasone Sodium Phosphate	2			
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline	1			15%
Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride	1			
Bretylium Tosylate	1			
Brinzolamide	1			44%
Bupivacaine Hydrochloride; Epinephrine	1	Yes		
Butabarbital Sodium	1			41%
Butoconazole Nitrate	1			7%
Calcium Chloride; Dextrose; Glutathione Disulfide; Magnesium Chloride; Potassium Chloride; Sodium Bicarbonate; Sodium Chloride; Sodium Phosphate	1			13%
Calcium Chloride; Dextrose; Lactic Acid; Magnesium Chloride; Potassium Chloride; Sodium Bicarbonate; Sodium Chloride	1			
Calcium Chloride; Dextrose; Magnesium Chloride; Sodium Chloride; Sodium Lactate	2			

Calcium Chloride; Dextrose; Magnesium Sulfate; Potassium Chloride; Sodium Bicarbonate; Sodium Chloride; Sodium Phosphate, Dibasic, Heptahydrate	1			
Calcium Chloride; Magnesium Chloride; Potassium Chloride; Sodium Acetate; Sodium Chloride	1			
Calcium Chloride; Magnesium Chloride; Potassium Chloride; Sodium Chloride	2			
Calfactant	1			
Captopril; Hydrochlorothiazide	1			399%
Carbachol	1			
Carboprost Tromethamine	2			
Carglumic Acid	1			
Carteolol Hydrochloride	1			256%
Cetrorelix	1			
Chenodiol	1			25%
Chlorambucil	1		Yes	80%
Chloramphenicol Sodium Succinate	1		Yes	
Chlordiazepoxide Hydrochloride	2			0%
Chlordiazepoxide Hydrochloride; Clidinium Bromide	1			
Chlorothiazide	2			
Chlorpheniramine Maleate	1			
Chlorpheniramine Maleate; Hydrocodone Bitartrate; Pseudoephedrine Hydrochloride	2			
Chlorpheniramine Maleate; Ibuprofen; Phenylephrine Hydrochloride	1			
Chromic Chloride	1			
Cidofovir	2			6%
Ciprofloxacin Hydrochloride; Hydrocortisone	1			8%
Ciprofloxacin; Ciprofloxacin Hydrochloride	2			-1%
Citric Acid; Gluconolactone; Magnesium Carbonate	1			3%
Citric Acid; Urea C-13	1			
Clemastine Fumarate	2			3%
Clocortolone Pivalate	1			
Clomiphene Citrate	1		Yes	28%
Codeine Phosphate; Pseudoephedrine Hydrochloride; Triprolidine Hydrochloride	1			
Codeine Sulfate	2			7%
Colchicine; Probenecid	2			6%
Colestipol Hydrochloride	2			
Colistin Sulfate; Hydrocortisone Acetate; Neomycin Sulfate; Thonzonium Bromide	1			
Copper	1			
Corticorelin Ovine Triflutate	1			
Corticotropin	1			6%
Cortisone Acetate	1			9%
Crotamiton	2			116%
Cupric Chloride	1			

Cyclopentolate Hydrochloride; Phenylephrine Hydrochloride	1			
Cycloserine	1		Yes	309%
Cysteamine Hydrochloride	1			34%
Cysteine Hydrochloride	1			
Dalfopristin; Quinupristin	1			
Danazol	2			33%
Delavirdine Mesylate	1			7%
Desflurane	2			
Desvenlafaxine	1			8%
Dexchlorpheniramine Maleate	2			
Dextromethorphan Hydrobromide; Promethazine Hydrochloride	2			37%
Dextrose; Magnesium Acetate; Potassium Acetate; Sodium Chloride	1			
Dextrose; Magnesium Chloride; Potassium Chloride; Potassium Phosphate, Dibasic; Sodium Acetate	1			
Dextrose; Magnesium Chloride; Potassium Chloride; Potassium Phosphate, Monobasic; Sodium Chloride; Sodium Lactate	1			
Dextrose; Magnesium Chloride; Potassium Chloride; Potassium Phosphate, Monobasic; Sodium Lactate; Sodium Phosphate, Monobasic Anhydrous	1			
Dextrose; Magnesium Chloride; Potassium Chloride; Sodium Acetate; Sodium Chloride; Sodium Gluconate	1			
Diatrizoate Meglumine	1		Yes	
Diatrizoate Meglumine; Diatrizoate Sodium	2			
Diazoxide	1		Yes	11%
Diclofenac Epolamine	1			17%
Dicloxacillin Sodium	2			37%
Diethylpropion Hydrochloride	2			
Dimenhydrinate	1			
Dimercaprol	1		Yes	
Dimethyl Sulfoxide	1			132%
Dinoprostone	2		Yes	
Diroximel Fumarate	1			
Docetaxel	1			
Docosanol	2			
Doxapram Hydrochloride	2			
Doxycycline Calcium	1			92%
Dyclonine Hydrochloride	1			
Echothiophate Iodide	1	Yes		24%
Edetate Calcium Disodium	1		Yes	
Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate	2		Yes	
Eflornithine Hydrochloride	1		Yes	
Enfuvirtide	1			9%
Epinephrine Bitartrate; Lidocaine Hydrochloride	1		Yes	
Epinephrine Bitartrate; Prilocaine Hydrochloride	2			
Epinephrine; Lidocaine Hydrochloride	2	Yes		25%

