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Generic Drug Shortages and How a Race to the Bottom in Price has Upended 30 years of Hatch-Waxman

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The Coalition for a Prosperous America

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Executive Summary

While COVID-19 has brought one public health emergency to the forefront of American policy discussions, a second healthcare crisis impacting nearly every American has continued to worsen: America's dependence on foreign manufacturers — particularly China and India — for essential, life-saving generic medicines. This reliance exacerbated the impacts of COVID-19, as American hospitals faced drug shortages, while Chinese pharmaceutical factories shut down and India restricted exports of critical medications.[1] Even before the pandemic, drug shortages were an all-too-common occurrence in American hospitals, with over half of healthcare workers claiming that drug shortages were a daily struggle.[2] Nearly half of all generic pharmaceuticals on the Food and Drug Administration's (FDA) newly created essential medicines list appear in some form on the FDA's drug shortage list. [3]

Reliance on foreign manufacturers, particularly those in China and India where manufacturing quality and oversight standards are poor, has proven to be a major factor in causing shortages. The FDA itself notes that two-thirds of drug shortages are caused by quality issues, and China and India have established themselves as world leaders when it comes to evading FDA regulations and getting deadly, ineffective drugs to American patients.

When manufacturers in these countries detain FDA inspectors, delete or fabricate data, and sell medications contaminated with rocket fuel or metallic particles,[4] they leave the FDA between a rock and a hard place: Restricting imports from these manufacturers will likely lead to a drug shortage; failing to do so will embolden the manufacturers to continue selling substandard, unsafe products that can potentially kill American patients.

One of the primary reasons that the FDA is left facing such impossible decisions in these cases is because of a lack of competition for the manufacturing of these essential generics. As this report shows, foreign manufacturers have a long history of slashing prices or acquiring their American competitors to gain a monopoly over the production of one drug, only to gouge customers by raising prices as much as 2,000 percent once they eliminate their competition.[5]

The lack of competition defined by this slash-and-gouge pattern is driven by three key factors:

1. Strong government support for manufacturers in these countries, including a wide range of subsidies, grant payments, and procurement supports for their manufacturers;
2. A lack of support for domestic manufacturers in the U.S., whether through trade policy, federal procurement, reimbursements, or direct payments; and
3. A lack of regulatory oversight in these developing countries, which allows companies to cut as much as 25 percent off their production costs.[6]

As a result of these factors, America's generic pharmaceutical manufacturing industry is all but gutted, while U.S. reliance on China and India continues to grow for essential, lifesaving medicines. The unfortunate reality is that the hollowing out of America's public health industrial base is largely a result of the Hatch-Waxman Act, a 1984 law designed specifically to create more competition in the generic drug market. While that law rolled back some regulatory barriers in order to make it easier for new companies to enter the market, the law's original intent was never to create a race to the bottom that forced companies to cut corners in order to manufacture drugs for less than the price of a cup of coffee in order to remain competitive.

In order to bring back competition, strengthen U.S. domestic supply chains, and resolve price gouging and rampant quality control issues for generic drugs made by foreign manufacturers, America must stop this dangerous race to the bottom. This can be accomplished with a combination of three policies that the federal government can undertake to support American manufacturers, and accomplish the original goals of the 1984 Hatch-Waxman Act.

First, the U.S. government must create a reliable source of demand for domestic manufacturers. The Centers for Medicare and Medicaid Services (CMS) spent nearly $300 billion on drug expenditures in 2019,[7] making it a larger market than any other country in the world.[8] Generic drugs account for 20 percent of this total drug spending.[9] Using this buying power to provide a small incentive — even a 10 percent price premium — for American made generic medicines would have a dramatic impact on the market and strengthen American (and global) pharmaceutical supply chains.

Second, the U.S. government must use trade remedies to defend domestic manufacturers from predatory policies by foreign governments and manufacturers. American companies do not receive the same government support that their foreign counterparts do to enable them to withstand extended periods of losses. As a result, they are vulnerable to foreign companies selling their products below cost in order to corner the market, only to immediately raise their rates by several orders of magnitude. The U.S. government has a wide range of trade remedies available to stop this predatory behavior, and fully utilizing these authorities to combat price gouging would significantly reduce overall healthcare costs while supporting resilient domestic supply chains. In other words, successfully utilizing trade remedies can help combat shortages of critical and lifesaving medicines.

Finally, because America's pharmaceutical industrial base has been so thoroughly depleted, there needs to be some direct financial support to re-establish America as a global pharmaceutical manufacturing leader. While the Biden Administration's American Rescue Plan provides some initial funding to launch these efforts, far more support will be needed over the coming years to reinvigorate America's public health industrial base, whether it be through tax incentives or direct government funding.

In addition to these three policies that, if implemented jointly, would fundamentally reshape the economic incentives for companies to move their drug manufacturing overseas in a dangerous race to the bottom, this paper also outlines a few additional policies that could help reshore this critical industry. These include strengthening the regulatory oversight on foreign-made drugs, providing a "first to file" preference for American manufacturers which would allow them to become the first entrants in new generic markets, and providing more transparency about quality issues and country of origin information to consumers.

If implemented together, these policies would represent the most significant change in the American generic manufacturing market since the 1980s, and would finally accomplish the Hatch-Waxman Act's goal of creating competition for generic pharmaceuticals. Accomplishing this would leave America far more prepared for a future pandemic, and ensure that essential medicines are safe, affordable, and readily accessible for all Americans.

Introduction

Over the past 20 years, the U.S. generic drug industry has been hollowed out. Today, the U.S. struggles to manufacture even the most basic essential medicines needed by hospital on a daily basis. This crisis has been facilitated by large generic drug manufacturers moving their operations overseas. In a bid to maximize shareholder return, corporate leaders decided to gamble and move manufacturing to developing nations with limited infrastructure and less regulatory oversight.

Today, the U.S. is reliant on imports for at least two-thirds of its generic medicines, and nearly 90 percent of generic Active Pharmaceutical Ingredient (API) facilities are overseas.[10] The majority of those supply chains run through China and, to a lesser extent, India, leaving Americans in a vulnerable position.[11]

As the U.S. generic drug industry offshored, shortages and price increases in generic medicine have been a recurring theme over the last decade. This paper will examine the history of generic drugs in America and how a race to the bottom in pricing has led to shortages and price gouging. We will examine what can be done to address this national crisis— and how a three-step approach could ensure greater stability in access and affordability for generic drugs.

History of the Generic Drug Industry in America

Before Hatch-Waxman

While generics comprise about 90 percent of the market for prescriptions dispensed in the U.S. today, that has not always been the case historically.[12] For much of the 20th century, the FDA only regulated drugs for safety, and made no assessment on whether a drug was actually effective.[13] In 1962, the Federal Foods, Drug, and Cosmetic Act was amended to include a proof of efficacy requirement for new drug approval. While this was welcomed and supported by the research-based "branded" industry, it meant that generic manufacturers were no longer able to gain FDA approval based on existing medical or scientific literature showing that chemical was safe. Instead, they typically needed to conduct clinical trials to gain regulatory approval. [14]

While this may sound reasonable in theory, in practice it had the effect of preventing generics from entering the market altogether. In fact, estimates provided in Congressional testimony found that post-1962, less than ten percent of off-patent drugs had a generic manufacturer because generic companies were unwilling to spend the time and money doing the clinical trials needed to get to market.[15] As a result, generics accounted for less than 20 percent of total drug consumption in the U.S. prior to Hatch-Waxman.[16] After a drug went off-patent, branded manufacturers only faced competition from their generic counterparts at most 35 percent of the time. Even when they did, generic manufacturers were not allowed to begin conducting any of the research or work necessary to apply for FDA approval until after the patent expired.[17] As a result, it typically took three to five years after the patent had expired for the generic manufacturer to enter the market, and it was extremely rare to have more than one generic manufacturer for any given product.[18] The lack of competition that resulted often gave branded manufacturers a monopoly over their products for far longer than was needed to incentivize research, and led to high prices for many of the medicines needed to save lives.

Hatch-Waxman (1984)

The Hatch-Waxman Act, formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, was designed as an effort to balance the need to incentivize drug research and development with a desire to increase competition and make drug prices more affordable. While the plan can be traced back to the Carter Administration's initial efforts in 1978, Hatch-Waxman ultimately represented a major bipartisan initiative between a Democratic Congress and the Reagan Administration, which supported the proposal.[19] The new legislation made several key changes that initially helped foster competition in the drug manufacturing space and drove down the cost of essential medicines.

First and foremost, Hatch-Waxman created a separate process for approving generic versions of drugs that had previously been approved. For new drugs, innovators were still required to file a new drug application (NDA), which, as the agency explains, is "supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed

and packaged."[20] However, once a drug goes off-patent, manufacturers of generic equivalents can gain approval by filing an abbreviated new drug application (ANDA), which allows them to rely on the safety and efficacy studies conducted by the original developer of the drug.[21] This change removed by far the most significant barrier to entry for generic manufacturers after drugs went off-patent, and helped spur competition in the pharmaceutical manufacturing space.

