

United States Senate Committee On  
**HOMELAND SECURITY  
& GOVERNMENTAL AFFAIRS**

Chairman Gary Peters

A stylized eagle with its wings spread, rendered in a dark blue color. Above the eagle's head are seven gold stars, arranged in a slight arc. The eagle is centered on a dark blue background.

**SHORT SUPPLY**

*The Health and National Security  
Risks of Drug Shortages*

HSGAC Majority Staff Report

March 2023

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## **EXECUTIVE SUMMARY**

Shortages of critical medications continue to rise—including drugs used in hospital emergency rooms and to treat cancer, prescription medications, and even common over-the-counter treatments like children’s cold and flu medicine. The number of active drug shortages in the U.S. reached a peak of 295 at the end of 2022. However, drug shortages are not a new problem. They are caused by a number of factors, including economic drivers, insufficient supply chain visibility, and a continued U.S. overreliance on both foreign and geographically concentrated sources for medications and their raw materials. These shortages have cascading effects on patient care, causing delays in treatment, increasing the risk of medication errors, and requiring the use of less effective alternative treatments. Hospitals have also experienced increased costs, medication waste, and limited staffing capacity to address and remedy shortages.

U.S. Senator Gary Peters previously identified these concerns and in December 2019, released a report examining drug shortages in the U.S. The report found that critical generic drugs, particularly sterile injectable products regularly used in hospitals, were at an increased risk for shortages, and that nearly 80% of manufacturing facilities that produce active pharmaceutical ingredients (API)—the key ingredients that give a drug its intended effect—are located outside of the U.S. The report concluded that U.S. overreliance on foreign sources for these drugs posed a national security risk and that in the event of a crisis, such overreliance could have devastating impacts on hospitals, health care providers, and patients.

Just months following the release of Senator Peters’ 2019 report, a new SARS-CoV-2 virus spread around the world. The ensuing COVID-19 pandemic further exposed longstanding vulnerabilities in the U.S. medical supply chain and the growing threat to the U.S. from an overreliance on China and other countries for manufacturing key drugs, medical supplies, and the raw materials needed to make these products. Additionally, the COVID-19 pandemic exacerbated already lean supply lines and left providers scrambling for alternative drug options to care for patients.

At the direction of Senator Peters, Chairman of the Senate Homeland Security and Governmental Affairs Committee, Majority Committee staff conducted a follow-up review to evaluate the current state of drug shortages and identify needed reforms. The report assesses the continued impact of drug shortages on patients, hospitals, and health care providers, evaluates federal and private sector efforts to address these shortages, and examines the ongoing threat posed by U.S. overdependence on foreign and geographically concentrated sources for key drugs, and their critical inputs, including key starting materials and APIs. The report finds that the federal government’s inability to comprehensively assess U.S. pharmaceutical supply chain vulnerabilities and address known causes of shortages for critical drugs continues to frustrate efforts to predict drug shortages and effectively mitigate their impact on patient care.

While the Food and Drug Administration (FDA) prevented a record number of drug shortages in 2021, active drug shortages are currently on the rise. Recent efforts by Congress, the Executive Branch, and industry aim to increase pharmaceutical supply chain visibility and bolster domestic manufacturing capabilities for critical drug products. However, significant gaps remain.

Many critical generic drugs require highly complex manufacturing processes, but ultimately cost pennies on the dollar. The Administration for Strategic Preparedness and Response (ASPR) estimates that 90 to 95 percent of generic sterile injectable drugs used for critical acute care in the U.S. rely on key starting materials from China and India. Between 2010 and 2015, the number of Chinese-based API manufacturers that registered with the FDA more than doubled.

Neither the federal government nor industry has end-to-end visibility of the pharmaceutical supply chain—from the key starting materials, APIs, finished dosage and various other manufacturers that are “upstream”—to the “downstream” suppliers, which include purchasers and providers. This lack of transparency limits the federal government’s ability to proactively identify and address drug shortages. Although some generic drugs appear to have multiple and diverse drug suppliers, they in fact may rely on the same API source or manufacturer. As a result, the universe of actual suppliers for a particular drug may be much smaller than it appears, increasing the risk of shortage if that API source or manufacturer withdraws supply. The FDA is currently unable to assess the percentage of life-supporting and life-sustaining medications that have fewer than three manufacturers or rely on only one API supplier because the FDA does not have a list of life-supporting and life-sustaining drugs. The Department of Defense (DOD) is equally reliant on the commercial market for pharmaceutical products, and told the Majority Committee staff it lacks “authoritative data” on the sources of drugs it purchases from the private sector.

Congress, the Executive Branch, and industry must work together to respond to this decades-long problem by obtaining needed supply chain visibility to proactively identify risks, investing in quality systems and advanced manufacturing technologies, and ensuring supplier diversification through strategic onshoring for critical generic drugs regularly used by healthcare providers throughout the country.

## FINDINGS OF FACT

- 1. Drug shortages are increasing, lasting longer, and impacting patient care:** Between 2021 and 2022, new drug shortages increased by nearly 30 percent. At the end of 2022, drug shortages experienced a record five-year high of 295 active drug shortages. While the average drug shortage lasts about 1.5 years, more than 15 critical drug products have been in shortage for over a decade. Shortages continue to have devastating consequences for patients and health care providers, including medication errors and treatment delays, and in some cases, have led to doctors having to ration lifesaving treatments.
- 2. Overreliance on foreign and geographically concentrated sources for critical drugs and their key starting materials and limited domestic manufacturing capabilities create health and national security risks:** Between 2010 and 2015, the number of Chinese-based API manufacturers registered with the FDA more than doubled from 188 in 2010 to 445 in 2015. U.S. Pharmacopeia, an independent nonprofit designated under federal law to set quality standards for medicines marketed in the U.S., reported that India accounted for the majority of FDA-approved API facilities as of 2021. ASPR told the Majority Committee staff that its “biggest concerns” are that 90 to 95 percent of generic sterile injectable drugs for critical acute care in the U.S. rely on key starting materials and drug substances from China and India. The Defense Logistics Agency, which purchases drugs for the U.S. military, said with the exception of three drugs that rely on API manufacturers based solely in China, it is “unable to determine with certainty if any of the drugs it purchases rely solely on sources in China or India.”
- 3. The FDA still lacks critical information that could help mitigate shortages:** During the onset of the COVID-19 pandemic, foreign governments instituted export bans on a number of critical medical products, contributing to supply disruptions and shortages. Increased demand has also resulted in drug shortages. Under current law, manufacturers are not required to report increased demand or export restrictions for life-supporting and life-sustaining drug products to the FDA. Group Purchasing Organizations (GPOs) and distributors are also not required to report potentially helpful data, such as hospital fill rates (e.g. what is ordered versus received), to the FDA.
- 4. While the FDA retains certain data from manufacturers on the pharmaceutical supply chain, such as key starting materials needed to make drug substances, that data is currently not provided or stored in a useable format to aid supply chain visibility:** The FDA has data from manufacturers’ submissions, including applications and drug master files, which include information on the raw materials needed to make drug products, such as key starting materials used to make APIs. However, in response to questions from Majority Committee staff, the FDA acknowledged that it has been unable to use this data to conduct analyses or predictive modeling because the information is “unstructured” and “buried in PDFs within individual drug applications.”

5. **Industry and the federal government lack end-to-end visibility into the pharmaceutical supply chain and efforts to map supply chains are not sufficiently coordinated:** Federal agencies, GPOs, and representatives for manufacturers and distributors uniformly acknowledged to Majority Committee staff that they do not have sufficient data to track each stage of the pharmaceutical supply chain. This lack of visibility, specifically into the key starting materials and other manufacturers involved in the production process, coupled with limited data sharing and integration across agencies, impairs both the federal government's and industry's ability to conduct comprehensive risk assessments and utilize predictive modeling to prevent or lessen the impact of potential shortages.
6. **The FDA lacks authority to require manufacturer recalls for most drug products:** While the FDA has authority to recall food products, biological products (e.g. vaccines), medical devices, and controlled substances, it does not have the authority to recall all drug products. Currently, the FDA can only recommend that a company voluntarily recall a drug. In 2020, when the FDA asked companies to recall unsafe hand sanitizer products that flooded the market and contained a potentially toxic substance, some companies failed to comply and others did not act immediately.

## **RECOMMENDATIONS**

1. **Invest in domestic advanced manufacturing capabilities for critical generic drug products regularly in shortage:** The federal government should build upon its efforts to engage industry and academic partners through private-public partnerships that incentivize strategic onshoring and advanced domestic manufacturing technologies for critical generic drugs. These partnerships should encourage the use of advanced manufacturing technologies for critical drugs prone to shortages and bolster ongoing collaboration between academia and industry to further build opportunities for workforce training programs that bridge the gap from research and development to commercialization. The federal government should also explore opportunities to engage in long-term contracts with diverse suppliers of critical generic drugs.
2. **Conduct regular interagency medical supply chain risk assessments:** To ensure the federal government is adequately prepared to identify and mitigate vulnerabilities in the medical supply chain, Congress should require HHS, DOD, and DHS to jointly conduct regular risk assessments. These assessments should also account for cybersecurity threats. The federal government, in coordination with industry partners should also regularly update the Essential Medicines list and use that as a guide for investing in critical drug products in the U.S.
3. **Require manufacturers of life-supporting and life-sustaining drug products to report increased demand and export restrictions to the FDA:** To improve the FDA's ability to predict and prevent potential drug shortages, Congress should require manufacturers to report when they experience an increase in demand or export restriction. Congress should also require GPOs and distributors to report low hospital fill rates (e.g. what is ordered versus received), for example, if a hospital receives less than 80 percent of the product they ordered, to help increase the FDA's visibility into downstream supply chain distributors and providers, and help minimize the gap between supply and demand.

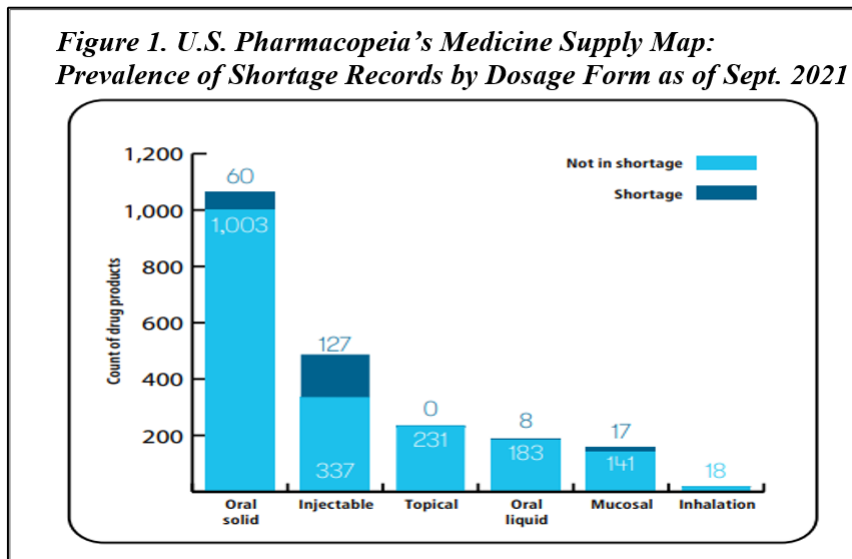
4. **The FDA should take steps to ensure its supply chain data can be used to monitor supply chain vulnerabilities and conduct predictive modeling:** The FDA should prioritize its development of a key starting material database and improve coordination with interagency and industry partners to assess end-to-end supply chain visibility. As part of its continued data modernization efforts, the FDA should document how it plans to utilize manufacturer volume data to proactively identify supply chain risks and predict drug shortages.
5. **Streamline private and public efforts to predict and mitigate potential supply chain vulnerabilities:** The federal government should better coordinate efforts to integrate data sharing between interagency and industry partners through a singular initiative to map the entire pharmaceutical supply chain—from key starting material and API sources to distribution information. The initiative should use digital technologies to regularly conduct predictive analyses and proactively identify vulnerabilities.
6. **Provide the FDA with mandatory recall authority for all drug products:** Congress should provide the FDA with mandatory recall authority for drug products that present a serious danger to individuals' health.

## I. Drug Shortages Continue to Pose Health and National Security Risks

The COVID-19 pandemic laid bare the longstanding vulnerabilities within the U.S. pharmaceutical supply chain. Just-in-time manufacturing practices, overreliance on both foreign and geographically concentrated sources for critical drug products, and insufficient supply chain visibility, among many other challenges, have resulted in widespread shortages of critical drug products over recent decades. Shortages of critical medical products, which are commonly used in hospital emergency rooms and outpatient settings, worsened throughout the COVID-19 pandemic as global demand increased and countries began initiating export bans to keep needed products.

The subsequent surge in respiratory viruses in the fall and winter of 2022, with a confluence of COVID-19, RSV, and influenza cases, resulted in increased demand for prescription and over-the-counter medications, further stressing the pharmaceutical supply chain. In addition, staffing shortages and transportation delays continue to present challenges. Since Senator Peters released his 2019 report on drug shortages, the

number of active drug shortages has generally continued to rise.<sup>1</sup> As shown in Figure 1, injectable drug products, which can include supportive care medications (like IV saline), sedatives (such as propofol), and chemotherapy drugs, are more than twice as likely to experience shortages compared to other dosage forms, such as oral tablets or topical products.<sup>2</sup> However, recent shortages of basic over-the-counter medications, like pediatric Tylenol and Motrin used to treat children’s flu and fever, have also spiked due to increased demand, leaving many shelves bare and pharmacies limiting sales.<sup>3</sup>



<sup>1</sup> The FDA defines a drug shortage as “a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply of the drug.” See 21 U.S.C. § 356c(h)(2). ASHP takes a more practitioner focused approach to shortages, which they define as “a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.” See Drug Shortages FAQs, American Society of Health-System Pharmacists (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-faqs>) (accessed Mar. 1, 2023). This report relies on data from both FDA and ASHP.