Eprosartan Mesylate	1	Yes		19%
Ergoloid Mesylates	1			21%
Ergotamine Tartrate	1			
Erythromycin Lactobionate	1	Yes		722%
Erythromycin Stearate	1			78%
Estradiol Acetate	1			26%
Estradiol Cypionate	1			26%
Estradiol Valerate	2			
Estradiol; Levonorgestrel	1			11%
Estradiol; Norgestimate	1			10%
Estramustine Phosphate Sodium	1			20%
Estrogens, Conjugated	1			24%
Estrogens, Conjugated; Medroxyprogesterone Acetate	1			
Estrogens, Esterified	1			31%
Estropipate	2			26%
Ethanolamine Oleate	1			
Ethinyl Estradiol; Etonogestrel	1			15%
Ethinyl Estradiol; Norelgestromin	1			10%
Ethionamide	1		Yes	
Ethotoin	1			29%
Etidronate Disodium	1			2%
Etoposide Phosphate	1			
Fenoprofen Calcium	2			
Ferric Hexacyanoferrate(Ii)	1			
Flavoxate Hydrochloride	2			2%
Floxuridine	2			
Fluocinolone Acetonide; Neomycin Sulfate	1			65%
Fluorescein Sodium	2	Yes		
Fluorometholone	1			
Fluorometholone Acetate	1			10%
Fluoxymesterone	1			6%
Flurazepam Hydrochloride	1	Yes		54%
Flurbiprofen	2			35%
Flurbiprofen Sodium	2			-1%
Flutamide	2			10%
Foscarnet Sodium	1			
Fosfomycin Tromethamine	1		Yes	10%
Gadobenate Dimeglumine	1			
Gadodiamide	1			
Gadoteridol	1			
Gallium Citrate Ga-67	2			
Ganciclovir	1			17%
Ganirelix Acetate	2			
Gemifloxacin Mesylate	2	Yes		
Gentamicin Sulfate; Prednisolone Acetate	1			109%

Glucagon Hydrochloride	2			19%
Guanabenz Acetate	1			
Guanidine Hydrochloride	1			
Halcinonide	2			96%
Hexachlorophene	1			
Hyaluronidase	2			
Hydralazine Hydrochloride; Hydrochlorothiazide	1			
Hydrochlorothiazide; Methyldopa	1			32%
Hydrochlorothiazide; Metoprolol Succinate	1			12%
Hydrochlorothiazide; Propranolol Hydrochloride	1			6%
Hydrocortisone Acetate	2			
Hydrocortisone Acetate; Neomycin Sulfate; Polymyxin B Sulfate	1			9%
Hydrocortisone Acetate; Pramoxine Hydrochloride	2			
Hydrocortisone Acetate; Urea	1			
Hydrocortisone Probutate	1			25%
Hydrocortisone Sodium Succinate	1		Yes	94%
Hydroxocobalamin	2		Yes	
Hydroxyamphetamine Hydrobromide; Tropicamide	1			
Hydroxypropyl Cellulose	1			9%
Ibuprofen Sodium	2			
Ibuprofen; Oxycodone Hydrochloride	2			0%
Ibuprofen; Phenylephrine Hydrochloride	2			
Ibutilide Fumarate	2			
Icatibant Acetate	2			10%
Icodextrin	1			
Iloprost	1			
Imiglucerase	1			0%
Imipramine Pamoate	2			18%
Inamrinone Lactate	1			
Indium In-111 Chloride	1			
Indium In-111 Oxyquinoline	1			
Indium In-111 Pentetate Disodium	1			
Indium In-111 Pentetreotide Kit	1			
Insulin Glargine	1			
Insulin Recombinant Human	1			
Iobenguane Sulfate I-123	1			
Iodine Povacrylex; Isopropyl Alcohol	1			
Ioflupane I-123	1			
Iohexol	2		Yes	
Iopamidol	2			
Iopromide	1			
Iothalamate Meglumine	1			
Iothalamate Sodium I-125	1			
Ioversol	1			
Iron Dextran	1			