While allowing the patent-holders safety and efficacy data to be used by their eventual competitors was a major victory for the generic manufacturers, Hatch-Waxman did give the drug innovators some significant protections in exchange. First, it offered branded manufacturers a 5-year exclusivity period during which generic competitors cannot submit FDA applications for generic versions of their products. In addition, Hatch-Waxman also restored some of the patent term that had previously been "wasted" during the period after the patent was granted and before the company gained FDA approval, and it allowed for an additional 3-year exclusivity period for improved versions of the branded drugs that required additional clinical studies.[22]

In addition to creating a streamlined regulatory approval process for generic manufacturers, Hatch-Waxman also created a number of other changes to support generic drug manufacturing while protecting drug innovation. It allowed the generic manufacturers to begin conducting the work necessary to file for an ANDA while the original drug was still under patent, eliminating the unintended de-facto exclusivity period after a patent expired before a generic manufacturer could gain approval for a bioequivalent.[23] It also created a 180-day exclusivity period, wherein the first generic manufacturer to file a substantially complete ANDA after the branded drug's exclusivity period (commonly referred to as the "first to file") is granted 180 days before any additional generic competitors can enter the market.

Effects of Hatch-Waxman

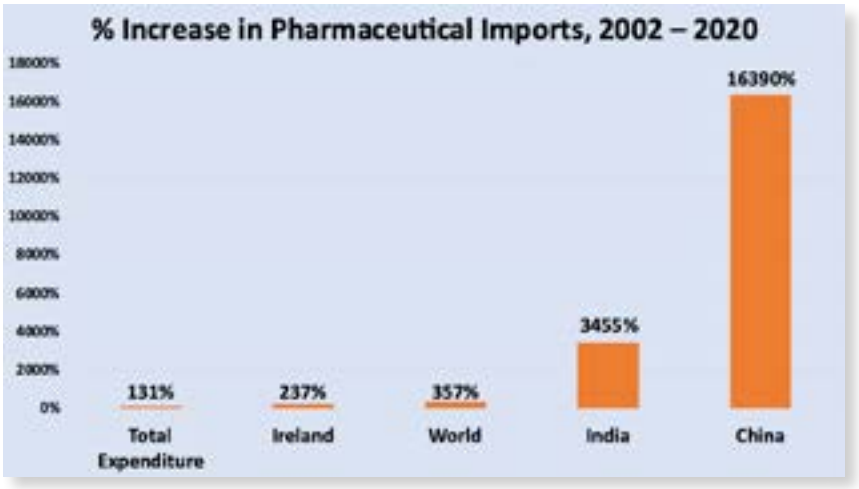
Initially, Hatch-Waxman appeared to be performing remarkably well at achieving its dual goals of supporting research and innovation and increasing drug manufacturing competition in order to provide affordable drugs to patients. Depending on the estimate used, annual spending on drug research and development increased from twofold to sixfold between the signing of Hatch-Waxman and the turn of the century, significantly exceeding its 1970s growth rate, and the number of drug targets increased sixfold over this period. [24] Meanwhile, generic manufacturing surged, ultimately 90 percent of the total drug market, compared to under 20 percent prior to Hatch-Waxman. [25] The share of drugs that had a generic version available soared from less than 35 percent to over 80 percent. [26]

Unfortunately, Hatch-Waxman failed to anticipate the ultimate race to the bottom in pricing that came as a result of the offshoring of the U.S. generic drug manufacturing base.

As Figure One demonstrates below, since the turn of the century in particular, America has become increasingly reliant on foreign providers for their pharmaceutical products. For example, while America's total expenditure on pharmaceuticals has slightly more than doubled, global imports of these products have increased to 4.5x their 2002 levels.

For India and China, where poor quality controls, environmental degradation, and cheap labor combine to allow prescription drugs to be produced for the cost of a pack of gum, the increase in pharmaceutical imports has been even more drastic. Since 2002, imports from India have increased 35-fold, while the floodgates have opened to allow imports from China to rise to an astounding 165x their 2002 levels.

Figure One: Increase in American Pharmaceutical Import Reliance



Sources: Centers for Medicare and Medicaid Services [27], World Bank[28]

This race to the bottom has been exacerbated by the role of middlemen in the pharmaceutical industry. Group Purchasing Organizations (GPOs) and Pharmacy Benefit Managers (PBMs) — also known as middlemen — all have the common goal of maximizing margins and short-term profit. While the GPOs and PBMs' efforts to maximize return at the expense of any other considerations have created their own set of quality control and safety issues,[29] their efforts to secure the lowest possible price point for drugs have also provided implicit support for overseas manufacturers that can cut corners on environmental and worker standards to manufacture drugs below the market rate. The result of America's dependence on India and China is extreme volatility — both in price and product availability. Three reoccurring patterns of events have emerged as a result of this dependence:

1. The foreign manufacturer will flood the U.S. market with product priced below the market rate — causing other competition to leave the marketplace — leaving just one manufacture for the product in question;
2. After eliminating all competition — the foreign manufacturer raises the price above the average price prior to eliminating all other manufacturers;
3. This sole source dependence is now more vulnerable to supply chain shortages due to quality control violations or supply chain disruptions, jeopardizing patient health and safety.

In the reoccurring pattern of events described above, Hatch-Waxman is effectively evaded. As a result, the goals of increased competition are eliminated. Offshoring and a race to the bottom in price has taken the generic drug industry back in time — prior to 1984. Prior to 1984, there was a lack of competition for generics because regulatory barriers made it too difficult for generic manufacturers to enter the market. Hatch-Waxman solved that problem, but it never intended to allow manufacturers to sell lifesaving prescriptions for less than the price of a cup of coffee. Pricing below a cup of coffee is the byproduct of offshoring to nations with cheap labor and limited regulatory oversight.

In large part, the problems associated with the pattern of events described above are the direct results of generic pharmaceutical manufacturing moving overseas. The reliance on imports from foreign countries is a major contributor to the fragility of America's pharmaceutical supply chains. The next three sections examine how the above-mentioned pattern of events are assisted and implemented.

Foreign Subsidies

First and foremost, American generic pharmaceutical manufacturers have struggled to compete with their foreign counterparts because they do not receive anywhere near the same level of government support. For example, China's "Made in China 2025" plan openly states Beijing's goal of having their top 20 national champion manufacturers of essential drugs control at least 80 percent of the global market for those goods.[30] As part of their strategy to accomplish this, China imposes 5.5 percent to 6.5 percent tariffs on most drug imports, in addition to a 17 percent value-added tax on all imported goods, which works similarly to an additional tariff. By contrast, the U.S. imposes no cost on imports. One only has to look up our pharmaceutical tariffs — Chapter 30 of the Harmonized Tariff Schedule of the United States — to see that we have eliminated all incentive to produce here. Virtually every tariff subheading is listed as "free." Thus, if a company were looking to manufacture a generic medicine for sale into both of the world's largest pharmaceutical markets, in order for them to choose to manufacture in the U.S. over China, their costs would not only have to be lower in America than China, but also low enough for them to overcome the market entry costs in China. That inherently puts American manufacturers at a significant disadvantage. In addition to these market entry costs, the Chinese government also pours billions each year into supporting its pharmaceutical industry's development.

China is certainly not alone in providing support to its domestic pharmaceutical manufacturers. India, for example, offers funding to its pharmaceutical manufacturers through the production linked incentive (PLI) scheme.[31] This scheme offers to provide companies with grants worth up to 10 percent of their additional incremental sales of targeted pharmaceutical goods for a 6-year span.[32] Subsidizing these increases in output (rather than profit) is one of the many factors that make it possible for foreign manufacturers to temporarily sell below their production costs as they attempt to gain a monopoly on the market for a generic drug. In Europe, EU member states also offer a wide range of incentives to support domestic manufacturing of pharmaceuticals. For example, Belgium pays a 10 percent price premium to domestic pharmaceutical manufacturers.[33]

It is not hard to see the impact of some U.S. federal support for pharmaceutical manufacturers. While the U.S. currently does very little to match these foreign subsidies, the U.S. government has not always

been so hesitant to offer incentives that have supported domestic manufacturing of pharmaceuticals. For example, from 1976 until 1996, Section 936 of the U.S. tax code granted U.S. corporations a tax exemption on income originating in Puerto Rico.[34] Because nearly all of a pharmaceutical manufacturer's income nominally comes from the manufacture of their drugs (rather than the research), and the actual manufacturing comprised a relatively small portion of the total cost, this worked as a strong incentive for pharmaceutical manufacturers in particular to move their production to Puerto Rico. The island in turn became one of the top pharmaceutical manufacturing hubs in the world, with drug production accounting for over half of Puerto Rico's GDP at its peak. As Section 936 was phased out over a ten-year period from 1996 to 2006, the pharmaceutical industry truly began its march overseas. In 2005, Puerto Rico entered a decade long recession, while manufacturing fell to account for only one-third of the island's GDP. While Section 936 may be long gone, it is clear from this experience that some government support — whether it be through tax incentives, grant funding, or government procurement — to compete with the incentives that pharmaceutical manufacturers receive overseas can go a long way in reshoring America's generic drug manufacturing base.