<sup>2</sup> Vizient, U.S. Pharmacopeia, and Angels for Change, *Quantifying drivers of supply chain resilience in pediatric oncology medications*, at 5 (Sept. 2021) (<https://www.usp.org/sites/default/files/usp/document/supply-chain/pediatric-oncology-drugs-and-supply-chain.pdf>) (noting “drugs with higher manufacturing complexity are more vulnerable to supply disruptions”) (hereinafter “Vizient/USP/Angels for Change Report”). See also Minje Park, *The impact of pharmaceutical supply chain disruptions on buyers’ behavior, medication errors, and market share*, Boston University, Questrom School of Business Dissertation (2022) (<https://open.bu.edu/handle/2144/45042>) (hereinafter “Park Dissertation, Boston University”) (finding “generic injectable drugs are particularly vulnerable to shortages due to their low-profit margins, complex manufacturing processes, high market concentrations, and heavy reliance on overseas suppliers”).

<sup>3</sup> *National drug stores limit sale of children’s medicine amid shortages: What to know*, Today (Dec. 22, 2022); *Why we (still) can’t find any children’s Tylenol*, Axios (Jan. 5, 2023).



Throughout the past few decades, drug manufacturers have gradually shifted facilities overseas as foreign governments have offered tax incentives, fewer regulations, and other financial and logistical incentives.<sup>4</sup> While innovations in technology and transportation have resulted in a globalized pharmaceutical supply chain with increased efficiencies, such developments also pose increased risks, such as cybersecurity threats, regulatory challenges, and an overreliance on foreign sources.<sup>5</sup>

According to the American Society of Health-System Pharmacists (ASHP), which collects the most robust data on drug shortages, a drug remains in shortage for an average of nearly 1.5 years (537 days).<sup>6</sup> However, certain therapeutic categories may experience shortages for longer periods of time. For example, hormonal agents, which can help slow the onset of certain health conditions, have an average shortage duration of 1201 days; local anesthetics, 878 days; chemotherapy agents, 621 days; and cardiology agents, 618 days.<sup>7</sup> Over fifteen basic critical care drugs—the majority of which are injectable products—have remained in shortage for over a decade.<sup>8</sup> See Figure 2.

**Figure 2. Drug Products in Shortage for Over a Decade<sup>9</sup>**

Drug Product	Therapeutic Category	Reason for Shortage	First Notified	Date Resolved	Approx. Duration
Acetylcysteine inhalation solution	Respiratory	Manufacturing delays	2011	Ongoing	11 ½ years
Ampicillin Sulbactam	Antimicrobial	Raw material	2011	Ongoing	11 years
Atropine	Autonomic	Production delays	2009	Ongoing	13 ½ years
Bupivacaine plain	Local anesthetic	Unknown*	2011	Ongoing	11 years
Cefotaxime injection	Antimicrobial	Increased demand	2012	Ongoing	10 years
Ceftazidime	Antimicrobial	Manufacturing delays	2011	Ongoing	11 years
Clindamycin Injection	Antimicrobial	Manufacturing delays	2012	Ongoing	10 years
Dexamethasone sodium phosphate	Hormonal	Increased demand	2011	Ongoing	11 ½ years
Diltiazem injection	Cardiology	Unknown*	2010	Ongoing	12 ½ years
Doxorubicin	Chemotherapy	Manufacturing delays	2010	Ongoing	12 ½ years
Ketorolac injection	Central Nervous Sys.	Unknown	2009	Ongoing	13 years
Leucovorin injection	Chemotherapy	Manufacturing delays	2010	Ongoing	12 ½ years
Lidocaine injection plain**	Local anesthetic	Increased demand	2011	Ongoing	11 years
Morphine Injection	Central Nervous Sys.	Manufacturing delays	2010	Ongoing	12 years
Multivitamin injection (adult)	Vitamins	Manufacturing delays	2009	Ongoing	13 years
Vancomycin injection	Antimicrobial	Unknown*	2009	Ongoing	14 years
Vecuronium	Central Nervous Sys.	Manufacturing delays	2008	Ongoing	14 years

\*While manufacturers are required to report the reason for an interruption or discontinuance in manufacturing to the FDA, the agency is not required to make this information public.

\*\*Formerly listed as just 2% and includes mix in dextrose.

<sup>4</sup> White House, *Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017*, at 9 (June 2021) (hereinafter “White House 100-Day Supply Chain Review”).

<sup>5</sup> See Food and Drug Administration, *Pathway to Global Product Safety and Quality*, at 116 (July 2021); National Academies of Sciences, Engineering, and Medicine, *Building Resilience into the Nation’s Medical Product Supply Chains* (Mar. 2022) (hereinafter “NASEM Supply Chain Report”).

<sup>6</sup> Dr. Erin Fox Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Aug. 24, 2022).

<sup>7</sup> *Id.*; see also Mayo Clinic, *Hormone therapy: Is it right for you?* (Dec. 6, 2022) (<https://www.mayoclinic.org/diseases-conditions/menopause/in-depth/hormone-therapy/art-20046372>).

<sup>8</sup> *Id.* at 9.

<sup>9</sup> Dr. Erin Fox Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Aug. 24, 2022).

Of these products, nearly one third are antimicrobial agents, such as antibiotics, used to prevent and treat bacterial infections.<sup>10</sup> In 2020, the White House directed the FDA to develop a list of “essential medicines, medical countermeasures, and critical inputs” that are “medically necessary to have available at all times.”<sup>11</sup> The Essential Medicines list that the FDA created in response to this directive includes drugs that, according to FDA, are most needed for patients in U.S. acute care medical facilities, which specialize in short-term treatment for severe injuries or illnesses, and urgent medical conditions.<sup>12</sup> Nearly half of the antimicrobial agents listed on the FDA’s Essential Medicines list created in response to this directive, “have no domestic API manufacturing.”<sup>13</sup>

The Department of Defense (DOD) has acknowledged that it is “wholly dependent” on the commercial market for pharmaceutical products to ensure the “health, safety, and wellbeing of DOD personnel.”<sup>14</sup> As Christopher Priest, then Acting Deputy Assistant Director for Health Care Operations and Tricare for the Defense Health Agency, stated in testimony before the U.S.-China Economic and Security Review Commission in 2019, “[t]he national security risks of increased Chinese dominance of the global API market cannot be overstated . . . [s]hould China decide to limit or restrict the delivery of APIs to the United States, it would have a debilitating effect on U.S. domestic production and could result in severe shortages of pharmaceuticals for both domestic and military uses.”<sup>15</sup> A 2021 Department of Homeland Security (DHS) Key Threats Assessment found that medical products “sourced from abroad or that depend on global supply chains will remain especially vulnerable to disruptions due to sustained demand, foreign government actions to secure supplies of such goods for their country’s use, and the length of time required to reconstitute these production capabilities elsewhere.”<sup>16</sup>

In a briefing with hospital pharmacists organized by the American Hospital Association, Holly Bones, System Director of Pharmacy Procurement and Formulary Services for Geisinger Health in Pennsylvania, told Majority Committee staff that “historically, shortages impacted low utilization and hard to come by items where there was only one manufacturer. Now, we are seeing shortages in products like lidocaine, neuromuscular blockers, sodium chloride, and sterile water where there are multiple manufacturers but the product is completely unavailable.”<sup>17</sup> Dr. Erin Fox, Associate Chief Pharmacy Officer at the University of Utah, leads the collection of drug shortage data for ASHP. Dr.

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<sup>10</sup> *Id.*

<sup>11</sup> Food and Drug Administration, FDA Publishes List of Essential Medicines, Medical Countermeasures, Critical Inputs Required by Executive Order (<https://www.fda.gov/news-events/press-announcements/fda-publishes-list-essential-medicines-medical-countermeasures-critical-inputs-required-executive>) (accessed Mar. 16, 2023).

<sup>12</sup> Food and Drug Administration Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023) (noting FDA’s Essential Medicines list does not include “every life-supporting or life-sustaining drug”).

<sup>13</sup> Administration for Strategic Preparedness and Response, *Supply Chain/Industrial Analysis for Pharmaceuticals*, at 6 (undated) (hereinafter “ASPR Supply Chain and Industrial Analysis Report”) (on file with Committee).

<sup>14</sup> Christopher Priest, Principal Deputy, Deputy Assistant Director of Healthcare Operations at the Defense Health Agency, Remarks as Prepared for Delivery at the U.S.-China Economic and Security Review Commission, *Hearing Exploring the Growing U.S. Reliance on China’s Biotech and Pharmaceutical Products* (Jul. 31, 2019).

<sup>15</sup> *Id.*

<sup>16</sup> Department of Homeland Security, Office of Intelligence and Analysis, *Key Threats to the Homeland Through 2021 (IA-44764-20)*, at 11 (Oct. 2020) (on file with Committee).

<sup>17</sup> American Hospital Association, Briefing with Committee on Homeland Security and Governmental Affairs Staff (Sept. 8, 2022) (hereinafter “American Hospital Association Briefing”).

Fox told the Majority Committee staff that “shortages are lasting longer and there is still a high baseline number of shortages that have not improved.” She provided the example of lidocaine injection, a local anesthetic which was first approved in 1976 and has remained in shortage for over a decade.<sup>18</sup> Lidocaine injections have low profit margins (generally costing less than 10 cents per unit) and high manufacturing complexities (requiring a sterile environment).<sup>19</sup> While 39 percent of the lidocaine product marketed in the U.S. in 2022 is manufactured domestically, there are no known domestic API suppliers registered with the FDA.<sup>20</sup>

## II. Underlying Causes Remain the Same as in 2019

The underlying causes of drug shortages have generally not changed since Senator Peters’ first report in 2019, which examined the central causes of drug shortages.<sup>21</sup> These primarily include economic drivers, quality issues, overreliance on foreign sources, increased demand, and logistical and regulatory challenges. The FDA’s 2019 report, *Drug Shortages: Root Causes and Potential Solutions*, drew many of the same conclusions about the causes of drug shortages.<sup>22</sup> Many of the causes are interrelated. While this section discusses the underlying causes of drug shortages throughout the years, emerging threats, including future biological threats or natural disasters as well as the risk of cybersecurity attacks, are also important concerns that could impact future shortage threats. For example, the healthcare supply chain industry is estimated to be at risk of experiencing “a 30 percent increase in cyberattacks each year until 2025.”<sup>23</sup>

As part of the Committee’s analysis, Majority staff received a briefing from U.S. Pharmacopeia (USP), a non-profit private entity founded in 1820 that publishes standards for drug substances, drug products, and excipients recognized under U.S law.<sup>24</sup> USP’s analysis of actual drug shortages recorded by the FDA and ASHP assessed over 200 factors potentially contributing to drug shortages and

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<sup>18</sup> Erin Fox, Associate Chief Pharmacy Officer of Shared Services and Adjunct Professor, College of Pharmacy, University of Utah, Interview with Senate Committee on Homeland Security and Governmental Affairs (Aug. 23, 2023) (hereinafter “Interview with Erin Fox”).

<sup>19</sup> Drugs.com, Lidocaine Prices, Coupons and Patient Assistant Programs (<https://www.drugs.com/price-guide/lidocaine>) (accessed Mar. 6, 2023); see also U.S. Pharmacopeia Briefing with Committee on Homeland Security and Governmental Affairs Staff (March 2, 2023) (hereinafter “USP Briefing”). Throughout this report, the Majority Committee staff cites to the Average Wholesale Price (AWP) and notes that this price may be different depending on a number of factors, many of which are explained in the Committee’s 2019 report, see Minority Staff, Senate Committee on Homeland Security and Governmental Affairs, *A Price Too High: Cost, Supply, and Security Threats to Affordable Prescription Drugs* (Dec. 2019) (hereinafter “HSGAC Minority Staff Report, *A Price Too High*”).

<sup>20</sup> USP Briefing.

<sup>21</sup> HSGAC Minority Staff Report, *A Price Too High*.

<sup>22</sup> Food and Drug Administration, *Drug Shortages: Root Causes and Potential Solutions* (updated Feb. 21, 2020) (hereinafter “FDA Drug Shortages Report”). In addition to the numerous economic and visibility concerns, health care supply chain companies noted labor shortages, rising transportation and materials costs, fulfillment delays and finished goods shortages as key challenges. See, Ernst and Young, *How the US biopharmaceutical and medical product supply chain adapted to disruptions – and plans to build strategies for the future: Report prepared for the Healthcare Distribution Alliance (HDA) Research Foundation*, at 9-10 (Dec. 2022) (hereinafter “EY Report for Healthcare Distribution Alliance”) (noting 78 percent of healthcare providers surveyed stated labor shortages were the “most impactful” and shipping costs rose by more than 250 percent between January 2021-January 2022, with a 22 percent increase in trucking costs”).

<sup>23</sup> EY Report for Healthcare Distribution Alliance, at 7.