Iron Sucrose	1			
Isocarboxazid	1	Yes		-4%
Isoniazid; Pyrazinamide; Rifampin	1		Yes	
Isoniazid; Rifampin	1		Yes	
Isradipine	2			11%
Lamivudine; Tenofovir Disoproxil Fumarate	2			
Leuprolide Acetate; Norethindrone Acetate	1			
Levoleucovorin	1			
Levonordefrin; Mepivacaine Hydrochloride	1			
Levorphanol Tartrate	2			38%
Lincomycin Hydrochloride	2			30%
Lindane	2			3%
Lithium Citrate	2			41%
Lodoxamide Tromethamine	1			9%
Lomustine	1			71%
Loteprednol Etabonate; Tobramycin	1			15%
Magnesium Chloride; Potassium Chloride; Potassium Phosphate, Monobasic; Sodium Acetate; Sodium Chloride; Sodium Gluconate; Sodium Phosphate, Dibasic, Heptahydrate	1			
Magnesium Sulfate	1			
Magnesium Sulfate; Potassium Chloride; Potassium Phosphate, Monobasic; Sodium Chloride; Sodium Phosphate	1			
Malathion	1			5%
Manganese Chloride	1			
Mannitol; Sorbitol	1			
Maprotiline Hydrochloride	1			21%
Mebendazole	1		Yes	0%
Mecamylamine Hydrochloride	1			10%
Mecasermin Recombinant	1			
Meclofenamate Sodium	1			-6%
Mefloquine Hydrochloride	2		Yes	16%
Melphalan	2		Yes	9%
Menotropins (Fsh;Lh)	1			
Metaproterenol Sulfate	1			2%
Methacholine Chloride	1			
Methohexital Sodium	1			
Methscopolamine Bromide	1			3%
Methsuximide	1			14%
Methyclothiazide	1			15%
Methyltestosterone	2			36%
Metyrapone	1			
Metyrosine	1			155%
Mexiletine Hydrochloride	1			6%
Miglitol	2			
Miglustat	2			14%
Mitotane	1			4%

Molindone Hydrochloride	1			-7%
Mupirocin Calcium	1	Yes	Yes	
Nabilone	1			
Nafarelin Acetate	1			18%
Nalbuphine Hydrochloride	2	Yes		15%
Natamycin	1		Yes	20%
Nedocromil Sodium	2			12%
Nefazodone Hydrochloride	1			2%
Nelarabine	1	Yes		
Nelfinavir Mesylate	1			9%
Neomycin Sulfate; Polymyxin B Sulfate	2			47%
Nilutamide	2			
Nisoldipine	2			
Nitazoxanide	1			66%
Nonoxynol-9	1			
Olanzapine Pamoate	1			11%
Olive Oil; Soybean Oil	1			
Olsalazine Sodium	1			12%
Orlistat	2			10%
Oxandrolone	2			5%
Oxazepam	2			19%
Oxiconazole Nitrate	2			
Oxymetholone	1			19%
Pancuronium Bromide	2			
Paromomycin Sulfate	2		Yes	50%
Pegaptanib Sodium	1			
Pegvisomant	1			
Penicillin G Benzathine	1		Yes	26%
Penicillin G Benzathine; Penicillin G Procaine	1			24%
Penicillin G Procaine	1		Yes	
Penicillin G Sodium	1		Yes	-2%
Pentamidine Isethionate	2		Yes	
Pentetate Calcium Trisodium	1			
Pentetate Zinc Trisodium	1			
Pentosan Polysulfate Sodium	1			12%
Pentostatin	2			
Phenelzine Sulfate	2			
Pimozide	1			
Piperacillin Sodium	1			
Podofilox	2			
Poractant Alfa	1			
Porfimer Sodium	1			
Potassium Acetate	2	Yes		92%
Potassium Phosphate, Dibasic; Potassium Phosphate, Monobasic	1			
Pralidoxime Chloride	2			