Foreign Regulatory Loopholes

An additional factor of the generic pharmaceutical manufacturing industry's decision to move production offshore is the role of regulatory policy. The FDA imposes a wide range of regulations on pharmaceutical manufacturers which, by and large, do an excellent job of protecting patient health and safety. For drugs made in the U.S., where the FDA enforces these regulations through regular on-site inspections, these policies give hospitals and patients the confidence that the drugs they are using are safe, not tainted with dangerous carcinogens, and contain the appropriate amount of active ingredients as indicated by the label.

The problem that arises is not the regulations themselves, but the FDA's enforcement of them — including lack of enforcement for foreign drug manufacturers, particularly in China and India. For factories in the U.S., the FDA is allowed to inspect the facilities with no advanced notice, and they often send teams of multiple inspectors on multi-day trips to assess every minutia of a company's manufacturing operations multiple times per year. To ensure they pass FDA inspections, American manufacturers typically tend to comply with the "good manufacturing practices" (GMP) designed to ensure product safety, and even so, they often get flagged for minor infractions that pose no real threat to consumer safety. [35]

Conversely, overseas manufacturers tend to be able to evade the bulk of the FDA's oversight. As FDA inspectors abroad have no statutory authority in foreign countries, their ability to inspect facilities is restricted to the level of access that foreign countries and companies are willing to provide. In China, for example, FDA inspectors typically must provide several weeks or months' notice before inspections, during which time the manufacturer typically attempts to make changes to appear GMP-compliant. Despite this, FDA inspections of overseas manufacturers still often read like pages of Upton Sinclair's The Jungle Book, with rodents running through factory floors and clean room facilities that lack clean running water.[36]

Overseas manufacturers' willingness to cut corners on safety and quality control is worsened by the fact that, if their products do ultimately kill Americans or cause other health issues, they are not liable for any of the damages caused.

In fact, Chinese manufacturers have openly admitted that their lack of liability contributes to their decision to ignore quality issues in the name of pursuing the lowest possible price.

As a U.S. lawyer with first-hand knowledge of liability concerns with Chinese manufacturer notes, "we are not liable for consumer protection. If we were liable, the product would be very, very expensive. If you want a cheap product, the price is that we do not take any liability for consequential damages." [37]

When the pandemic hit, China went even further to stymie American regulators, prompting one former FDA official to write that China effectively declared war on the FDA, and won, in 2021. [38] A key element of that effort was to require all entrants to China to be vaccinated with its proprietary vaccines — such as the one developed by Sinovac that has shown to be just above 50 percent effective against COVID-19 — despite the fact that the U.S. FDA has not received a submission for any vaccine from China, making it nearly impossible for American regulators to comply with this requirement.[39] As a result, the FDA has developed an extensive backlog of inspections in China, and has substituted many in-person inspections for video tours, where it is even easier for manufacturers to hide their compliance issues.[40] As an example of the extent to which the FDA's efforts to regulate overseas manufacturers have been stymied, consider that, despite American manufacturers generally operating at the highest global manufacturing standards and producing a relatively small share of pharmaceuticals, in the first half of 2021, the FDA's Center for Drug Evaluation and Research (CDER) issued only two negative observation reports to Chinese manufacturers, and four to the rest of the world, in comparison to 66 for American manufacturers.[41] Incredibly, as of 2016, one in three foreign drug establishments had no FDA inspection history.[42]

The issue with these FDA health and safety regulations is by no means the policies themselves. In fact, these regulations tend to receive broad support from the American manufacturers affected by them, and the drug industry as a whole. However, the FDA's uneven enforcement of these laws has essentially created a multi-billion-dollar regulatory loophole for overseas manufacturers that simultaneously undermines the FDA's efforts to protect patients and incentivizes companies to shift their production beyond the reach of the FDA's inspectors, thereby weakening pharmaceutical supply chains and exposing American patients to potentially harmful and substandard medicines.

In addition to the FDA's enforcement issues, manufacturers in countries like China and India tend to be able to manufacture for lower costs than their American counterparts by flouting many of the processes designed to mitigate environmental damage. For example, in India, pharmaceutical waste has led to antibiotic concentrations 1,000 times higher in the Musi River than those in developed countries, contributing to antimicrobial resistance and the death of hundreds of thousands of fish[43]. In China, over half of people above the age of 35 in Xinchang county suffer from liver disease as a result of pollution from the region's pharmaceutical industry.[44]

In this sense, the offshoring of America's pharmaceutical industry is not only a health security issue, but it also creates a slew of other issues as well: It has created a human rights crisis among people living near foreign pharmaceutical manufacturing facilities, caused catastrophic environmental degradation, and is potentially creating a future pandemic by contributing to antimicrobial resistance, making the need to reshore the U.S. pharmaceutical supply chain even more urgent.

Production Costs

In addition to the role of government policy, there are structural issues that contribute to making pharmaceutical manufacturing in America more expensive than in developing countries. The most significant of these is the higher labor costs that manufacturers face in the U.S. With average salaries for drug manufacturing workers generally being in the range of $46,000 per worker in the U.S.[45], compared to $5,000 - $6,000 per year in India[46], manufacturers could cut their labor costs by 80 percent or more by manufacturing overseas.

Even so, labor is only one of the many costs associated with creating pharmaceutical products, and America's pharmaceutical industry is not alone in offering high wage rates. Europe has similar issues, as do other American manufacturing sectors that have managed to grow despite foreign competition. America does also provide some significant advantages over its less developed counterparts, including a relatively higher skilled workforce that can support more automation and improved manufacturing processes, proximity to the end consumers, a more stable investment climate, and less political risk. While these factors may not fully offset the increased manufacturing costs that result from wage discrepancies, they do help ensure America remains competitive as a potential manufacturing base for generic pharmaceuticals.

Labor costs alone clearly cannot fully explain the offshoring of America's pharmaceutical industry, as manufacturing has continued to shift overseas to China and India over the past decade despite the relative wage gap closing between these countries during this timeframe.[47] While the importance of these labor costs should not be understated, it by no means is a death knell for American pharmaceutical manufacturing.

Examples of Foreign Manufacturers Undercutting Price

Above we discussed the reoccurring pattern that leads to volatility in price and availability in the generic drug industry. We also examined outside contributing factors that have exacerbated the current state of play for the U.S. generic manufacturing industry. Below we examine specific products that have followed the slash-and-gouge pattern and underscore the real impact these patterns are having on access and affordability.

Mitomycin 8x More Expensive After Competition Eliminated

Our first case study highlights the impact that foreign competition had on the market for Mitomycin from 2010 to 2017. As a critical care drug used to treat several different types of cancer, hospitals could not (and should not) reasonably refuse to pay whatever the market demanded for access to these medicines. At the beginning of the decade, that was not a problem: U.S. producers controlled some 65 percent of the market for Mitomycin manufacturing and were selling doses for about $65 a piece. However, the American manufacturer was still held in check by foreign suppliers offering to sell the drug for a slightly higher price, and who were able to maintain control over the remaining third of the market. In many ways, this equilibrium that existed in 2010 reflected what the true goal of the 1984 Hatch-Waxman legislation was: To create competition in the generic manufacturing market to keep drug prices in control and maintain access to essential medicines.

Unfortunately, this balance did not last. In 2011, Accord Healthcare, an Indian manufacturer, began to slash its prices to gain control of the industry. That year, Accord was able to capture two-thirds of the market, and by 2012, it had successfully gained monopoly control over the market. The American manufacturer, Bedford Labs, was forced to cut production down to 3 percent of its 2010 levels, while Accord accounted for 98 percent of all Mitomycin sales.

By 2014, Bedford had exited the market entirely, and Accord was able to begin raising its prices. From 2013 to 2014, Accord raised its price from $97 to $170, or $73 per vial — a price increase greater than the total price that Bedford had been selling for in 2010.

Figure Two:
Price Gouging in the Mitomycin Market[48]

Not only does this example highlight how monopolistic practices by foreign manufacturers can drive American manufacturers out of the market for essential generic medicines, since American companies are unable to withstand extended periods of selling below cost, but it also highlights the practical costs that customers face as a result of losing an American presence in the market. For example, even if costs of Mitomycin had increased from 2010-2017 at the same rate as CPI inflation, by 2017 each vial would have cost less than one-sixth of what was being charged in the healthcare system. For this one drug alone, added costs to the healthcare system were over $50 million per year, and that final cost to consumers would likely be several times higher after GPO's and other middlemen used the higher prices to line their own pockets.