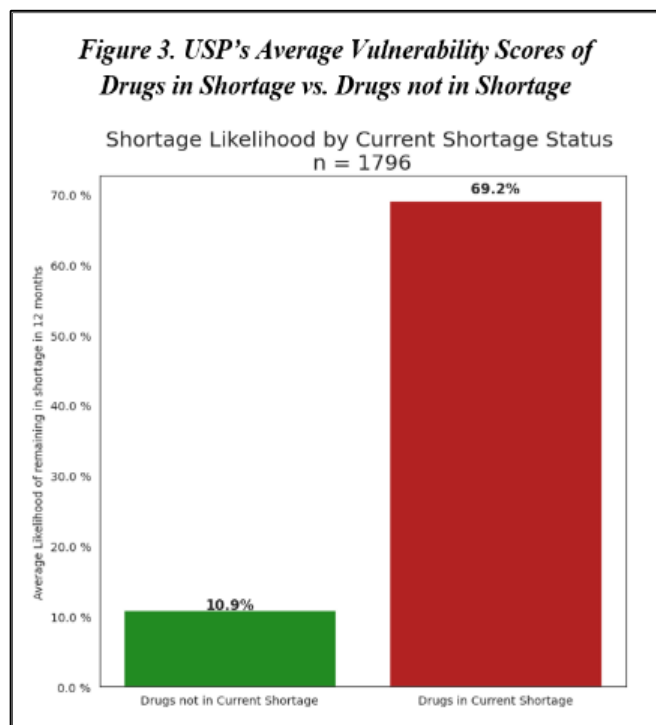
<sup>24</sup> USP Briefing.

identified at least four key factors as driving shortages: low manufacturer profit margins, quality issues, geographic concentration, and manufacturing complexities. USP assigned vulnerability scores to drugs, based on historic patterns that predict risk of a future drug shortage. As shown in Figure 3, USP assessed that drugs in shortage as of January 2023 had an average vulnerability score of 69.2 percent, meaning these drugs exhibited many of the key shortage factors (e.g. low profit margins, quality issues, etc.). In comparison, drugs that were not currently in shortage, had a vulnerability score of only 10.9 percent.<sup>25</sup>

### A. Economic Drivers

As discussed in detail below, IV saline, sterile water, propofol, and ciprofloxacin are all sterile injectable drugs that cost less than 50 cents per unit, but involve complex manufacturing processes. Without these products, healthcare providers would not be able to safely administer needed medications, put patients to sleep before surgeries, or treat life-threatening bacterial infections. Despite their critical importance, these drugs—and over 200 other life-supporting or life-sustaining drugs—are all currently in shortage, according to ASHP.<sup>26</sup>

Drug shortages predominately affect older generic drug products. Generic drugs account for approximately 90 percent of drugs sold throughout the U.S., but only represent 18 percent of all drug costs.<sup>27</sup> By comparison, the average cost of unbranded generic drug prices in the U.S. are 16 percent lower than other countries. Brand name drugs, however, are 344 percent more expensive in the U.S. than abroad.<sup>28</sup> The Association for Accessible Medicines (AAM), which represents generic drug manufacturers, told Majority Committee staff that generic drug prices have generally fallen throughout the past decade.<sup>29</sup> According to the FDA, of the drugs that went into shortage between 2013 and 2017,



<sup>25</sup> *Id.*; see also USP, *USP Medicine Supply Map Insights: Report to the HSGAC* (Mar. 2, 2023) (on file with Committee) (hereinafter “USP Medicine Supply Map Presentation”).

<sup>26</sup> ASHP Drug Shortages Website (accessed Mar. 19, 2023).

<sup>27</sup> Association for Accessible Medicines, *The U.S. Generic and Biosimilar Medicines Savings Report* (Oct. 2021) (<https://accessiblemeds.org/resources/blog/2021-savings-report>).

<sup>28</sup> Rand Corporation, *International Prescription Drug Price Comparisons: Current Empirical Estimates and Comparisons with Previous Studies* (2021) ([https://www.rand.org/content/dam/rand/pubs/research\\_reports/RR2900/RR2956/RAND\\_RR2956.pdf](https://www.rand.org/content/dam/rand/pubs/research_reports/RR2900/RR2956/RAND_RR2956.pdf)); see also ASPR Supply Chain and Industrial Analysis Report, at 7.

<sup>29</sup> Association for Accessible Medicines, Interview with Senate Committee on Homeland Security and Governmental Affairs (Jan. 31, 2023) (hereinafter “Interview with Association for Accessible Medicines”); Statista, Profit margin for generics manufacturers worldwide from FY 2016 to FY 2019 (<https://www.statista.com/statistics/1248196/profit-margin-for-generics-manufacturers-worldwide/>) (accessed Mar. 16,

67 percent were generic products with a median price of \$8.73 and approximately 35 years since the product was first approved.<sup>30</sup>

## 1. Lack of Incentives and Market Exits

The economics of generic drug manufacturing, including the complex manufacturing process, have resulted in increased barriers for manufacturers to both enter and remain in the market.<sup>31</sup> Between 2004 and 2016, 40 percent of generic drug markets were supplied by one manufacturer and the median number of manufacturers in each drug market was two.<sup>32</sup> The FDA’s 2019 report, *Drug Shortages: Root Causes and Potential Solutions*, identified “a lack of incentives for manufacturers to produce less profitable drugs” as a key cause of drug shortages.<sup>33</sup> Vizient, a Group Purchasing Organization, told the Majority Committee staff that of the medications currently listed on their Essential Medications List (approximately 80 percent of which are generic) that identifies medications considered essential from a hospital and health system perspective, over half were approved before 1990, and approximately 30 percent were approved before 1980.<sup>34</sup>

In an interview with Majority Committee staff, Dr. Yoram Unguru, a pediatric hematologist/oncologist, said “the biggest issue” is the limited number of manufacturers, noting “with the exception of nelarabine, none of [the available children’s oncology drugs] are new drugs—they have been around for decades and companies do not get a lot of return on their investment.” Dr. Unguru explained, “childhood cancer is a rare disease and it is difficult to get enough manufacturers that want to make these products.”<sup>35</sup> With few incentives to enter or remain in the market for a narrow but critical set of generic drugs, manufacturers of these products often decide to leave the market, and few if any others decide to enter, which can lead to shortages and have lingering effects on a product’s availability over time.<sup>36</sup> The case studies below demonstrate the impact of limited suppliers and manufacturers exiting the marketplace on a lifesaving drug product.

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2023); Association for Accessible Medicines, IQVIA: US Pharmaceutical Trends, Issues and Outlook [AAM] (Feb. 16, 2023) (on file with Committee).

<sup>30</sup> FDA Drug Shortages Report, at 5.

<sup>31</sup> See FDA Drug Shortages Report, at 21; White House 100-Day Supply Chain Review, at 214.

<sup>32</sup> Ernst R. Berndt, et al., *The Landscape of US Generic Prescription Drug Markets, 2004-2016*, National Bureau of Economic Research (July 2017).

<sup>33</sup> FDA Drug Shortages Report, at 21.

<sup>34</sup> Vizient, Inc., Interview with Senate Committee on Homeland Security and Governmental Affairs (Sept. 8, 2022) (hereinafter “Interview with Vizient”).

<sup>35</sup> Dr. Yoram Unguru, Pediatric Hematologist/Oncologist at The Herman and Walter Samuelson Children’s Hospital at Sinai and Core Faculty Member at The Johns Hopkins Berman Institute of Bioethics, Chairman of Sinai Hospital Ethics Committee, and Associate Professor, The Johns Hopkins School of Medicine, Interview with Senate Committee on Homeland Security and Governmental Affairs (Jan. 30, 2023) (hereinafter “Interview with Dr. Yoram Unguru”).

<sup>36</sup> See Food and Drug Administration, *Report to Congress: Drug Shortages for Calendar Year 2020*, at 2; see also FDA Drug Shortages Report.

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## VINCRIStINE

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**What is it?** Vincristine is a critical adult and pediatric chemotherapy drug used to treat various types of cancer with no alternative treatment. The FDA first approved vincristine in 1963 and generic manufacturers began filing for approval to make the drug in 1987.<sup>37</sup>

**What is the concern?** Vincristine continues to go in and out of shortage, which has resulted in cancer patients not being able to receive needed treatments.<sup>38</sup> Of the nine companies that received FDA approval to market vincristine (including the branded manufacturer), seven have discontinued the product.<sup>39</sup> There are currently two approved manufacturers, Hospira and Teva, but only Hospira is actively making vincristine for the U.S. market.<sup>40</sup> Vincristine currently costs anywhere from \$12 to \$26 per unit.<sup>41</sup> According to USP, Vincristine currently has a vulnerability score of 53.2 percent based on low profit margins, high manufacturing complexities, and geographic concentration.<sup>42</sup> Other complicating manufacturing factors include that because Vincristine’s active ingredient is cytotoxic and hazardous, it is expensive to manufacture and requires a dedicated facility.<sup>43</sup> Additionally, there is only one “chemical manufacturing route” to create Vincristine, which leaves no alternatives in the event the active pharmaceutical ingredients and key starting materials are unavailable.<sup>44</sup>

In August 2022, Teva announced it would discontinue its vincristine product (Vincasar PFS) after it closed its Irvine, California manufacturing site, but said it would transfer production of its vincristine to another facility.<sup>45</sup> Teva’s Irvine, California manufacturing site had struggled with quality control problems and by October 2021, Teva recalled over 2.5 million vials of the drug, including cancer treatments that may have been contaminated with mold due to water leaks.<sup>46</sup> Teva told the Majority Committee staff it exhausted the last of its Vincasar PFS inventory in February 2023.<sup>47</sup> Teva has not started actively marketing vincristine from its new site. A lapse in production could lead to another shortage, resulting in a single supplier responsible for the entire market, which happened four years ago in 2019.

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<sup>37</sup> See Food and Drug Administration, *Drugs@FDA: FDA-Approved Drugs* (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>) (accessed Mar. 1, 2023).

<sup>38</sup> HSGAC Minority Staff Report, *A Price Too High*, at 34.; *How one mom headed off a drug shortages*, CNN (Dec. 29, 2022) (<https://www.cnn.com/2022/12/29/health/drug-shortage-mom-angels-for-change/index.html>).

<sup>39</sup> Food and Drug Administration, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (<https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>) (accessed Mar. 1, 2023).

<sup>40</sup> National Library of Medicine, *DailyMed, Vincristine* (<https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=vincristine&pagesize=20&page=1>) (accessed Mar. 1, 2023); Food and Drug Administration, *Drug Shortages Website* ([https://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_ActiveIngredientDetails.cfm?AI=Vincristine%20Sulfate%20\(Vincasar%20PFS\)%20Injection&st=d](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Vincristine%20Sulfate%20(Vincasar%20PFS)%20Injection&st=d)) (accessed Mar. 14, 2023) (reporting Teva’s discontinuation of Vincasar PFS and noting “product is available with an expected supply duration until AUG 2022. No future production expected for an extended period”).

<sup>41</sup> *Drugs.com, Vincristine Prices, Coupons and Patient Assistance Programs* (<https://www.drugs.com/price-guide/vincristine>) (accessed Mar. 1, 2023). The Majority Committee staff cites to the Average Wholesale Price (AWP) and notes that this price may be different depending on a number of factors, many of which are explained in the Committee’s 2019 report, see HSGAC Minority Staff Report, *A Price Too High*.

<sup>42</sup> USP Briefing and Medicine Supply Map Presentation.

<sup>43</sup> *Id.*

<sup>44</sup> USP Briefing.

<sup>45</sup> Food and Drug Administration, *FDA Drug Shortages* (<https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>) (accessed Mar. 1, 2023) (hereinafter “FDA Drug Shortages Website”).

<sup>46</sup> *Teva Recalls U.S.-Made Drugs Following Contamination Fears*, Bloomberg (Oct. 4, 2021) (<https://www.bloomberg.com/news/articles/2021-10-04/teva-recalls-u-s-made-drugs-following-contamination-fears>).

<sup>47</sup> Teva Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

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## BACILLUS CALMETTE-GUERIN (BCG)

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**What is it?** Bacillus Calmette-Guerin (BCG) live is an immunotherapy biologic drug used to treat bladder cancer.<sup>48</sup> The FDA first approved BCG live in 1976, and two manufacturers subsequently filed for approval to manufacture additional biologics beginning in 1989.<sup>49</sup> Since 2000, no additional manufacturers have entered the market. A 50 mg dose of BCG live may cost anywhere between \$180 and \$190.<sup>50</sup>

**What is the concern?** BCG live has been in shortage since 2019 due to an increase in “global demand” for the product.<sup>51</sup> In 2016, one of BCG’s two suppliers, Sanofi, decided to stop production of BCG after experiencing multiple production problems at their manufacturing facility in Canada.<sup>52</sup> Sanofi reported spending “considerable time and effort” to find another supplier, but “ultimately no party would commit to take on this product.” Beginning in 2019, Merck became the sole supplier of BCG for the U.S. market. As of mid-February 2023, “thousands of people” were unable to access full treatments of BCG.<sup>53</sup> Due to the shortage, Merck’s TICE BCG Live—the only product available in the U.S.—is currently on allocation, leaving many patients unable to access needed treatment.<sup>54</sup> In a recent survey of 20 academic medical centers conducted by the End Drug Shortages Alliance, all providers reported using at least one mitigation strategy, such as prescribing an alternate product or reducing a patient’s dose.<sup>55</sup> The shortage of BCG also extends to the BCG vaccine, which is used to prevent tuberculosis (TB), and could present challenges in countries where TB is still a public health concern.<sup>56</sup>

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<sup>48</sup> Cleveland Clinic, Bacillus Calmette-Guerin (BCG) Treatment (<https://my.clevelandclinic.org/health/treatments/17908-bacillus-calmette-guerin-bcg-treatment>) (accessed Mar. 1, 2023).