Pramlintide Acetate	1			
Praziquantel	2		Yes	335%
Prednisolone Acetate	2			
Prednisolone Acetate; Sulfacetamide Sodium	1			
Prednisolone Sodium Phosphate; Sulfacetamide Sodium	1			
Prilocaine Hydrochloride	1			
Procarbazine Hydrochloride	1		Yes	23%
Prochlorperazine	2			
Propantheline Bromide	1			95%
Propylthiouracil	2		Yes	33%
Protamine Sulfate	1		Yes	
Purified Water	1			
Pyrazinamide	2		Yes	55%
Pyridoxine Hydrochloride	1		Yes	
Pyrimethamine	1		Yes	0%
Quinidine Gluconate	1			70%
Quinidine Sulfate	2			17%
Ranitidine	1			
Rasagiline	1			
Remifentanil Hydrochloride	2	Yes		
Rifabutin	2		Yes	3%
Rifapentine	1		Yes	1%
Rimantadine Hydrochloride	2			1%
Rubidium Chloride Rb-82	2			
Salmeterol Xinafoate	1			25%
Samarium Sm-153 Lexidronam Pentasodium	1			
Saquinavir Mesylate	1			10%
Secobarbital Sodium	1			36%
Secretin Synthetic Human	1			
Selegiline	1			43%
Selenium Sulfide	2		Yes	15%
Sertaconazole Nitrate	1			69%
Sodium Acetate	2	Yes		176%
Sodium Ferric Gluconate Complex	2			
Sodium Iodide I-123	2			
Sodium Iodide I-131	1			
Sodium Lactate	1			
Sodium Phosphate, Dibasic, Heptahydrate; Sodium Phosphate, Monobasic, Anhydrous	1			
Sodium Tetradecyl Sulfate	1			
Somatropin Recombinant	2			
Sorbitol	2			
Soybean Oil	2			
Streptomycin Sulfate	1		Yes	168%
Streptozocin	1			

Strontium Chloride Sr-89	1			
Succimer	1		Yes	17%
Sucralfate	2			
Sulconazole Nitrate	1			58%
Sulfadiazine	1		Yes	9%
Sulfanilamide	1			9%
Technetium Tc-99m Albumin Aggregated Kit	1			
Technetium Tc-99m Bicisate Kit	1			
Technetium Tc-99m Exametazime Kit	2			
Technetium Tc-99m Mebrofenin Kit	2			
Technetium Tc-99m Medronate	1			
Technetium Tc-99m Medronate Kit	1			
Technetium Tc-99m Mertiatide Kit	2			
Technetium Tc-99m Oxidronate Kit	1			
Technetium Tc-99m Pentetate Kit	1			
Technetium Tc-99m Pyrophosphate Kit	2			
Technetium Tc-99m Red Blood Cell Kit	1			
Technetium Tc-99m Sulfur Colloid Kit	1			
Tegaserod Maleate	1			
Terbinafine	1		Yes	
Tetracaine Hydrochloride	2		Yes	45%
Tetrahydrozoline Hydrochloride	1			
Thioguanine	1			66%
Thioridazine Hydrochloride	1	Yes		33%
Thiothixene	2	Yes		69%
Thyrotropin Alfa	1			
Ticlopidine Hydrochloride	2			
Timolol	2			27%
Tioconazole	2			
Tolazamide	1			23%
Tolbutamide	1			18%
Tolmetin Sodium	2			43%
Toremifene Citrate	2			18%
Trandolapril; Verapamil Hydrochloride	2			
Triamcinolone Hexacetonide	1			
Triamterene	2			105%
Trifluoperazine Hydrochloride	2	Yes		1%
Trimethoprim Hydrochloride	1			
Trimipramine Maleate	2			
Trypan Blue	1			
Urea, C-14	1			
Valrubicin	2			
Velaglucerase Alfa	1			4%
Verteporfin	1			
Vinblastine Sulfate	2	Yes	Yes	

Vitamin A Palmitate	1			
Xenon Xe-133	2			
Zafirlukast	2			
Zanamivir	1			0%
Zinc Acetate	1			
Zinc Chloride	1			
Zinc Sulfate	1		Yes	
Ziprasidone Mesylate	1			28%

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112 "Essential Medicines Selection," World Health Organization, https://www.who.int/selection_medicines/committees/en/; "Essential Medicines and Health Products," World Health Organization, https://www.who.int/medicines/services/essmedicines_def/en/.

113 Essential medicines and health products information portal: a World Health Organization resource. Geneva: World Health Organization, 2016 (http://apps.who.int/medicinedocs/en/d/Js4875e/5.2.html#Js4875e.5.2).

114 Because staff defined a drug, for the purposes of this analysis, as an active pharmaceutical ingredient, the 427 drugs identified by staff as having one or two manufacturers are not delineated by dosage form, though different forms or strengths may exist. Thus, when staff identified one of the 427 drugs in the Medicare Part D Spending database, but that drug was included in multiple dosage forms in the database, it was excluded for the purposes of this analysis.