In 2015, Accord began gouging hospital systems even further, more than doubling prices from $170 to a whopping $393 per vial. By 2017, prices reached $540, or more than 8x what they had been when American manufacturers were in the market.

However, this does provide an excellent example of how a trade remedy or domestic procurement preference could have both supported American health security, by maintaining a manufacturing presence in the U.S., and helped reduce costs to the healthcare system as a whole. Consider, for example, that the Indian manufacturer did not have an average sale price that was more than 10 percent lower than Bedford for any individual product line (i.e., 5mg vials, vs. 20mg or 40mg) until 2013. Even then, the largest price difference, which was on 20mg vials, was only 13 percent. That 13 percent figure is effectively the upper bound of the scale of trade remedy or domestic procurement preference that would have been needed to keep Bedford in the market and maintain competition for generic drugs. In reality, a much smaller level of support — say 5 percent, which more than covers the 2013 price differential on 5mg vials — would have sufficed.

Even using that highest estimate of 13 percent, and under a worst-case scenario where 100 percent of the costs of a trade remedy are passed on to consumers (which is unlikely), the increased costs of a trade remedy would be dwarfed by the skyrocketing prices that result from foreign monopoly control over the production of essential medicines. Even if Accord still managed to grow its market share from 35 percent to 50 percent with the tariff in place, assuming prices stayed around their pre-monopoly rates, a 13 percent tariff would have led to about $700,000 in increased costs per year, or about 1.5 percent of the $50 million cost incurred in the scenario where the government provided no support to U.S. domestic manufacturers.

Sadly, Mitomycin is just one of many products where this has occurred. Most notably, this was the same strategy used to put the last U.S. manufacturer of penicillin out of business in 2004.[49] When the costs imposed in the Mitomycin market are multiplied by the hundreds of drugs on the FDA's essential medicines list, the cost to U.S. consumers of losing American drug manufacturing is easily in the tens of billions of dollars per year.

Middlemen Exacerbate the Race to the Bottom

While slightly higher labor costs have led GPOs, PBMs, wholesalers, and other drug supply middlemen to procure product from China and India to secure the lowest short-term prices possible, in the long run, these practices have made drugs far more expensive for consumers overall than they would be if they could simply source them from American manufacturers.

For example, in the case of Mitomycin, GPOs procuring from India were able to save about 10 percent on their costs in 2010 and 2011. However, once the American manufacturer was forced out of the market the product became far more costly for consumers, and consequently more profitable for GPOs, who actually benefit from the higher prices. In fact, when comparing the cost added by the Indian manufacturer in 2017 above what the U.S. manufacturer had previously supplied, the added cost of relying on India was more than 5 times the amount that the U.S. had spent in total on Mitomycin when there was an American manufacturer in the market — and this is despite the fact that the quantity of Mitomycin used actually declined slightly over this period.

Carmustine

The history of pricing for Carmustine from 2010 to 2017 provides an excellent example of another mechanism that foreign companies can use to monopolize the production of essential medicines for the American market, and, equally important, the dangers of letting these monopolies be run by foreign, rather than domestic, entities.

Like Mitomycin, Carmustine is an essential oncology medicine. It is approved to treat brain tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma.[50] Accordingly, maintaining access to Carmustine is essential for hospitals to be able to save the lives of their patients. As a result, they are essentially forced to pay whatever price they are charged for access to the drug.

This inelastic demand makes the threat of a monopoly particularly costly for American patients, as they would have no choice but to pay the higher prices if a malign actor elected to begin price gouging. From 2010 to 2012, there was indeed a monopoly for the production of Carmustine, held by New York-based Bristol Myers Squibb (BMS). Fortunately, despite their monopoly, BMS did not engage in any particularly egregious price gouging, charging a very steady price of between $157 to $161 per dose over this period.

However, at the beginning of 2013, BMS sold the rights to manufacture and market its Carmustine injection to India-based Emcure Pharmaceuticals.[51] Predictably, the price gouging began immediately. That year, the average price per vial skyrocketed from $160 to $820. Prices went up by another $1,000 in both 2014 and 2015, before settling in the $3,000 - $3,500 per vial range — a twenty-fold increase.

When distributors or manufacturers with a large U.S. footprint engage in price fixing, America's federal and state governments have a range of legal options to sue the companies, as happened in the widely reported lawsuit that twenty state Attorneys General filed against Teva, Mylan, and four smaller companies in 2016.[52] However, in a case like this, where the manufacturer is entirely based in India, the manufacturer may face little to no legal consequences for price fixing or price gouging. In fact, when U.S. businesses sued Chinese companies that had formed a cartel to raise Vitamin C prices by 600 percent, the Chinese government asserted in federal court that Chinese law required the companies to do so.[53]

Figure Three: Carmustine Price Gouging[54]

Despite these skyrocketing prices, hospitals were left with no option but to pay, and pass their exorbitant costs onto patients, health insurers, and the Centers for Medicare and Medicaid Services. Over this entire period, annual quantities remained between 24,500 and 27,500 vials every year. The amount spent on a nearly identical quantity of product, however, jumped by $75 million per year.

Unfortunately, Carmustine is far from the only example of foreign manufacturers beginning to price gouge once a monopoly shifted from the hands of a domestic producer to a foreign one. Prochlorperazine offers yet another sickening example of foreign manufacturers gouging American patients as soon as they were able to gain control over the market for a critical drug.

Prochlorperazine

Prochlorperazine is a critical anti-nausea product marketed for children undergoing chemotherapy. From 2010 to 2013, an American manufacturer, Bedford Labs, held a monopoly control over the pricing for the drug. Over this period, Bedford maintained relatively low, stable, and affordable prices that allowed them to remain profitable while keeping supplies of this critical product available to patients. The average price charged by Bedford over this period was only $2.56 per dose — less than a cup of coffee.

Conversely, once Indian manufacturer Heritage Pharma took over Bedford's position in the market in 2014, they immediately raised prices by over 450 percent. Over the period from 2014 - 2017, Bedford's unit price averaged out to $12 per vial —a roughly 4.5x increase over Bedford's prices.

Figure Four: Prochlorperazine Pricing[55]

In many ways, the actions taken by Emcure can and should be compared to those taken by the infamous Martin Shkreli, who raised the price of Daraprim from $13.50 to $750 per pill overnight in 2015. While Americans were rightly outraged by this move, and Shkreli eventually wound up in prison for his actions, foreign companies are able to get away with similar levels of price gouging on a near-daily basis, while American regulators, whose jurisdiction stops at the country's borders, are unable to do anything to control these transgressions.

That American regulators are unable to stop overseas producers from engaging in price gouging makes it ever more important for the U.S. government to ensure that domestic manufacturers are able to compete in the market for essential medicine manufacturing, as domestic competitors have proven time and time again that they are able to combat this price gouging by making high quality medicines at affordable prices. While these prices may still be somewhat higher than in countries where forced labor and starvation wages are the norm, the costs of price gouging dwarf the marginal cost increases associated with buying from domestic manufacturers of essential medicines.

These examples also highlight that industry-wide data on imports greatly underestimate how vulnerable the U.S. is to foreign supply disruptions. While estimates vary on how reliant the U.S. is on foreign imports of pharmaceuticals, even the most optimistic estimates show the U.S. relies on imports for at least half of our prescriptions.[56] While large pharmaceutical companies sometimes claim that this demonstrates a "strong, global supply chain," there is a very significant difference between being 50 percent import reliant on 100 percent of products, versus being 100 percent import reliant on 50 percent of products. In the former, the U.S. would always maintain some domestic production capability and surge capacity in case there were foreign supply chain disruptions. However, the latter is very common, as shown in these examples, and far more dangerous, because it leaves America completely dependent on foreign countries to provide critical healthcare products to our citizens.

Drug Shortages in the United States

As the sections above highlight, creating a reliance on foreign importers can lead to extreme volatility in drug prices. The exorbitant rates that result from allowing foreign companies to secure monopolies over the production of essential, life-saving generic medicines can add billions to America's total healthcare costs each year. In some cases, these prices also contribute to patients not receiving the care they need, as approximately 60 percent of prescriptions that cost over $500 never get filled, compared to 5 percent of prescriptions that are free.[57]

However, these exorbitant prices are not even the most pernicious impact of America's reliance on overseas manufacturers for generic drugs. Far too often, American hospitals, pharmacies, and patients are unable to access the lifesaving medicines they need because there is simply no available supply of these drugs. Largely as a result of America's reliance on foreign manufacturers, these drug shortages have persisted for decades, with no meaningful improvement.