<sup>49</sup> Food and Drug Administration, Purple Book Database of Licensed Biological Products (<https://purplebooksearch.fda.gov/results?query=BCG%20Live&title=Tice%20Bcg>) (accessed Mar. 1, 2023).

<sup>50</sup> Healio, *BCG: a real-world example of health care rationing* (Aug. 9, 2019) (<https://www.healio.com/news/hematology-oncology/20190805/bcg-a-realworld-example-of-health-care-rationing>) (noting “BCG Live commands an average wholesale price of about \$180 to \$190 per 1mL/50-mg vial in the United States”).

<sup>51</sup> Food and Drug Administration, CBER-Regulated Products: Current Shortages (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages>) (accessed Mar. 1, 2023); American Society of Health-System Pharmacists, Current Drug Shortages (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=519&loginreturnUrl=SSOCheckOnly>) (accessed Mar. 1, 2023).

<sup>52</sup> *Sanofi shuts down bladder cancer drug production: inevitable drug shortage to harm patients* (Nov. 17, 2016) (<https://www.forbes.com/sites/benjamindavies/2016/11/17/sanofi-shuts-down-bladder-cancer-drug-production-inevitable-drug-shortage-to-harm-patients/?sh=3675f199c132>); *Sanofi Pasteur abandons bladder cancer drug*, Biospace (Nov. 18, 2016) (<https://www.biospace.com/article/sanofi-pasteur-abandons-bladder-cancer-drug-/>); American Urological Association, *Announcement from Sanofi* (<https://www.auanet.org/documents/press-media/important-news/theracys-stakeholder-communication-111516.pdf>) (accessed Mar. 1, 2023). Sanofi told the Majority Committee staff it ceased production in mid-2017. See Sanofi Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 16, 2023).

<sup>53</sup> *Thousands can’t access a vital cancer drug treatment*, Becker’s Hospital Review (Feb. 16, 2023) (<https://www.beckershospitalreview.com/pharmacy/thousands-cant-access-a-vital-cancer-drug-treatment.html>); *Thousands of people can’t get full treatments of a lifesaving cancer drug*, CNN (Feb. 17, 2023) (<https://www.cnn.com/2023/02/15/health/cancer-drug-shortage-bcg/index.html>).

<sup>54</sup> Food and Drug Administration, CBER-Regulated Products: Current Shortages (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages>) (accessed Mar. 1, 2023); American Society of Health-System Pharmacists, Current Drug Shortages (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=519&loginreturnUrl=SSOCheckOnly>) (accessed Mar. 1, 2023).

<sup>55</sup> End Drug Shortages Alliance, *Implications of the National BCG Drug Shortages* (Feb. 2023) ([https://www.enddrugshortages.com/files/BCG\\_White\\_Paper.pdf](https://www.enddrugshortages.com/files/BCG_White_Paper.pdf)).

<sup>56</sup> Mary Van Beusekom, *Longtime drug shortage leads to substandard care for thousands of US bladder cancer patients*, University of Minnesota, Center for Infectious Disease Research and Policy Newsletter (Feb. 15, 2023) (<https://www.cidrap.umn.edu/resilient-drug-supply/longtime-drug-shortage-leads-substandard-care-thousands-us-bladder-cancer>).

According to the FDA, 25 percent of Center for Drug Evaluation and Research (CDER) products on the FDA’s Essential Medicines list have three or fewer finished dosage form manufacturers—the final step in the manufacturing process before packaging—and 10 percent have one finished dosage form manufacturer.<sup>57</sup> Of the Center for Biologics Evaluation and Research (CBER) regulated products on FDA’s Essential Medicines list, 53 have three or fewer finished dosage form manufacturers and 43 have only one finished dosage form manufacturer.<sup>58</sup> Nearly 40 percent of the products on the Essential Medicines list have three or fewer API manufacturers and approximately 10 percent have one API manufacturer. The FDA, however, is currently unable to assess the percentage of life-supporting and life-sustaining drugs that rely on each API supplier for several reasons, discussed further in Section IV, A.

## 2. Lack of Investment in Quality Systems

All manufacturers approved to market a drug product must adhere to the FDA’s current good manufacturing practices (cGMPs), which help ensure a product is “safe, effective, and of sufficient quality.”<sup>59</sup> While manufacturers must meet this baseline quality requirement, drug quality does not necessarily correlate with a manufacturer’s supply chain resilience. For example, both brand and generic manufacturers are required to adhere to the same level of product quality, but brand manufacturers often implement robust risk management plans and maintain redundant supply in the event of a potential manufacturing disruption or increase in demand.<sup>60</sup> The FDA found that between 2013 and 2017, over 60 percent of drugs that experienced shortages were because of quality issues.<sup>61</sup> A 2021 study by Vizient and U.S. Pharmacopeia reported that drug products manufactured at facilities with a greater number of manufacturing violations had a “statistically significant higher likelihood of a shortage event.”<sup>62</sup>

Oftentimes, generic drug manufacturers operate at full capacity and therefore are not able to adequately respond to manufacturing disruptions or increases in demand.<sup>63</sup> In addition, generic drug products often rely on a single production line for multiple weeks to increase efficiency, creating challenges if a line is contaminated or experiences a production problem that requires the manufacturer

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<sup>57</sup> Food and Drug Administration, *Response to Committee Questions* (received Sept. 21, 2022) (on file with Committee) (hereinafter “FDA Response”).

<sup>58</sup> *Id.*

<sup>59</sup> Food and Drug Administration, *Center for Drug Evaluation and Research, An Office of Pharmaceutical Quality (OPQ) White Paper: Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals*, at 2 (hereinafter “FDA Quality Management Maturity White Paper”).

<sup>60</sup> White House 100-Day Supply Chain Review, at 217 (finding brand name manufacturers implement risk management plans as a standard practice, which may include alternate manufacturing sites, inventory reserves, a range of global suppliers, and logistics planning).

<sup>61</sup> FDA Drug Shortages Report, at 111.

<sup>62</sup> Vizient/USP/Angels for Change Report, at 6.

<sup>63</sup> ASPR, Advanced Regenerative Manufacturing Institute (ARMI), and the Next Foundry for American Biotechnology (NextFAB), *Essential Medicines Supply Chain and Manufacturing Resilience Assessment*, at 19 (May 2022) (noting generic manufacturers “must operate at close to full capacity to be financially viable,” limiting the ability to surge capacity during shortages or increases in demand) (hereinafter (“ASPR, ARMI, and NextFAB Report”). See also Premier, *Inscript: Drug Shortages: Pervasive Challenges, Proven Solutions*, at 7 (Feb. 2022) (available at <https://offers.premierinc.com/DrugShortagesThesis-LandingPage.html>) (hereinafter “Premier Drug Shortages Report”).



to shut down the line to remedy the problem, which could take “weeks to months” to fix.<sup>64</sup> Supply chain disruptions have been directly linked to a loss of market share. According to a 2022 dissertation study by Dr. Minje Park, generic drug products lose 10.8 percent of their market share during a supply chain disruption and “do not fully recover” from this loss even after recovering from the supply chain disruption.<sup>65</sup> Specifically, Dr. Park’s study found that approximately 30 percent of products that experienced a manufacturing disruption could not recover their pre-disruption market within a year. Below is an example of how issues with quality have impacted manufacturing and can ultimately lead to drug shortages.

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## PROPOFOL

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**What is it?** Propofol emulsion injection (“propofol”), a sterile injectable sedative often given to patients to put them to sleep before surgeries, has gone in and out of shortage over the years. Propofol costs anywhere from 12 cents to 35 cents per unit.<sup>66</sup>

**What is the concern?** Propofol is currently in shortage, according to ASHP.<sup>67</sup> Throughout the past fifteen years, manufacturers of propofol have experienced quality problems (which have led to product recalls), manufacturing delays, market exits, and unprecedented demand during the COVID-19 pandemic. According to USP, propofol injection currently has a vulnerability score of 89.5 due to its low profit margins and manufacturing complexities.<sup>68</sup>

As one example, in 2009 the FDA issued a warning letter to Teva due to quality problems at their Irvine, California manufacturing facility.<sup>69</sup> Teva did not resume production of the product until 2011.<sup>70</sup> Teva told the Majority Committee Staff that in 2010, it transferred propofol manufacturing from its Irvine, California site to Corden Pharma in Italy. According to Teva, it continued to supply the market with propofol manufactured by Corden Pharma in Italy until the COVID-19 pandemic when Corden Pharma “either could not supply or would not supply Teva with the product.”<sup>71</sup> In March 2022, Teva announced it would stop supplying propofol.<sup>72</sup> In the summer of 2022, Hospira issued a voluntary recall for one lot of propofol after observing particulates in two vials.<sup>73</sup> A combination of a market exits, manufacturing

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<sup>64</sup> ASPR, ARMI, and NextFAB Report, at 16, 18.

<sup>65</sup> Park Dissertation, Boston University at 5, 90.

<sup>66</sup> Drugs.com, Propofol Prices, Coupons and Patient Assistant Programs (<https://www.drugs.com/price-guide/propofol>) (accessed Mar. 16, 2023). The Majority Committee staff cites to the Average Wholesale Price (AWP) and notes that this price may be different depending on a number of factors, many of which are explained in the Committee’s 2019 report, see HSGAC Minority Staff Report, *A Price Too High*.

<sup>67</sup> American Society of Health-System Pharmacists, Current Drug Shortages (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=651>) (accessed Mar. 6, 2023) (hereinafter “ASHP Drug Shortages Website”).

<sup>68</sup> USP Briefing and Presentation.

<sup>69</sup> Letter from FDA to Teva Parenteral Medicines, Inc., *Warning Letter* (Dec. 11, 2009); *Update 1-US FDA warns Teva on California plant problems*, Reuters (Apr. 27, 2010) (<https://www.reuters.com/article/teva-fda/update-1-us-fda-warns-teva-on-california-plant-problems-idINN2711731020100427>).

<sup>70</sup> *Teva resumed production at Irvine, California facility*, Outsourcing-Pharma (Apr. 26, 2011) (<https://www.outsourcing-pharma.com/Article/2011/04/27/Teva-resumes-production-at-Irvine-CA-facility>).

<sup>71</sup> Teva Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

<sup>72</sup> FDA Drug Shortages Website ([https://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_ActiveIngredientDetails.cfm?AI=Propofol%20Injectable%20Emulsion&st=d](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Propofol%20Injectable%20Emulsion&st=d)) (accessed Mar. 19, 2023). Teva told the Majority Committee staff that it finished the last of its remaining propofol in December 2022 and discontinued the product in January 2023. See Teva Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 20, 2023).

<sup>73</sup> Food and Drug Administration, Hospira Issues a Voluntary Nationwide Recall for One Lot of Propofol Injectable Emulsion (Containing Benzyl Alcohol), Due To The Potential Presence of Visible Particulates (Jul. 13, 2022 and Aug. 22, 2022).

delays, and a continued increase in demand has again resulted in the product being placed on ASHP’s drug shortage list.<sup>74</sup> While ASHP’s drug shortage list includes propofol, the FDA’s drug shortage website does not currently list this product as being in shortage.

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Due to the COVID-19 pandemic, in March 2020, the FDA temporarily suspended routine in-person surveillance inspections and relied on manufacturers to provide records upon request, among other alternative inspectional tools to evaluate compliance until resuming routine surveillance inspections in February 2022.<sup>75</sup> The FDA’s surveillance inspections are important for identifying and ensuring manufacturers remedy problems early on before they worsen. Dr. Stephen Schondelmeyer, a professor of pharmaceutical economics at the University of Minnesota, expressed concern about insufficient FDA monitoring of manufacturers and what he called, “the Boeing Effect,” referencing the Federal Aviation Administration (FAA)’s reliance on the airline industry to comply with standards and voluntary reporting requirements. He explained, “when a regulatory agency counts on voluntary compliance and does not adequately monitor industry, quality problems will eventually arise.”<sup>76</sup>

Despite its temporary suspension of routine in-person surveillance inspections, the FDA continued to identify a number of quality problems that led the FDA to request that companies voluntarily recall their products. Because the FDA does not have mandatory recall authority for all drug products, the agency is unable to require a company to recall most drugs. Therefore, recalls must be voluntary with respect to most drug products, even though the FDA has the authority to require product recalls for food, biological products (e.g. vaccines), and controlled substances.<sup>77</sup> As one example, when a multitude of quality issues arose with toxic hand sanitizer on the market during the spring and summer of 2020, the FDA requested that certain manufacturers voluntarily recall their product. While some complied, some did not, and others did not act immediately. The FDA added companies to import alerts for products based on adulteration and other violations. The FDA also established a public list of hand sanitizers that consumers should not use, which included instances where FDA recommended that companies recall their products because they were unable to mandate recalls.<sup>78</sup>

The FDA has repeatedly advocated for manufacturers to invest in systems that maintain “consistent, reliable, and robust” processes and go beyond the baseline manufacturing requirements to achieve a state of “quality management maturity,” which would help differentiate a generic drug

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<sup>74</sup> ASHP Drug Shortages Website (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=651>) (accessed Mar. 19, 2023).