Drug Shortage Data

As Figure Five shows below, since the beginning of the century, drug shortages have increasingly become a more frequent and dangerous occurrence in the American healthcare system. For example, in the first five years of the century, there were an average of 83 new drug shortages per year, which is an unacceptably high figure. Despite this, the problem has continued to worsen throughout the century. In the last five years prior to the pandemic, an average of 159 new drug shortages were identified annually. Many of these drugs have also remained in shortage for long periods of time, such as Lidocaine Hydrochloride (Xylocaine), which has been on the FDA's drug shortage list since 2012. As of the date of this report's publication, the FDA considers over 100 generic drugs in over 1,000 unique product/dosage forms to currently be in shortage.[58]

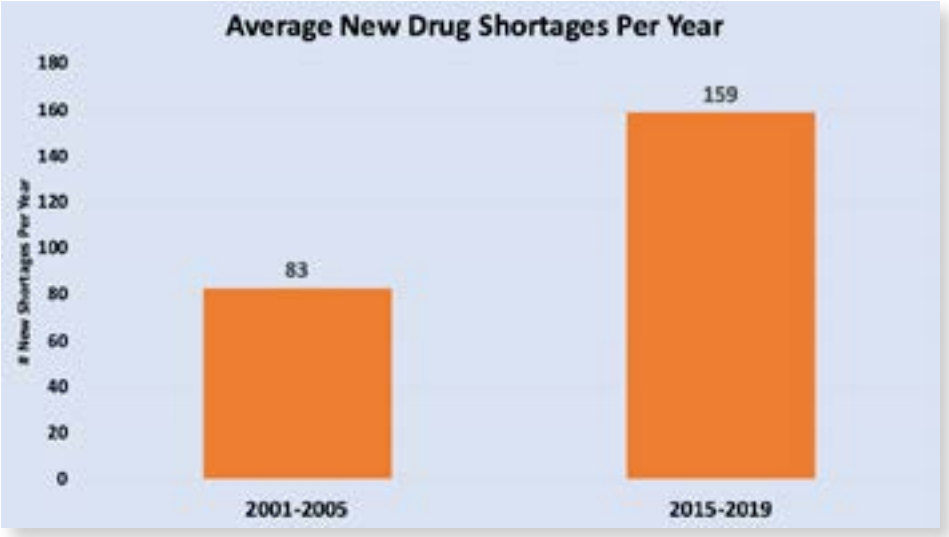


Figure Five: New Drug Shortages, 2001-2005 vs 2015-2019 [59]

While the annual new drug shortages spiked in 2011, when 267 new drug shortages were identified, new drug shortages have remained relatively steady since 2012. The importance of these drug shortages should not be overlooked by policymakers.

While the sheer volume of these shortages is staggering, cross-refencing the FDA's drug shortage list with the newly created essential medicine list helps provide perspective on the prevalence of these shortages. As Figure Six shows, nearly 50 percent of all pharmaceutical products on the FDA's essential medicines list also appear, in some form, on the FDA drug shortage list. While some of these products have recently been removed from the drug shortage list or did not have every dosage of their drug added to the drug shortage list, their presence on this list does indicate that their supply chains are, at best, unreliable and prone to disruptions.

Figure Six: Share of Essential Pharmaceutical Products on Drug Shortage List

It is important to note here that the FDA essential medicines and medical countermeasures risk was created in response to a COVID-era Executive Order and was designed to provide policymakers and government officials with information to evaluate the full spectrum of medical products that would pose threats to American health security if they were not available in a time of need.[60] This includes everything from surgical gloves and gowns to ventilators and blood plasma. Because this report is focused only on generic pharmaceutical products, blood products, vaccines, medical equipment, and products used for responding to chemical, biological, radiological, and nuclear (CBRN) threats are excluded from this analysis.

These drug shortages affect virtually every aspect of the healthcare system in America. As Figure Seven shows, healthcare professionals working in virtually every setting, from emergency and cardiovascular care to gynecology and psychiatry reported facing drug shortages. The results of the survey, which had nearly 300 respondents, showed that over half of respondents across all sectors reported more than 20 drugs they worked with were involved in shortages in the six months prior to the survey, and that drug shortages were a daily struggle.[61]

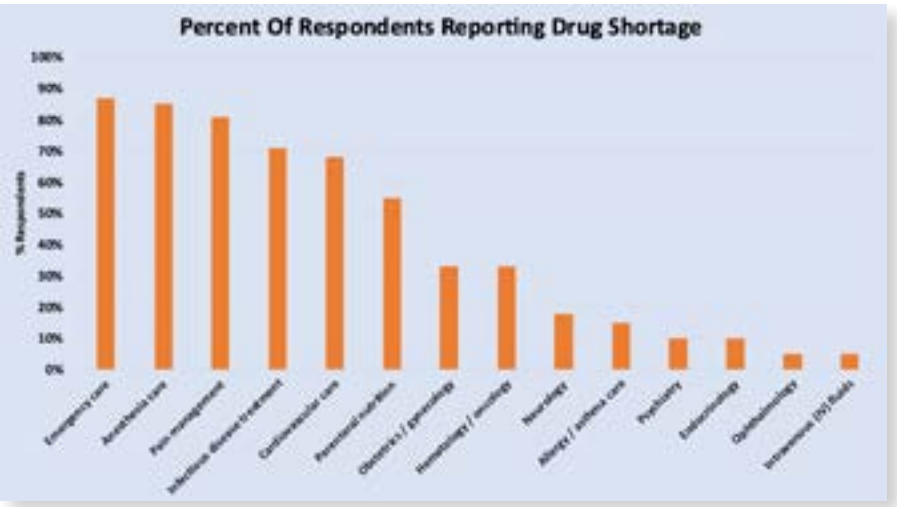


Figure Seven: Prevalence of Drug Shortages by Use Case[62]

Patients suffered as a result of these shortages. According to the survey, 71 percent of respondents were unable to provide patients with the recommended treatments due to shortages.[63] 75 percent also stated that patient treatments were delayed due to drug shortages, which can lead to worse patient outcomes or death, which was also reported.[64]

Causes of Drug Shortages

As part of the drug shortage list, the FDA collects data on the causes of drug shortages in the U.S.

Overwhelmingly, these shortages are caused by one of two factors: quality issues (64 percent), or raw material shortages (27 percent).

The remaining 9 percent of shortages are attributed to increased demand (5 percent), product discontinuation (2 percent), and the loss of a manufacturing site (for example, due to a natural disaster or acquisition) (2 percent).[65]

Unfortunately, the FDA does not report the manufacturing locations of drugs in shortage, but with two-thirds of all drug shortages being caused by quality issues, it is impossible to ignore the role of the shoddy manufacturing practices in places like China and India as important contributors to drug shortages in the U.S. Examples of these foreign manufacturing quality issues leading to supply chain disruptions are plentiful in the pharmaceutical industry. For example, the FDA found one Chinese manufacturer guilty of concealing test results, then had a company employee literally run away from the inspector with a thumb drive from a chromatography machine, leading the FDA to initially suspend imports of the drug that the factory was producing, only to overturn that decision shortly thereafter due to a shortage of that drug. [66]

Undoubtedly, reducing America's reliance on countries known for failing to live up to GMP manufacturing standards would go a long way towards alleviating drug shortages.

Policy Needed to Restore American Generic Manufacturing

Weaknesses in the American supply chains add billions in expenses to the American healthcare system every year and have undoubtedly led to the preventable deaths of far too many Americans. The COVID-19 pandemic highlighted these risks and laid bare the additional risks that they present during times of national crisis, when additional strain is placed on healthcare systems to meet surging demand for lifesaving medicines. While the policies designed to promote competition for the manufacturing of generic medicines have not been significantly updated since 1984, a series of smart policy choices could restore resiliency to America's pharmaceutical supply chains and, in doing so, improve patient outcomes, create jobs, and restore America's health security. This section highlights four policies that, if implemented together, would go a long way towards solving the challenges facing American pharmaceutical supply chains.

Utilizing the U.S. Government as a Buyer of American Made Generics

A customer base is essential for any industry to survive and get to scale. The U.S. government is best positioned to meet this challenge by providing a benefit to those generic products Made in the U.S.A. One way to do this would be to leverage the role of the Centers for Medicare and Medicaid Services (CMS) to incentivize a much larger customer base to buy from domestic producers. With over 80 million Americans[67] enrolled in Medicare, Medicaid, or the Child Health Insurance Program (CHIP), and Medicare and Medicaid patients accounting for more than 60 percent of all care provided by hospitals nationwide, nearly every major hospital must accept Medicare and Medicaid patients and comply with the requirements that CMS sets for them to do so.[68] This provides tremendous ability to leverage these programs to support domestic manufacturers.