<sup>75</sup> Food and Drug Administration, *COVID-19 Update: FDA Outlines Inspection and Assessment Activities During Pandemic, Roadmap for Future State of Operations* (May 5, 2021) (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-outlines-inspection-and-assessment-activities-during-pandemic>).

<sup>76</sup> Dr. Stephen Schondelmeyer, Professor of Pharmaceutical Economics, College of Pharmacy, University of Minnesota, Interview with Senate Committee on Homeland Security and Governmental Affairs (Aug. 22, 2022) (hereinafter “Interview with Dr. Stephen Schondelmeyer”).

<sup>77</sup> Food and Drug Administration, Center for Drug Evaluation and Research, *Drug Safety Priorities 2021*, at 10-11 (Jan. 2022) (<https://www.fda.gov/media/155795/download>).

<sup>78</sup> Food and Drug Administration, FDA updates on hand sanitizers consumers should not use (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use>) (accessed Mar. 16, 2023).

product by a metric other than price.<sup>79</sup> To achieve this, the FDA has proposed a Quality Management Maturity (QMM) rating system for manufacturing facilities.<sup>80</sup> According to the FDA, the implementation of a QMM rating system would help “inform regulators and purchasers about the performance and robustness of drug manufacturing facilities and give consumers increased confidence in the availability of drugs.”<sup>81</sup> After conducting two pilot programs on the initiative, the FDA’s Advisory Committee voted unanimously in favor of establishing a QMM program.<sup>82</sup> While the FDA is hopeful this initiative will reduce potential supply chain vulnerabilities by investing in resilient manufacturing practices, Premier expressed concern that “a rating system approach may generate unintended downstream consequences that exacerbate drug shortages and create new operational challenges for U.S. health care providers.”<sup>83</sup>

### 3. Market Consolidation and Contracting Practices

Consolidation of various sectors of the health care systems have led to unintended consequences by pushing manufacturers out of the market.<sup>84</sup> As of 2018, the four largest Group Purchasing Organizations (GPOs) accounted for 90 percent of the medical supply market.<sup>85</sup> According to the FDA, “GPOs account for over \$100 billion of the drugs purchased in this country in a given year.”<sup>86</sup> The distributor market is also heavily consolidated with three distributors representing approximately 80 percent of the market.<sup>87</sup>

For nearly a decade, government watchdogs, federal agencies, and researchers have raised concerns about the effect of contracting practices on drug shortages.<sup>88</sup> In a written response to questions from the Majority Committee staff, the Department of Homeland Security (DHS) told the Majority Committee staff, “concentration in the pharmaceutical distribution market drives negotiating power for intermediaries, resulting in lower retail costs to final consumers, but also in lower margins for manufacturers.”<sup>89</sup> The FDA and ASPR raised similar concerns suggesting that GPOs market

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<sup>79</sup> FDA Quality Management Maturity White Paper, at 3.

<sup>80</sup> Food and Drug Administration, Office of Pharmaceutical Quality, *2022 Annual Report*, at 3 (undated) (<https://www.fda.gov/media/165352/download>).

<sup>81</sup> *Id.*, at 3.

<sup>82</sup> *Id.*, at 4.

<sup>83</sup> Premier, Interview with Senate Committee on Homeland Security and Governmental Affairs (Sept. 16, 2022) (hereinafter “Interview with Premier”). Premier stated that “a quality rating system can unintentionally select winners and losers in an already-constrained environment – further increasing barriers to entry and discouraging competition.”

<sup>84</sup> See FDA Drug Shortages Report, at 49; White House 100-Day Supply Chain Review, at 226-227; ASPR, ARMI, and NextFAB Report, at 20.

<sup>85</sup> White House 100-Day Supply Chain Review, at 226. Currently, the top four GPOs with the most affiliated staffed beds are Vizient, Premier, Inc., HealthTrust Purchasing Group (HPG), and Premier-ASCEND. See Definitive Healthcare, *Top 10 GPOs by staffed beds* (Feb. 2023) (<https://www.definitivehc.com/blog/top-10-gpos-by-staffed-beds>).

<sup>86</sup> FDA Quality Management Maturity White Paper, at 9.

<sup>87</sup> Healthcare Distribution Alliance, Interview with Senate Committee on Homeland Security and Governmental Affairs (Feb. 1, 2023) (hereinafter “Interview with Healthcare Distribution Alliance”).

<sup>88</sup> Government Accountability Office, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability* (GAO-14-194) (Feb. 10, 2014); FDA Drug Shortages Report, at 7; White House 100-Day Supply Chain Review, at 226-227.

<sup>89</sup> Department of Homeland Security, *Response to Committee Questions* (received Aug. 23, 2022) (on file with Committee) (hereinafter “DHS Response”).

consolidation creates “unintended consequences,” such as race to the bottom pricing and limiting the number of suppliers available for hospitals to choose from.<sup>90</sup> Dr. Aaron Kesselheim, Director of the Program on Regulation, Therapeutics, and Law at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School, told Majority Committee staff that “while there are concerns that GPOs have driven down prices, a lot of agreements happen behind the scenes . . . and it would be good to have a better understanding of what role a GPO has,” cautioning, “we don’t want consolidated manufacturers taking advantage of a disparate buyer market.”<sup>91</sup>

A 2019 study by Conrad and Lutter found the more manufacturers that entered the market, the lower the cost of the drug. For example, the average price of a drug product with a single generic manufacturer was 39 percent lower than the branded product compared to the average price of a generic drug product with six or more manufacturers, which was 95 percent lower than the branded product.<sup>92</sup> The Majority Committee staff found that low drug costs correlated with shortages. Sixty percent of pediatric oncology drug products that cost less than \$10 were currently in shortage.<sup>93</sup> Sterile water, a product that should be readily available in every hospital and has been around for over four decades, costs anywhere from 1 to 26 cents.<sup>94</sup> It has been in shortage since November 2021, despite having at least six suppliers.<sup>95</sup> Premier, a Group Purchasing Organization (GPO), reported in 2022 that of the more than 400 drugs they had under contract that cost \$3 or less per vial, 42 percent were actively in shortage compared to only six percent of drugs that cost more than \$10 per vial.<sup>96</sup>

The Majority Committee staff spoke with GPOs and representatives of manufacturers and distributors. Manufacturers blamed GPOs’ and distributors contracting practices for driving prices down and eliminating manufacturers from the market, pointing to “low price clauses” and “most favored nation clauses” as problematic.<sup>97</sup> The GPOs interviewed by Majority Committee staff denied contributing to drug shortages and “race to the bottom prices.” Specifically, Vizient told the Majority Committee staff that “they place a different value on essential drugs and have mitigation strategies in place, including requiring information on sourcing, monitoring national fill rates daily, requiring redundant inventory to be stored in the U.S. and sharing clinical alternative best practices, to reduce drug shortages,” noting, “we put more weight around resiliency and redundancy particularly when it

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<sup>90</sup> ASPR, ARMI, and NextFAB Report, at 20; FDA Drug Shortages Report, at 6.

<sup>91</sup> Dr. Aaron Kesselheim, Director of the Program on Regulation, Therapeutics, and Law and practicing physician at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School, Interview with Senate Committee on Homeland Security and Governmental Affairs (Aug. 16, 2022) (hereinafter “Interview with Dr. Aaron Kesselheim”).

<sup>92</sup> Ryan Conrad and Randall Lutter, *Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices*, Food and Drug Administration (Dec. 2019).

<sup>93</sup> Vizient/USP/Angels for Change Report, at 4 (stating “injectables with lower prices have more vulnerable supply chains” and “noting 60 percent of pediatric oncology injectable drug products that cost less than \$10 per unit recently experienced a shortage”).

<sup>94</sup> Drugs.com, Sterile Water Prices, Coupons and Patient Assistant Programs (<https://www.drugs.com/price-guide/sterile-water>) (accessed Mar. 6, 2023).

<sup>95</sup> FDA Drug Shortages Website (noting five out of six suppliers reported increased demand as a reason for the shortage).

<sup>96</sup> Premier Drug Shortages Report, at 7 (finding “of the more than 400 contracted drugs that cost \$3 or less per vial, nearly 42 percent were in active shortage . . . In contrast, only 6 percent of drugs that cost more than \$10 per vial were in shortage”).

<sup>97</sup> Interview with Association for Accessible Medicines.

comes to critical drugs.”<sup>98</sup> Premier cited their analytics products designed to predict and prevent shortages, their investments in competitive new entrants, their drug shortage program that secures long-term supply with multi-year buying commitments, and “stringent contracting and vetting process” required of manufacturers. When contracting, Premier told the Majority Committee staff it collects data on manufacturing locations for both FDF and API and requires manufacturers to provide redundancy and contingency plans, which Premier aggregates to score supply chain resilience risk for each product before its members make contracting decisions.<sup>99</sup> The Healthcare Distribution Alliance (HDA) also denied that distributors engaged in harmful contracting practices that could impact drug shortages and noted they do not have any line of sight into the types of contracts their members negotiate.<sup>100</sup>

## **B. Concentrated Geographic Reliance and Insufficient Supply Chain Visibility**

Another primary driver of drug shortages is an overreliance on production from concentrated geographic regions, a lack of supply chain visibility into where and by whom critical drug products are manufactured, and the inability to accurately predict and proactively mitigate shortage risks. ASPR has described the current state of the pharmaceutical supply chain as “largely opaque,” noting “the majority of generic drugs are sourced from overseas,” predominately China and India.<sup>101</sup>

**Shifts Overseas.** Throughout the past three decades, the generic pharmaceutical market has consolidated and “increasingly outsourced its production to countries with lower labor and manufacturing costs in response to low profit margins.”<sup>102</sup> A combination of domestic tax law incentives beginning in 1976 and foreign government investments have also contributed to pharmaceutical manufacturers shifting production first to Puerto Rico and then overseas.<sup>103</sup> Foreign government investments, mainly from China and India, also heavily subsidized pharmaceutical manufacturing, offering lower costs, skilled workers, and a less stringent regulatory environment.<sup>104</sup> A 2011 FDA report estimated the cost of API manufacturing in India was 15 to 40 percent less than in the United States.<sup>105</sup> In addition, anticompetitive practices by China and others, such as dumping products on the market at a price well below production costs to gain control of the market share, has also resulted in an overreliance on foreign sources.<sup>106</sup>

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<sup>98</sup> Interview with Vizient.

<sup>99</sup> Interview with Premier; Letter from Premier to Commissioner Robert M. Califf, M.D., *Re: Solicitation for Public Comments on Risk Management Plans to Mitigate the Potential for Drug Shortages Draft Guidance [Docket Number FDA-2022-D-0277]* (Aug. 31, 2022).

<sup>100</sup> Interview with Healthcare Distribution Alliance.

<sup>101</sup> ASPR Supply Chain and Industrial Analysis Report, at 6.

<sup>102</sup> DHS Response; *see also* Department of Defense, Office of Inspector General, *Evaluation of the Department of Defense’s Mitigation of Foreign Suppliers in the Pharmaceutical Supply Chain* (DODIG-2021-126) (Sept. 20, 2021) (hereinafter “DOD IG Report”).

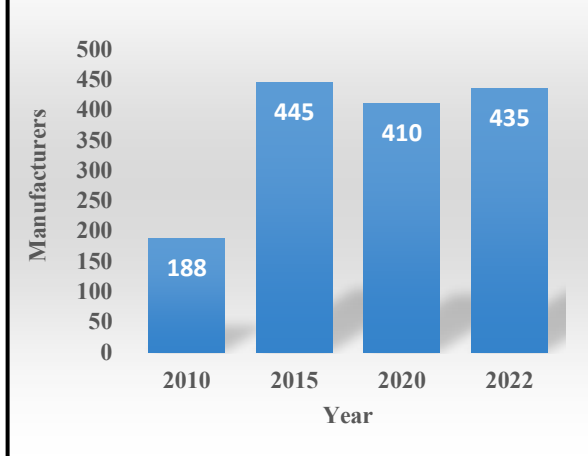
<sup>103</sup> ASPR, ARMI, and NextFAB Report, at 17; Tax Reform Act of 1976, Pub. L. No. 94-455.

<sup>104</sup> *See* White House 100-Day Supply Chain Review, at 213; *see also* International Society for Pharmaceutical Engineering, *Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients*, at 6 (Dec. 2020).

<sup>105</sup> Food and Drug Administration, Pathway to Global Product Safety and Quality, at 10 (July 7, 2011).

<sup>106</sup> DHS Response; ASPR, ARMI, and NextFAB Report, at 16.