There are a number of ways that CMS could be used to accomplish the goal of securing reliable medical supply chains for all Americans. The easiest would likely be to just reimburse health care providers slightly more for using domestically manufactured medicines than foreign ones. While this would only leverage the implicit "buying power" of the 80 million Americans on Medicare and Medicaid, rather than the entire healthcare system, the combined Medicare and Medicaid spending of over $1.5 trillion per year would still make CMS larger than any other country in the world's entire healthcare system.[69]

In addition to potentially providing higher premiums for domestically produced goods, CMS could merge this concept with another produced in the recent White House report on "Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth" of having the FDA create a quality-rating system, and then tailoring reimbursement rates to the FDA quality assessments.[70] This approach has already been used by numerous countries overseas, including China, which pays a 10 percent premium to domestic producers creating high-quality drugs.[71]

While increasing reimbursement rates for hospitals that use domestically produced pharmaceuticals would be a highly efficient way to incentivize domestic manufacturing, another option to leverage CMS, which may be a bit easier to accomplish in practical terms, would be to have CMS impose a requirement on hospitals that if they want to continue to be able to accept Medicare and Medicaid patients, they must buy a certain percentage of the pharmaceuticals that they use from domestic sources. While this would still give hospitals the ability to assess which products could be produced most affordably by domestic sources, and not limit their ability to secure any products that had no domestic production from overseas suppliers, this could have a dramatic impact on American pharmaceutical manufacturing, especially if the percentage requirement were gradually ratcheted up over several years.

Whether it be a small price premium for high-quality domestic producers, or a de facto quota for procurement of American-made pharmaceuticals, leveraging CMS to accomplish either of these approaches would have a dramatic impact on American pharmaceutical manufacturing. Not only would this help secure pharmaceutical supply chains and decrease America's reliance on overseas countries (including adversaries), but by keeping American manufacturers in the market, it would encourage competition and keep prices far below the rates that get charged when foreign suppliers develop monopolies on essential medicines. In the long run, this would undoubtedly save American hospitals, patients, and taxpayers billions in expenses.

In addition to leveraging the power of CMS, the federal government should, at a bare minimum, provide priority to domestic producers when agencies are procuring drugs directly. However, simply buying from these producers on the "spot market" will not be sufficient to give American manufacturers the confidence that they need to continue operating. Instead, the Department of Veteran's Affairs, the Department of Health and Human Services' (HHS) Strategic National Stockpile, and the Department of Defense's (DOD) Defense Health Agency should all prioritize signing long-term contracts with domestic manufacturers to give them the confidence of knowing that they will have a buyer for multiple years.

Unfortunately, contracting officers at these agencies are often unable to negotiate long-term contracts for these products because they are only appropriated funding for one fiscal year at a time. In order

to give these contracting officers more flexibility to support domestic manufacturers, Congress should consider creating and funding working capital funds for each of these agencies to allow them to enter into long-term contracts without relying on their current year's funding to finance procurements several years into the future.

While encouraging federal agencies to enter into long-term contracts with domestic sources would provide some level of a guaranteed customer base, these agencies collectively account for slightly less than 5 percent of total healthcare spending in the country. As such, leveraging the power of CMS, in combination with the other policies listed below, would have a much greater impact on reshoring America's pharmaceutical manufacturing base.

Trade Remedies to Support American manufacturers

Fulsome deployment of U.S. trade remedies laws is an integral component of ensuring a customer base for American manufacturers. It is long overdue for policymakers and elected officials to earnest enforcement of U.S. trade remedies laws. As has been shown throughout this report, subsidies by foreign governments and predatory policies by foreign manufacturers have been one of the greatest causes of eliminating competition in the generic marketplace.

The first trade remedies laws appeared just over a century ago and were understood as key components of the antitrust system of laws Congress was then writing. Because the Department of Justice cannot bust up foreign cartels, the U.S. needed to ensure predatory behavior by foreign cartels and state-supported 'national champions' was checked at the border.

In cases like Mitomycin, where foreign manufacturers sell below cost to force American manufacturers out of business before hiking prices eightfold, America needs to use trade remedies to stabilize the market. In cases where foreign companies and countries engage in behavior that meets the legal standards for imposing antidumping and countervailing duties (AD/CVD), the Commerce Department and U.S. ITC need to enforce these policies to the full extent of the law. However, these traditional AD/CVD remedies have become costly and time consuming to deploy thanks to an army of well-funded attorneys representing foreign governments and corporations, including foreign multinationals with operations in the U.S. These are often times not viable for smaller producers to litigate.

For this reason, the U.S. needs to consider additional trade measures to protect its domestic manufacturers, and therefore maintain competition, supply chain resiliency, and affordable prices, through trade policy.

Given the pharmaceutical export restraints imposed even by allies like Europe following the outbreak of COVID-19, the use of Section 232 of the Trade Expansion Act of 1962 is entirely justified in ensuring a resilient domestic supply chain. Section 232 authorizes the President to use duties or

quotas to ensure the United States can provide for its own essential goods during national security crises. The export restraints other countries imposed in March 2020 demonstrated that decades of positive rhetoric around international trade and globalization can be shoved aside at a moment's notice. For this reason, Section 232 duties and quotas should be phased in on all medicines listed in the FDA's essential medicine list to help bring about the necessary domestic investment in their production. One benefit of a Section 232 approach is that it provides the Administration with a great amount of flexibility to adjust rates and exempt specific products or countries when such changes are needed. They are also less prone to litigation risk than traditional AD/CVD cases.

Beyond the Section 232 national security measures, the U.S. should make active use of Section 301 of the Trade Act of 1974. Section 301 exists to authorize the President to deploy duties and quotas in response to unfair trade practices by foreign governments. The term "unfair trade practices" is defined quite broadly and captures a wide swath of foreign government activity happening today in the pharmaceutical industry. If a foreign country deploys policy tools to localize their pharmaceutical manufacturing, the best approach is to wish them no ill will, but to not stand by while they dump excess capacity on our market. Section 301 is the mechanism to advance this policy.

Finally, the U.S. could impose Section 201 safeguards to support domestic manufacturers. However, Section 201 provides some practical challenges to be able to implement. First, while Section 201 safeguards are typically requested by domestic manufacturers, these manufacturers would likely only be able to request safeguards for one product at a time, which would mean hundreds of investigations would need to be conducted to cover the full FDA essential medicines list. A broader investigation into the manufacture of essential medicines collectively could be requested by the Administration, but it is not clear whether the ITC would agree to such a broad scope. In addition, the Administration's ability to implement Section 201 safeguards are somewhat limited by the fact that they need an affirmative finding from the ITC to do so, as opposed to the Section 232 and 301 options where the President and Administration have the authority to elect to impose remedies at will. In addition, Section 201 actions are time-limited, with a maximum initial period of four years, and a maximum total period of eight years. Section 201 of the Trade Act of 1974 is different from traditional AD/CVDs or 301 tariffs, because foreign intention (whether subsidies, dumping, or other unfair practices) is not a prerequisite. Section 201 exists to allow manufacturers breathing space if a sudden surge in imports of a particular product occurs. Any domestic manufacturer who is threatened by an unforeseen surge should not hesitate to bring about a Section 201 case, and the U.S. can facilitate this by advertising the mechanism in the industry.

In any of these cases, there are some that will argue that these remedies will simply increase the costs of medicines in an already expensive healthcare system. While there may be a few instances where that is the case in the short run, these marginal increases would be dwarfed by the cost savings that result from the ability of these policies to reduce extreme price gouging. Recall that our trade remedies laws were developed parallel to our antitrust laws: The point is to promote competition and low prices for American consumers.

For example, even if we were to assume that a 10 percent across the board national security tariff was paid for entirely by importers (which it certainly would not be), it would require about 200 different

drugs (nearly the entire essential medicines list) to experience those price increases just to offset the costs savings that would result from supporting an American manufacturer to eliminate the price gouging in the Carmustine market alone. [72] Undoubtedly, there would be plenty of other drug products that would see American manufacturers return to or remain in the market as a result of these actions, further increasing the potential cost savings, while also diversifying supply chains. This would create greater stability in price and availability for these essential products.

Provide Financial Support to American Manufacturers

In addition to trade remedies and leveraging the government's buying power to provide domestic demand for American made generics, America's pharmaceutical manufacturing capabilities have been so thoroughly depleted that direct financial support may be necessary to rebuild America's public health industrial base.

The Biden Administration's American Rescue Plan provides an excellent starting point for this investment. The $10 billion appropriated to the Defense Production Act Fund that is earmarked for the COVID-19 response and pandemic preparedness will provide a major stimulus to America's pharmaceutical manufacturing base. However, this will still be insufficient for America to be able to manufacture all of its most essential generic medicines. For example, the U.S. has not been able to manufacture penicillin domestically since 2004. Building a facility to manufacture the API and finished drug form of just one penicillin product could easily cost $500 million, and not even be able to fill the majority of the U.S. demand for that product. In fact, just to be able to domestically produce two-thirds of America's antibiotic consumption domestically could require investment on the scale of $4 - 5 billion, and antibiotics represent only a small fraction of the total essential medicine list. Moreover, as new drug products and improved manufacturing techniques are developed, American manufacturers will need to be making continuous investments in their equipment to avoid shuttering facilities.

To that end,
Congress should consider creating some permanent financial incentives to support American manufacturers.

Such incentives could take many forms, including making a permanent program to continue allocating grant funding to support critical investments (though such a program should be transferred from DOD to HHS). These direct funding programs have the benefit of allowing HHS to select investments in the products that are most critical to American national security interests, which may not always be the most profitable.[73]

More cost-effective options may include the provision of subsidized loans, rather than grants, that can help small companies overcome some of the barriers to entry for pharmaceutical production. The Development Finance Corporation's (DFC) Defense Production Act (DPA) loan program provides some excellent cases of successfully incentivizing domestic investments through loans. For example, a $590 million loan from the DFC allowed ApiJect to scale its production of pre-filled syringes, while the government will likely receive the value of its loan back, in addition to some nominal interest earnings.[74]

Conversely, Congress could also create similar outcomes without relying on HHS to select the most critical investments through tax incentives. This could include tax credits for new investments in pharmaceutical manufacturing, or a tax credit for the sale of pharmaceutical products to essentially cut the tax rate that domestic manufacturers face.[75] Similarly, reshoring tax incentives to the island of Puerto Rico, which already has much of the infrastructure and workforce in place from when it was previously a global pharmaceutical manufacturing powerhouse, may support investments on the island.

Close Foreign Regulatory Loopholes

One of the simplest and most effective actions that policymakers could take to support supply chain resiliency and to rebuild America's pharmaceutical industrial base would simply be to ensure that foreign manufacturers are required to meet the FDA's safety and quality standards.

There are several mechanisms the FDA could use to achieve these outcomes.

First, while the FDA may not have authority to force its way into overseas manufacturing facilities if the company chooses not to allow them access without warning, the FDA has authority to consider a wide range of potential quality and safety issues when they choose to approve an NDA or ANDA. Moving forward, the FDA should use this authority to require that companies agree to allow the FDA access to inspect their facilities without warning, so that inspectors can get a more accurate assessment of the quality control measures in place during the factory's normal operations.

Second, the FDA should invest more resources to increase its inspections of overseas factories. While this may be less important for factories in Europe and other developed nations where local regulators already maintain strong controls, factories in India and China have a long history of violating GMP procedures, so the impact of additional regulators in these countries would have far more impact on improving drug safety than additional regulators in U.S. facilities would have.

Most importantly, the FDA should re-evaluate its approach to regulating overseas facilities altogether. While additional resources can help, the sheer volume of overseas facilities paired with the practical challenges of international inspections will make it nearly impossible to enforce the FDA's full range of regulations through inspections alone. What the FDA can do instead to ensure that drugs being imported live up to the FDA's standards is to engage in a process known as release testing. In essence, this means taking samples vials from each batch of imported drug product coming into the country and checking to see if there are any dangerous toxins or variabilities in the specified dosage amount once the medicine is in its final form. The clear benefit to this approach is that release testing would catch impurities caused by any weaknesses in the supply chains, whether they be during the production of the drug's active pharmaceutical ingredient, residue from previous chemical being processed in the same factories as the drugs, shoddy chemistry, improper storage, or any number of other potential causes of quality issues.

The FDA already possesses the ability to conduct this release testing, as its Office of Pharmaceutical Quality, led by Michael Kopcha, has over 1,300 employees and nearly a dozen testing facilities with the capability to conduct these tests. While the volume of products coming into the country would require additional resources to test every batch of pharmaceuticals entering the country, legislation could require overseas manufacturers to reimburse the FDA for costs associated with conducting this testing, rather than charging American consumers directly.

Forcing overseas manufacturers to pay for the cost of release testing on their own products would be the ultimate win-win for American interests: At no cost to taxpayers, Congress and the FDA could simultaneously solve one of the greatest safety issues in America's healthcare systems while simultaneously closing a loophole that has encouraged the offshoring of American manufacturing for decades.

Finally, Congress needs to provide the FDA with greater authority to crack down on overseas manufacturers that fail to meet their quality control expectations. Currently, when the FDA finds imported drugs that are failing to meet their quality control standards, the FDA simply places a warning on their products and continues to let the imports flow into the country — despite potential risks to American patients. While FDA warnings may work for food safety issues, as millions of Americans will readily throw out food when they hear news of a major salmonella outbreak, most Americans have no idea when the drugs they take are placed on an FDA warning list. Worse yet, even if Americans did know that their drugs were on a product warning list, they may not have the chance to find a safer alternative, as the drug procurement is typically done by PBMs and GPOs who readily ignore these warnings on a daily basis.

While release testing would provide the opportunity for the FDA to identify batches of imports that pose health and safety risks, they also need to be able to immediately dispose of those batches, and, for producers that consistently fail to meet the FDA's standards, the FDA needs to be able to temporarily revoke their NDA's and ANDA's, rather than simply adding them to a warning list that GPOs and PBMs consistently ignore.

Additional Policy Options

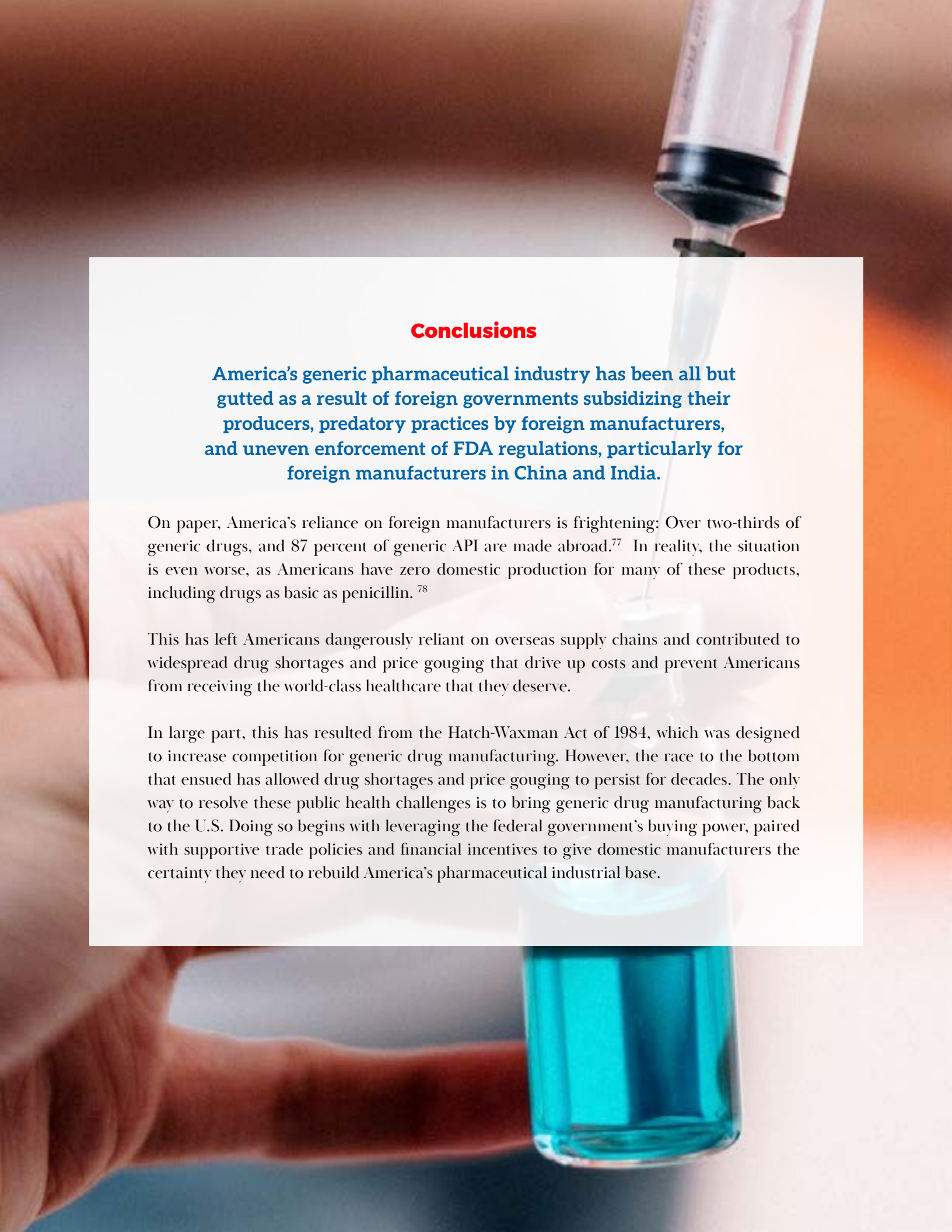
In addition to the four cornerstone policy ideas outlined above, there are a number of other smaller changes that Congress or the Executive Branch could take that would have a meaningful impact on the pharmaceutical market. First, Congress (or, potentially, CMS using its existing authority) could mandate that all pharmaceuticals contain a country-of-origin label on all products. In doing so, policymakers should ensure that the location of both the finished product and API production occur, which may require Congressional action due to the recent Acetris case.[76]

Similarly, Congress could require that hospitals, pharmacies, and other care providers share information about FDA warnings on any of the pharmaceutical products that they are providing to

patients, so that customers are more aware of the risks associated with their product. Given the public response to outbreaks of salmonella and E. coli, it is certainly possible that public awareness alone could help restore quality and resiliency to pharmaceutical supply chains.