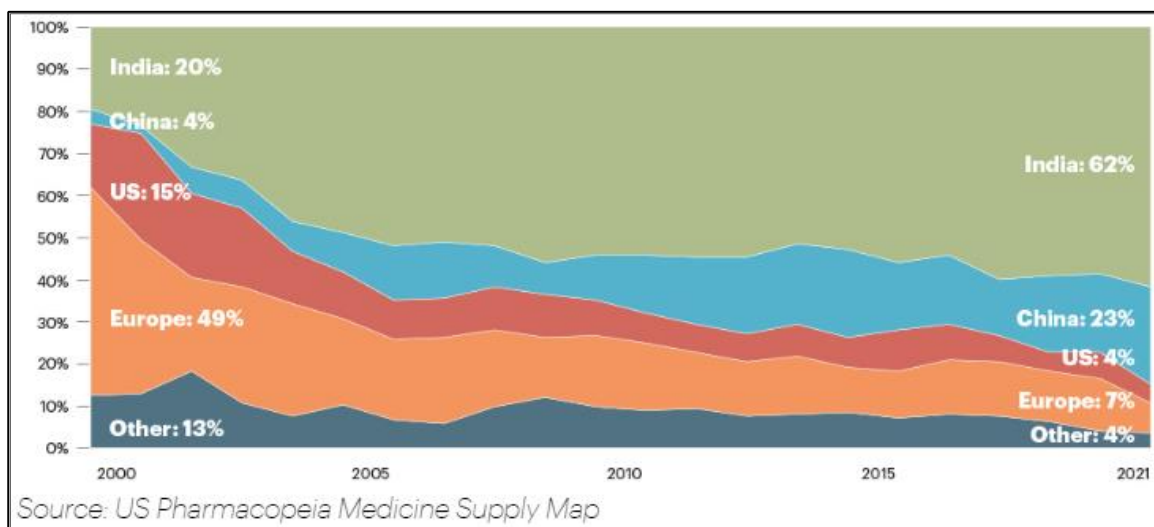
**Figure 4. Number of Chinese-based API manufacturers registered with the FDA for the U.S. market**



With these tactics, the U.S. has not been able to maintain robust domestic manufacturing capacity. The number of Chinese-based API manufacturers that registered with the FDA for the U.S. market between 2010 and 2015 more than doubled.<sup>107</sup> See Figure 4. By 2021, 87 percent of generic API manufacturing sites and 63 percent of generic finished dosage manufacturing sites were located overseas.<sup>108</sup> According to U.S. Pharmacopeia and as shown in Figure 5, the number of foreign API manufacturer drug master files (DMFs)—what new applicants may voluntarily submit to the FDA to show information about facilities, processes, and materials—has grown substantially since 2000. However, the number of domestic API manufacturer DMFs submitted to the

FDA that were still active in 2021 has decreased by 11 percent.<sup>109</sup> In a 2021 effort to map approximately 90 percent of active API DMFs submitted to the FDA, USP determined that India accounted for 48 percent, compared to 22 percent from Europe, 13 percent from China, and 10 percent from the U.S.<sup>110</sup> Ciprofloxacin, for example, is a critical antibiotic used to treat multiple bacterial infections, but there was only one known API manufacturing facility in the U.S. in 2023, compared to 20 in India and 6 in the EU.<sup>111</sup>

**Figure 5. Active API Drug Master Files submitted to the FDA by year of filing and country of manufacture**



<sup>107</sup> FDA Response.

<sup>108</sup> White House 100-Day Supply Chain Review, at 214.

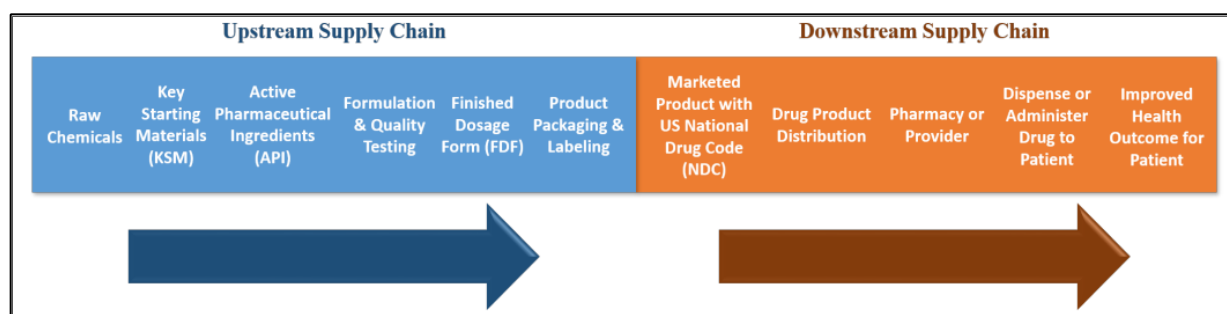
<sup>109</sup> U.S. Pharmacopeia, *Geographic concentration of pharmaceutical manufacturing: USP Medicine Supply Map analysis* (May 18, 2022) (<https://qualitymatters.usp.org/geographic-concentration-pharmaceutical-manufacturing>).

<sup>110</sup> *Id.*

<sup>111</sup> USP Briefing and Presentation.

**Insufficient Supply Chain Visibility.** End-to-end supply chain visibility is essential to identifying and mitigating risk. However, neither the federal government nor key sectors of the pharmaceutical supply chain, including manufacturers, GPOs, and distributors, have end-to-end supply chain visibility, from the key starting materials (chemicals, solvents, reagents, etc.) needed to manufacture API to the intermediaries, and ultimately downstream suppliers, such as GPOs, distributors, and providers.<sup>112</sup> Dr. Schondelmeyer compared the pharmaceutical manufacturing supply chain to building a house: “everything is contracted out. You hire a general contractor, and plumber, a roofer, and so on to build a house.”<sup>113</sup> Similarly, pharmaceutical manufacturers contract with a number of suppliers, such as key starting material sources, API manufacturers, finished dosage manufacturers, packagers, labelers, and repackagers.<sup>114</sup> The chart shown in Figure 6 below, provides a high-level overview of the pharmaceutical supply chain.

**Figure 6. Simplified Pharmaceutical Supply Chain Process<sup>115</sup>**



According to ASPR, “there can be up to 20 potential ‘key starting materials’ per pharmaceutical, and it is unknown which ones are used and in what quantities by each manufacturer, without specific input from the respective manufacturer.”<sup>116</sup> Manufacturers, however, do not always have insight into this information. In an interview with the Majority Committee staff, AAM stated manufacturers do not always know where their key starting materials are from and they generally do not know the API suppliers’ full capacity as the API manufacturer may be producing APIs for multiple vendors.<sup>117</sup> Premier told the Majority Committee staff, “we know where the finished dose manufacturers and API suppliers are, but we don’t know about the intermediaries and the key starting materials.”<sup>118</sup> The Healthcare Distribution Alliance (HDA), which represents pharmaceutical distributors, told the Majority Committee staff, “our members have line of sight into our suppliers, but may not have visibility into raw material supply chain.”<sup>119</sup> USP explained how insight into key

<sup>112</sup> White House 100-Day Supply Chain Review, at 235-236; *see also* Interview with Dr. Stephen Schondelmeyer; Interview with Premier; Interview with Vizient; Interview with Association for Accessible Medicines; Interview with Healthcare Distribution Alliance.

<sup>113</sup> Interview with Dr. Stephen Schondelmeyer.

<sup>114</sup> NASEM Supply Chain Report, at 39.

<sup>115</sup> University of Minnesota, CIDRAP Resilient Drug Supply Project, *COVID-19: The CIDRAP Viewpoint* (Oct. 21, 2020) (<https://www.cidrap.umn.edu/sites/default/files/downloads/cidrap-covid19-viewpoint-part6.pdf>).

<sup>116</sup> ASPR Supply Chain and Industrial Analysis Report, at 3 (on file with Committee) (noting “[t]here is no centralized database to determine what ingredients are shared between drugs, and it is labor-intensive to identify possible connections for each pharmaceutical”).

<sup>117</sup> Interview with Association for Accessible Medicines.

<sup>118</sup> Interview with Premier.

<sup>119</sup> Interview with Healthcare Distribution Alliance.

starting materials are critical in assessing supply chain risks and determining alternate chemical routes of synthesis for API manufacturing that could be sourced domestically or do not depend wholly on materials sourced abroad.<sup>120</sup>

In a 2021 report, DOD noted, “the root cause of transparency challenges is the lack of available authoritative data relating to the sourcing of pharmaceutical ingredients.”<sup>121</sup> DOD still lacks authoritative data on the sources of finished drugs, APIs, and other raw materials it purchases from the commercial sector. Currently, the Defense Logistics Agency (DLA), which is responsible for purchasing all drugs for service members, relies on a “robust network of manufacturers and suppliers” in the event of supply disruptions, but noted “with accurate source data[,] DLA could be much more efficient and proactive in mitigating these risks.”<sup>122</sup> For example, based on the supply chain information available to the federal government, DOD told the Majority Committee staff, that there are three drugs “with [API] manufacturers based only in China,” and “[w]ith those exceptions, DLA is unable to determine with certainty if any of the drugs it purchases rely solely on sources in China or India.”<sup>123</sup> ASPR told the Majority Committee staff that their “biggest concerns” are that 90 to 95 percent of generic sterile injectable drugs that are needed for critical for acute care in the U.S. rely on key starting materials and drug substances from China and India.<sup>124</sup> Drugs that have a geographically concentrated manufacturing base are more susceptible to shortages.<sup>125</sup>

Publicly available information on the pharmaceutical supply chain in the U.S. is extremely limited. By comparison, New Zealand provides a public database that lists all drugs on the market, their corresponding API source, and the manufacturing locations.<sup>126</sup> Dr. Schondelmeyer told the Majority Committee staff that he discussed the database with New Zealand’s government and they could not point to detrimental effects on making this information public.<sup>127</sup>

**False Appearance of Diversity in the Marketplace.** With a globalized supply chain, it is important to have diversity in sourcing and manufacturing to ensure unexpected disruptions do not lead to widespread shortages. Insufficient supply chain visibility coupled with numerous supply chain complexities, discussed above, often create a false appearance of diversity in the market.<sup>128</sup> Steven Lucio, Senior Principal of Pharmacy Solutions at Vizient, told the Majority Committee staff, “the layers [in the manufacturing process] can have the appearance of a diverse supply chain that is not

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<sup>120</sup> USP Briefing.

<sup>121</sup> DOD IG Report, at 32.

<sup>122</sup> Department of Defense, *Response to Committee Questions* (received Sept. 20, 2022) (on file with Committee) (hereinafter “DOD Response”).

<sup>123</sup> *Id.*

<sup>124</sup> Administration for Strategic Preparedness and Response, *Response to Committee Questions* (received Oct. 6, 2022) (on file with Committee) (hereinafter “ASPR Response”).

<sup>125</sup> Vizient/USP/Angels for Change Report, at 4 (finding “drugs with greater geographic concentration in their manufacturing base are more susceptible to shortages”).

<sup>126</sup> Medsafe, New Zealand Medicines and Medical Devices Safety Authority (<https://www.medsafe.govt.nz/>) (accessed Mar. 16, 2023).

<sup>127</sup> Interview with Dr. Stephen Schondelmeyer.

<sup>128</sup> See International Society for Pharmaceutical Engineering, *Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients*, at 6-7 (Dec. 2020).



there.”<sup>129</sup> Dr. Erin Fox independently relayed the same concerns to Committee staff and noted, “we do not know which companies are actually making products.”<sup>130</sup> This lack of visibility makes it difficult to accurately assess supply chain vulnerabilities. For example, oftentimes there is one contract manufacturer for multiple suppliers or one API supplier for multiple finished dosage manufacturers, providing a false sense of diversity in the marketplace.<sup>131</sup> Below is an example.

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## FLUDARABINE

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**What is it?** Fludarabine Phosphate (“fludarabine”) is an injectable generic drug often used in children and adults to treat multiple forms of cancer, including leukemia and lymphoma.<sup>132</sup> The FDA first approved fludarabine in 1991, and generic manufacturers began filing for approval beginning in 2003.<sup>133</sup> There are currently 12 FDA approved application holders for fludarabine injection, but only six appear to be actively marketing the product.<sup>134</sup>

**What is the concern?** Fludarabine is currently in shortage.<sup>135</sup> According to USP’s Medicine Supply Map, fludarabine currently has a vulnerability score of 95.4 percent.<sup>136</sup> A close look into the FDA’s publicly available data and the National Library of Medicine’s marketing information on “DailyMed” for fludarabine demonstrates the multiple layers of the supply chain and lack of transparency into which companies are actually engaged in the manufacture of fludarabine.<sup>137</sup> When the product was in shortage, Areva Pharmaceuticals raised the price of their fludarabine product to \$2,736 per vial, compared to other companies’ prices of less than \$300 per vial.<sup>138</sup>

**Who is manufacturing the fludarabine?** Based on publicly available information, it is not possible to determine which companies are actually engaged in the manufacture of fludarabine. For example, while there appear to be at least 5 suppliers of fludarabine, the web of manufacturers is far more complex.<sup>139</sup>

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<sup>129</sup> Interview with Vizient.

<sup>130</sup> Interview with Dr. Erin Fox.

<sup>131</sup> *Id.*; Interview with Dr. Stephen Schondelmeyer; Interview with Vizient.

<sup>132</sup> National Institutes of Health, National Cancer Institute, Fludarabine Phosphate (<https://www.cancer.gov/about-cancer/treatment/drugs/fludarabinephosphate>) (accessed Mar. 6, 2023); St. Jude Children’s Research Hospital, Fludarabine (<https://together.stjude.org/en-us/diagnosis-treatment/medicines-list/fludarabine.html>) (accessed Mar. 6, 2023).

<sup>133</sup> Food and Drug Administration, Drugs@FDA: FDA-Approved Drugs (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020038>; <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=076349>) (accessed Mar. 6, 2023).

<sup>134</sup> Food and Drug Administration, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (<https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>) (accessed Mar. 1, 2023).

<sup>135</sup> FDA Drug Shortages Website; ASHP Drug Shortages Website (accessed Mar. 6, 2023).

<sup>136</sup> USP Briefing and Presentation. USP cites the following vulnerability factors for fludarabine: low revenue for manufacturers, multiple labelers that all source from three facilities, and manufacturing complexities, including the difficulties surrounding the active ingredient, which is cytotoxic, hazardous, expensive, and requires the use of a separate facility.