In addition, the importance of gaining "First to File" status, and the 180 days of market exclusivity when a branded drug first goes generic should not be overlooked. Manufacturers often use these periods to lock customers into long-term contracts, thereby making it difficult for other manufacturers to enter the market for generic drugs. While the process of applying for an ANDA is less demanding than filing for an NDA for a new drug, it is still quite expensive and time-consuming. For American companies, the risk of devoting significant resources to filing for an ANDA, and then having the 180 days of exclusivity given to another party that was able to submit first instead is a significant business risk. One step that Congress or the FDA could take to encourage domestic manufacturers to proceed with filing for these ANDAs, and to help them secure a strong market position, is to give preference to the American manufacturer if two companies file an ANDA on the same day, rather than providing them with "joint-exclusivity" for the 180 days, which is the FDA's current policy.

Finally, as lawmakers seek to gain more detailed, granular data on pharmaceutical supply chains, one thing they may consider doing is using the survey authority given to the Commerce Department's Bureau of Industry and Security (BIS) to require domestic manufacturers, hospitals, GPOs, PBMs, and other companies in the healthcare supply chain to share additional information on the details of their supply chains and sourcing challenges that they face. However, since the process of developing and awaiting responses for a BIS survey takes several months at best, it is important that lawmakers only use this information to help inform future actions, and that they do not let perfect be the enemy of the good by waiting indefinitely for additional information.



Conclusions

America's generic pharmaceutical industry has been all but gutted as a result of foreign governments subsidizing their producers, predatory practices by foreign manufacturers, and uneven enforcement of FDA regulations, particularly for foreign manufacturers in China and India.

On paper, America's reliance on foreign manufacturers is frightening: Over two-thirds of generic drugs, and 87 percent of generic API are made abroad.[77] In reality, the situation is even worse, as Americans have zero domestic production for many of these products, including drugs as basic as penicillin. [78]

This has left Americans dangerously reliant on overseas supply chains and contributed to widespread drug shortages and price gouging that drive up costs and prevent Americans from receiving the world-class healthcare that they deserve.

In large part, this has resulted from the Hatch-Waxman Act of 1984, which was designed to increase competition for generic drug manufacturing. However, the race to the bottom that ensued has allowed drug shortages and price gouging to persist for decades. The only way to resolve these public health challenges is to bring generic drug manufacturing back to the U.S. Doing so begins with leveraging the federal government's buying power, paired with supportive trade policies and financial incentives to give domestic manufacturers the certainty they need to rebuild America's pharmaceutical industrial base.

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42. GAO-17-143, DRUG SAFETY: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices
43. Indian villagers say pharmaceutical waste is polluting water - YouTube; See also: Pharmaceutical Pollution in India and EU's role | stopAMR
44. Xinchang Jingxin Pharmaceutical Company, Zhejiang, China | EJAtlas
45. Pharmaceutical and Medicine Manufacturing - May 2020 OEWS Industry-Specific Occupational Employment and Wage Estimates (bls.gov)
46. India placed 72nd on global list with average monthly wage of Rs 32,800: Report - The Economic Times (indiatimes.com)
47. Adjusted net national income per capita (current U.S.$) - China, United States, India | Data (worldbank.org)
48. IQVIA Data
49. RosemaryGibsonTestimonyU.S.CCJuly152019.pdf
50. Carmustine - National Cancer Institute
51. Emcure buys rights for Bristol-Myers' chemotherapy brand | Business Standard News (business-standard.com)
52. 20 States Accuse Generic Drug Companies of Price Fixing - The New York Times (nytimes.com)
53. RosemaryGibsonTestimonyU.S.CCJuly152019.pdf
54. IQVIA Data

55. IQVIA Data
56. The White House Report in response to Executive Order 14017, for example, shows that the U.S. accounts for only 27 percent of API manufacturing facilities, and only 13 percent for generic API. For finished drug products, the corresponding figures are 48 percent for all drugs, and 37 percent for generics. FACT SHEET: Biden-Harris Administration Announces Supply Chain Disruptions Task Force to Address Short-Term Supply Chain Discontinuities | The White House Foreign manufacturing facilities, particularly in China and India, also tend to be significantly larger than American facilities, according to several industry sources who have operated in both the U.S. and internationally, so these figures likely overstate America's manufacturing capacity by volume.
57. Medicine Spending and Affordability in the U.S. - IQVIA
58. FDA Drug Shortages (Products listed as "resolved" are excluded from this count). As of August 7, 2021, 108 active ingredients, as listed on the FDA website, were marked as "Currently in Shortage". The FDA's full drug shortage download includes specific dosage forms and products in shortage. For example, Mylan and Teva both produce 350mg vials of Leucovorin Calcium Lyophilized Powder for Injection, and both are included on the FDA drug shortage list. This would count as two "unique product/ dosage forms", but only one generic drug.
59. Drug Shortages Statistics - ASHP
60. Executive Order 13944 List of Essential Medicines, Medical Countermeasures, and Critical Inputs; See also: GAO-14-194, Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability; The GAO report above from February 2014 uses the data from the University of Utah's Drug Information Service, which is what we rely on for years not included in the GAO report.
61. Drug Shortages Continue to Compromise Patient Care | Institute For Safe Medication Practices (ismp.org)
62. Drug Shortages Continue to Compromise Patient Care | Institute For Safe Medication Practices (ismp.org); See also: U.S. Drug Shortages: Root Causes and Statistics - Drugs.com
63. Drug Shortages Continue to Compromise Patient Care | Institute For Safe Medication Practices (ismp.org)
64. Drug Shortages Continue to Compromise Patient Care | Institute For Safe Medication Practices (ismp.org)
65. Drug Shortages Infographic | FDA
66. This example, and many more, can be found in Bottle of Lies: The Inside Story of the Generic Drug Boom by Katherine Eban. However, an abbreviated, publicly available version of this story can be found at 8 Ways Overseas Drug Manufacturers Dupe the FDA | WIRED
67. 2021 02 Preliminary applications, eligibility determinations, and enrollment data | Data.Medicaid.gov
68. Fact Sheet: Underpayment by Medicare and Medicaid | AHA
69. National Health Expenditure Projections, 2019–28: Expected Rebound In Prices Drives Rising Spending Growth | Health Affairs; See also: Current health expenditure per capita (current U.S.$) | Data (worldbank.org)
70. 100-day-supply-chain-review-report.pdf (whitehouse.gov) p247
71. 2081China020517.pdf (who.int) p14
72. This example assumes that the market for all 200 drugs is the same size as the market for Carmustine. While that is of course not the case, the logic remains valid, as there are plenty of other drug products that would be equally impacted, and, on balance, we would expect the average market size of the drugs where there is price gouging to be roughly equivalent to the average market size of all drugs affected by the tariffs.
73. One example of a proposed initiative to do this is the "Affordable Drug Manufacturing Act" introduced by Sen. Elizabeth Warren and Rep. Jan Schakowsky. This report does not take a position on the specific pieces of legislation, but it is linked here for reference: Warren, Schakowsky Introduce Bicameral Legislation to Radically Reduce Drug Prices Through Public Manufacturing of Prescription Drugs | U.S. Senator Elizabeth Warren of Massachusetts (senate.gov)
74. DFC Approves $590 Million Loan to ApiJect to Expand Infrastructure and Deliver Critical Vaccines in Response to the COVID-19 Pandemic
75. Several proposals for providing incentives for domestic pharmaceutical manufacturing have been proposed in the House of Representatives. This report does not take a position on the specific pieces of legislation, but they are linked here for reference as examples: U.S. Can Boost Domestic Production of Essential Medicines and Their Ingredients with Tax Incentives - Ways and Means Republicans (house.gov)
76. Federal Circuit Acetris Decision Changes Procurement Country of Origin Landscape | Hogan Lovells - JDSupra
77. FACT SHEET: Biden-Harris Administration Announces Supply Chain Disruptions Task Force to Address Short-Term Supply Chain Discontinuities | The White House
78. RosemaryGibsonTestimonyU.S.CCJuly152019.pdf