<sup>137</sup> See FDA Drug Shortages Website (accessed Mar. 6, 2023); National Library of Medicine, DailyMed, Fludarabine (<https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=fludarabine&pagesize=20&page=1>) (accessed Mar. 6, 2023). For purposes of this case study, the Majority Committee staff defines a “manufacturer” as a company that is involved in the actual production of the finished dose product and does not include packagers or labelers, or other subsequent steps in the manufacturing process.

<sup>138</sup> *Drugmaker raises the price of an old chemo medicine tenfold amid persistent shortages*, STAT Pharmalot (Oct. 27, 2022) (<https://www.statnews.com/pharmalot/2022/10/27/cancer-shortages-fludarabine-leukemia-chemo-areva-hospitals-pharmacy/>) (noting Areva Pharmaceutical attributed their high pricing to limited API manufacturers, regulatory challenges, and complex manufacturing processes).

<sup>139</sup> See National Library of Medicine, DailyMed, Fludarabine (<https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=fludarabine&pagesize=20&page=1>) (accessed Mar. 19, 2023).

According to publicly available information: Only one supplier (Fresenius Kabi) appears to be actually manufacturing their own product. Areva Pharmaceuticals is actively marketing the product, but relies on a manufacturer in Italy. Another supplier (Actavis) appears to rely on a manufacturer in Romania. Teva reported a shortage to the FDA, but is not an approved application holder actively manufacturing or marketing their own product—instead, Teva appears to be selling the Activas product. Teva acquired Actavis Generics in 2016.<sup>140</sup> Hikma Pharmaceuticals appears to be actively marketing the product under the label “Leucadia Pharmaceuticals,” but the company does not disclose who is manufacturing the product. Similarly, Sagent Pharmaceuticals appears to be actively marketing the product and also does not disclose who is manufacturing the product.

Companies’ Responses to HSGAC Majority Committee Staff: Fresenius Kabi confirmed to the Majority Committee staff that it manufactures its finished dose product.<sup>141</sup> Teva told Committee staff that it currently supplies fludarabine for the U.S. market from Sindan Pharma SRL, a facility it owns in Romania.<sup>142</sup> This product is then distributed by Actavis, a company that is owned by Teva.<sup>143</sup> Hikma Pharmaceuticals told Majority Committee Staff it “is not currently manufacturing or selling fludarabine phosphate for injection” and that the company acquired the product when it acquired Leucadia/Custopharm in April 2022.<sup>144</sup> According to Hikma Pharmaceuticals, Leucadia’s fludarabine was manufactured by Teva Pharmaceuticals in their Irvine, California manufacturing facility, but Teva ceased all production at that facility in October 2021 after experiencing quality issues and never restarted production.<sup>145</sup> As a result, Leucadia stopped selling fludarabine prior to April 2022.<sup>146</sup> Sagent also told the Majority Committee staff that it received fludarabine from Teva Pharmaceuticals, but “is transferring its source of supply from [Teva, which has ceased production], to another manufacturer.”<sup>147</sup>

What initially appeared to be a robust manufacturer supply chain, instead appears to more limited and complex. Dr. Fox told the Majority Committee staff, “there is no good real time database to show products that are no longer being marketed and we have no idea which company is making which product.”<sup>148</sup> According to USP, while there are multiple labelers of fludarabine, they all source from the same three facilities.<sup>149</sup> As shown in Figure 7, there are six API facilities registered with the FDA to manufacture fludarabine. Of those six facilities, three are located in China, two are in the U.S., and one location is not known.<sup>150</sup> It is not clear, however, if all six of these API suppliers are actively engaged in manufacturing fludarabine API. For example, some API manufacturers might not be actively making the product and finished-dose manufacturers may rely on the same API supplier.

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<sup>140</sup> FDA Drug Shortages Website and National Library of Medicine’s DailyMed Website. Teva acquired Actavis Generics in 2016. *See* Teva Pharmaceuticals, *Teva Completes Acquisition of Actavis Generics* (Aug. 2, 2016) (<https://www.tevapharm.com/news-and-media/latest-news/teva-completes-acquisition-of-actavis-generics/>).

<sup>141</sup> Fresenius Kabi Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

<sup>142</sup> Teva Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

<sup>143</sup> *See id.*; Teva Pharmaceuticals, *Teva Completes Acquisition of Actavis Generics* (Aug. 2, 2016) (<https://www.tevapharm.com/news-and-media/latest-news/teva-completes-acquisition-of-actavis-generics/>).

<sup>144</sup> Hikma Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 16, 2023).

<sup>145</sup> *Id.*; *see Teva temporarily padlocks a plant after FDA cites it for contamination*, Novartis (<https://endpts.com/teva-will-halt-its-operations-in-irvine-ca-after-handed-form-483/>); *Teva puts the brakes on troubled California sterile injectables plant: reports*, FiercePharma (Oct. 4, 2021) (<https://www.fiercepharma.com/manufacturing/teva-puts-more-300-staffers-permanent-shore-leave-drydocked-california-injectables>).

<sup>146</sup> Hikma Pharmaceuticals Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 16, 2023).

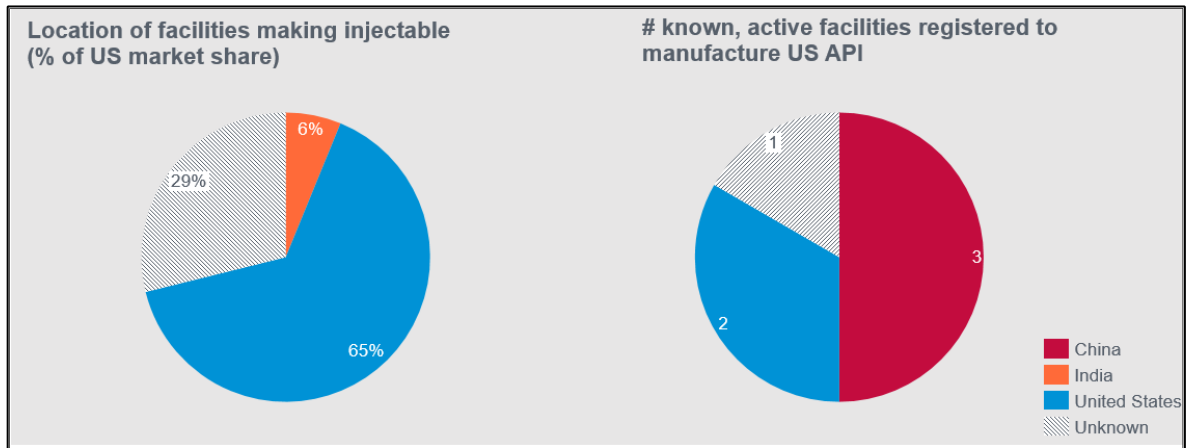
<sup>147</sup> Sagent Pharmaceuticals, Inc. Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 20, 2023).

<sup>148</sup> Interview with Dr. Erin Fox (Mar. 17, 2023).

<sup>149</sup> USP Briefing and Presentation.

<sup>150</sup> *Id.*

Figure 7. Fludarabine Finished Dosage and API Manufacturers, According to USP<sup>151</sup>



In an interview with the Majority Committee staff, Vizient explained that the problem with contract manufacturers is that “no one knows fully how all things interrelate.” While Vizient is able to identify where the API originates (something the FDA is still struggling to assess) and where the finished dosage manufacturing occurs for many medications, particularly those identified as essential, they have difficulty identifying the multiple suppliers in between those stages.<sup>152</sup>

### C. Increased Demand

Just-in-time manufacturing practices, a limited number of manufacturers, and the low cost of most key generic drugs limits many manufacturers’ ability to be flexible and surge production when there is a spike in demand.<sup>153</sup> The COVID-19 pandemic resulted in an unprecedented demand for numerous critical drug products.<sup>154</sup> Increased demand can also be related to other issues, such as manufacturing workforce shortages, inaccurate modeling projections, market exits, public health emergencies, natural disasters, or manufacturing disruptions. This past winter, the prevalence of influenza-like illnesses, according to IQVIA, was higher and peaked earlier than in years’ past. See Figure 8. As a result, demand surged for prescription medications, like amoxicillin and Tamiflu, and even over-the-counter cold and flu medication, such as children’s Tylenol and resulted in widespread shortages.<sup>155</sup>

<sup>151</sup> *Id.*

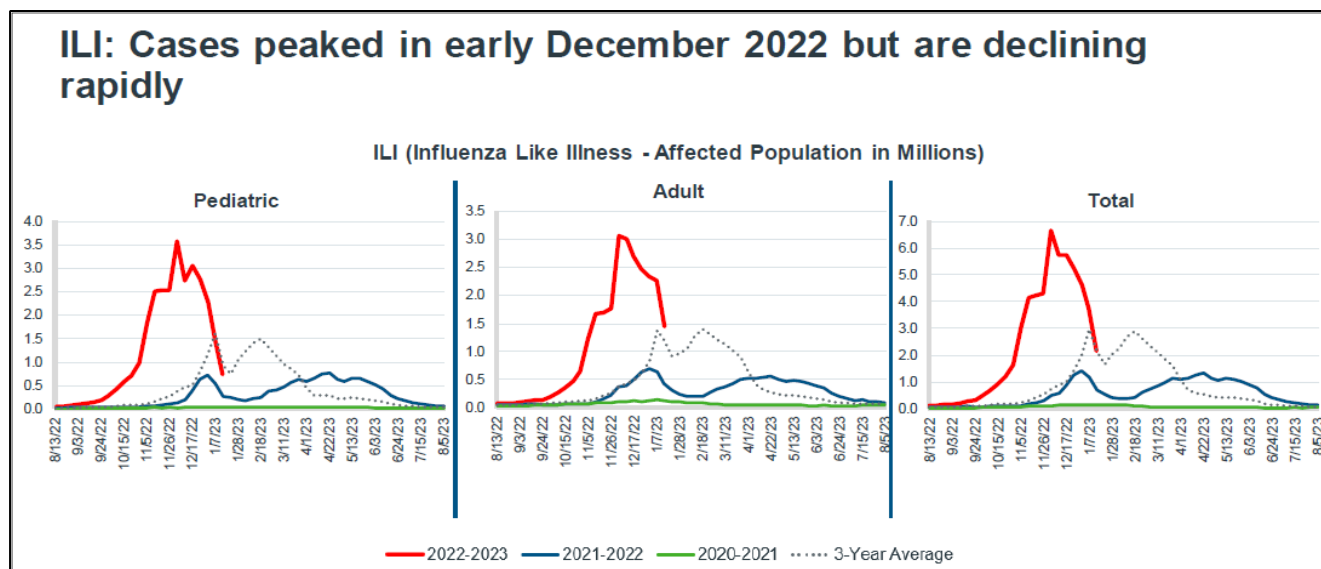
<sup>152</sup> Interview with Vizient.

<sup>153</sup> American Hospital Association Briefing.

<sup>154</sup> Food and Drug Administration, *Report to Congress: Drug Shortages for Calendar Year 2020*, at 11 (finding “the COVID-19 pandemic has also increased the risks of shortages due to sudden increases in demand for drugs used in hospitalized patients, particularly the most critically ill”).

<sup>155</sup> *Amoxicillin Shortage: Some Forms of this Common Antibiotic in Short Supply*, Healthline (Nov. 13, 2022) (<https://www.healthline.com/health-news/amoxicillin-shortage-some-forms-of-this-common-antibiotic-in-short-supply>); *Children’s Tylenol is getting harder to find. Here’s what to do.*, Washington Post (Dec. 7, 2022) (<https://www.washingtonpost.com/wellness/2022/12/07/childrens-tylenol-ibuprofen-shortages-parents-advice/>); *Why we (still) can’t find any children’s Tylenol*, Axios (Jan. 5, 2023) (<https://www.axios.com/2023/01/05/why-childrens-tylenol-shortage>); *Flu and R.S.V. Hit the Holidays, Heightening Demand for Antibiotics and Antivirals*, New York Times (Nov. 23, 2022) (<https://www.nytimes.com/2022/11/23/health/drug-shortages-flu-holidays.html>).

Figure 8. Influenza-Like Illnesses (ILI) throughout the U.S. from Aug. 2022 – Jan. 14, 2023<sup>156</sup>



Premier tracks fill rates for each drug product as one mechanism to help determine the “health of the supply chain: and considers a fill rate above 90 percent to be good. According to Premier, a fill rate that falls below 80 percent is “an early indication that demand is outpacing supply and that shortages may be imminent.”<sup>157</sup> IV saline’s historical fill rate was above 98 percent. However, in the fall of 2021 (October – November), the fill rate for IV saline dropped to a low of nearly 22 percent and did not exceed 51 percent when manufacturers were forced to prioritize COVID-19 vaccine production.<sup>158</sup>

Below is an example of how increases in demand often correlate with other underlying issues and can result in drug shortages. Despite the increasing demand for certain drugs over time, currently, manufacturers are not required to report increases in demand to the FDA.<sup>159</sup>

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### SODIUM CHLORIDE (IV Saline)

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**What is it?** Sodium chloride 0.9%, commonly known as “IV Saline,” is a critical supportive care hospital drug used to administer medications. The FDA first approved IV Saline in 1972 and generic manufacturers began receiving approval around 1985.<sup>160</sup> IV Saline is also on the FDA’s list of essential medicines.<sup>161</sup>

<sup>156</sup> Association for Accessible Medicines, IQVIA: US Generics and Biosimilars Trends, Issues & Outlook for AAM (Feb. 14, 2023) (on file with Committee).

<sup>157</sup> Premier Drug Shortages Report, at 10.

<sup>158</sup> *Id.*

<sup>159</sup> 21 U.S.C § 356c(a)(2).

<sup>160</sup> Food and Drug Administration, Drugs@FDA: FDA-Approved Drugs (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016366>) (accessed Mar. 6, 2023).

<sup>161</sup> Food and Drug Administration, *Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944* (Oct. 30, 2020) (<https://www.fda.gov/media/143406/download>).

**What is the concern?** IV saline has been in shortage since 2021 and has experienced dire shortages for at least a decade due to a variety of reasons, including low profitability for manufacturers, manufacturing complexities, quality problems that led to recalls (2013-2014; 2017), geographic manufacturing concentration and natural disasters (2017-2018), just-in-time delivery, insufficient investments in redundancy, and increased demand (2017-2018; 2021-2023).<sup>162</sup> According to USP, IV saline currently has a vulnerability score of 95 percent.<sup>163</sup> USP was not able to determine the location for 68 percent of IV saline finished dosage manufacturing facilities. For API suppliers, USP reported 10 manufacturers in the U.S. and 13 in the European Union, among a handful in other countries that were registered with the FDA; however, this does not mean the companies are actively manufacturing the product.<sup>164</sup> AAM told the Majority Committee staff that this past year demand for IV saline “skyrocketed” beyond manufacturers’ predictive modeling based on years prior.<sup>165</sup>

- **Manufacturing Complexities:** Due to the complexity of the manufacturing process, suppliers are only able to produce a limited amount of IV saline bags per day.<sup>166</sup> According to AAM, there is also a lag between the demand at a given time and the supply being produced.<sup>167</sup>
- **Cost:** While the demand for IV saline is high, the return (i.e. the amount paid per bag to generic manufacturers) is not.<sup>168</sup> Despite the multitude of manufacturing complexities involved, the average price of one injectable solution is between three and five cents.<sup>169</sup> Additionally, IV saline is “heavy and bulky, making air transport costly and shipment periods lengthy.”<sup>170</sup> In 2022, there were at least 28 companies that manufactured IV saline.<sup>171</sup> Studies have shown that increased generic competition leads to lower generic drug prices.<sup>172</sup>

**How are Health care Providers Impacted?** Shortages of IV saline and other supportive care injectable drugs result in a number of consequences. Shortages have affected staffing as one hospital reported having to rely on nurses to hang 250 bags of IV saline to draw up syringes when prefilled IV saline flush syringes were in shortage, noting, “we’ve had to revert to archaic practices, but did not have a choice.”<sup>173</sup> IV saline flush syringes are crucial to administer before providing a patient with an IV. Sheila Walker, Director of Pharmacy for Murray-Calloway County Hospital in Kentucky told Majority Committee Staff, “the shortage of manufactured saline syringes used for IV line flushing was particularly frustrating. In addition to having limited pharmacy-compounding staff, there was also the shortage of syringes and needles required to draw up saline syringes for nursing staff.”<sup>174</sup> Dr. Andrew Shuman recalled an instance when shortages of mini IV saline bags required the use of infusion pumps, which forced hospitals to rent these products,

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<sup>162</sup> See NASEM Supply Chain Report, at 105-106 (Box 4-2: Case Study on Saline); USP Briefing and Presentation.

<sup>163</sup> USP Briefing and Presentation. According to USP the primary drivers of vulnerability include low profitability and manufacturing complexity as evidenced by “recalls due to sterility issues.”

<sup>164</sup> *Id.*

<sup>165</sup> Interview with Association for Accessible Medicines.

<sup>166</sup> *Id.*

<sup>167</sup> *Id.*

<sup>168</sup> *Id.*

<sup>169</sup> Drugs.com, Sodium Chloride Prices, Coupons and Patient Assistant Programs (<https://www.drugs.com/price-guide/sodium-chloride>) (accessed Mar. 6, 2023). The Majority Committee staff cites to the Average Wholesale Price (AWP) and notes that this price may be different depending on a number of factors, many of which are explained in the Committee’s 2019 report, see HSGAC Minority Staff Report, *A Price Too High*.

<sup>170</sup> Maryann Mazer-Amirshahi, et al. *Saline Shortages – Many Causes, No Simple Solution*, New England Journal of Medicine (Apr. 19, 2018) (noting “logistics make it impractical to import [IV saline products] for long periods”).

<sup>171</sup> USP Briefing and Presentation.

<sup>172</sup> Ryan Conrad and Randall Lutter, *Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices*, Food and Drug Administration (Dec. 2019).

<sup>173</sup> American Hospital Association Briefing.

<sup>174</sup> *Id.*

resulting in added costs.<sup>175</sup> According to Mike Schiller, Senior Director of Supply Chain with the American Hospital Association, recent recalls of prefilled IV saline flush syringes have also caused shortages, which resulted in price hikes by 300 percent.<sup>176</sup>

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#### **D. Logistical and Regulatory Challenges**

While there is a need to balance both safety and efficiency, logistical and regulatory challenges can limit a manufacturer’s ability to rapidly respond to drug shortages.<sup>177</sup> In FDA’s 2019 Drug Shortages Report, it noted that regulatory requirements can “impede industry’s ability to mitigate shortages: e.g., by increasing the time and cost of responding to a supply disruption.”<sup>178</sup> Post-market approval requirements can also deter suppliers from implementing continual improvements and long approval wait times can discourage suppliers from entering the market.<sup>179</sup> The International Society for Pharmaceutical Engineering (IPSE) suggested that “novel or more flexible regulatory approaches [for API manufacturers] could lower costs and make manufacturers more willing to pursue continual improvements,” such as using a performance-based approach.<sup>180</sup> The FDA’s Unapproved Drug Initiative has also been cited as contributing to shortages.<sup>181</sup>

#### **E. Natural Disasters and Biological Incidents**

As the rate and severity of natural disasters and biological incidents continue to rise, concentrated geographic suppliers of critical drugs pose increased risks.<sup>182</sup> Although drug shortages have long impacted health care providers and patients throughout the country, natural disasters and biological incidents, such as the COVID-19 pandemic have exposed the risks of relying on suppliers from a concentrated geographic location.<sup>183</sup> The examples in Figure 9 below, illustrate how manufacturers of products in concentrated geographic locations were impacted by natural disasters and biological incidents, which ultimately resulted in drug shortages.

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<sup>175</sup> Dr. Andrew Shuman, Associate Professor of Otolaryngology-Head and Neck Surgery and Chief of the Clinical Ethics Service, Center for Bioethics and Social Sciences in Medicines, University of Michigan Medical School, Interview with Senate Committee on Homeland Security and Governmental Affairs Majority Staff (Jan. 30, 2023) (hereinafter “Interview with Dr. Andrew Shuman”).

<sup>176</sup> American Hospital Association Briefing.

<sup>177</sup> ASPR, ARMI, and NextFAB Report, at 23.

<sup>178</sup> FDA Drug Shortages Report, at 44.

<sup>179</sup> ASPR, ARMI, and NextFAB Report, at 23.

<sup>180</sup> International Society for Pharmaceutical Engineering, *Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients*, at 8 (Dec. 2020) (noting “[w]hile some countries agree to post-approval changes more quickly, companies are bound to expectations in multiple registrations, which gives them powerful business reasons *not* to pursue continual improvement. Many regulatory processes could be simplified with harmonized data requirements and approval timelines for typical post-approval changes”). *Id* at 10.

<sup>181</sup> Liam Bendicksen, et al. *The Vexing Voyage of Vasopressin: The Consequences of Granting Market Exclusivity to Unapproved Drugs*, American College of Chest Physicians Journal (Aug. 2022).

<sup>182</sup> See DOD IG Report.

<sup>183</sup> White House, *Why the Pandemic Has Disrupted Supply Chains* (Jun. 17, 2021) (<https://www.whitehouse.gov/cea/written-materials/2021/06/17/why-the-pandemic-has-disrupted-supply-chains/>).

**Figure 9. Select Examples of Natural Disasters and Biological Incidents Impacting Drug Shortages**

Year	Incident	Location	Drug Shortage
2011	An earthquake and tsunami resulted in an accident at the Fukushima Daiichi nuclear power plant. <sup>184</sup>	Japan	Doxycycline, a critical antibiotic <sup>185</sup>
2017	Hurricanes Maria and Irma caused a manufacturing plant closure. <sup>186</sup>	Puerto Rico	IV Saline, a critical supportive care drug <sup>187</sup>
2020	COVID-19 pandemic <sup>188</sup>	China/ Global	Widespread shortages of opioids, sedatives, analgesics, antibiotics, inhalers, and many other critical care hospital drugs. <sup>189</sup>
2021	Ice storm caused a manufacturing plant closure. <sup>190</sup>	Texas	Resin, a raw material used in pharmaceutical manufacturing for packaging and to make certain medical devices, such as syringes needed to administer saline flushes. <sup>191</sup>

Below is an example of how a manufacturing plant closure in China due to COVID-19 led to a shortage of IV contrast media throughout the U.S.

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### IV CONTRAST MEDIA

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**What is it?** IV contrast media is an essential drug needed for any CT scan. Omnipaque (iohexol) is a branded contrast media drug manufactured by GE HealthCare as an injection, as well as an oral solution. Visipaque (iodixanol) is also a

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<sup>184</sup> International Atomic Energy Agency, *Fukushima Daiichi Nuclear Accident* (<https://www.iaea.org/topics/response/fukushima-daiichi-nuclear-accident>).

<sup>185</sup> DOD IG Report, at 2.

<sup>186</sup> *Hurricane Maria shuts much of Puerto Rico's pharma manufacturing*, Fierce Pharma (Sept. 26, 2017) (<https://www.fiercepharma.com/manufacturing/hurricane-maria-shutters-pharma-manufacturing-puerto-rico>).

<sup>187</sup> Shortages of drugs and saline reported as Puerto Rico hurricane damage lingers, Fierce Pharma (October 12, 2017) (<https://www.fiercepharma.com/pharma/shortages-drugs-and-saline-reported-as-puerto-rico-hurricane-damage-lingers>).

<sup>188</sup> *The COVID-19 Pandemic Highlights Intensified Drug Shortages*, Forbes, (July 14, 2022) (<https://www.forbes.com/sites/forbestechcouncil/2022/07/14/the-covid-19-pandemic-highlights-intensified-drug-shortages/?sh=362ce1f85540>).

<sup>189</sup> American Society of Anesthesiologists, *Critical Care Drug Recommendations for COVID-19 During Times of Drug Shortages* (Jun. 25, 2020) (<https://www.asahq.org/about-asa/newsroom/news-releases/2020/06/critical-care-drug-recommendations-for-covid-19-during-times-of-drug-shortages>); Dr. Megan Ranney, *Opinion: Why the US is having shortages of antibiotics now*, CNN (Nov. 28, 2022) (<https://www.cnn.com/2022/11/28/opinions/drug-shortages-antibiotics-ranney/index.html>).

<sup>190</sup> *What the Winter Storm in Texas Taught Us About Risk Mitigation in Polyethylene Supply Chains*, Shell USA (<https://www.shell.us/business-customers/shell-polymers/resources-and-insights/what-texas-winter-storms-taught-us-about-polyethylene-supply-chains.html>).

<sup>191</sup> *Resin buyers struggle with high prices and short supply*, SupplyChainDive (Nov. 18, 2021) (<https://www.supplychaindive.com/news/preparation-mitigated-effects-of-hurricane-ida-but-resin-shortage-persists/607600/>); *Supply-Chain Snags Create Shortages of Lifesaving Medical Supplies in U.S.*, Forbes (May 3, 2022) (<https://www.forbes.com/sites/amyfeldman/2022/05/03/supply-chain-snags-create-shortages-of-life-saving-medical-supplies-in-us/?sh=79c2fde341b0>); American Hospital Association Briefing.

branded contrast media drug manufactured by GE HealthCare.<sup>192</sup> While there are other types of IV contrast on the market, these products are not always interchangeable.<sup>193</sup>

**What happened?** Since April 2022, some manufacturers have made the decision to discontinue certain types of IV contrast.<sup>194</sup> On February 21, 2023, GE HealthCare announced it would be discontinuing certain less used presentations of its iohexol product, but would continue to manufacture the more commonly used presentations of iohexol and Visipaque (iodixanol), another form of IV contrast media.<sup>195</sup> GE HealthCare told the Majority Committee staff that their announcement to discontinue certain versions of iohexol “was not a result of the shortage, but an effort to rationalize our offerings, given the lower utilization of certain [versions].”<sup>196</sup> Some types of IV contrast are currently in shortage.<sup>197</sup>

On April 19 2022, GE HealthCare announced to customers that its manufacturing facility in Shanghai, China “experienced an unexpected, temporary shutdown,” due to a recent COVID-19 outbreak. As a result, GE HealthCare announced that supply of Omnipaque, their branded IV contrast media drug product produced at the facility would be limited.<sup>198</sup> Premier, a GPO that contracts with GE Healthcare and relies on Shanghai for 90 percent of their IV contrast media told the Majority Committee staff, “GE was not upfront about their Shanghai shutdown until it was in crisis mode and by the time they told us, it was too late [to timely identify workarounds].”<sup>199</sup> Insufficient supply chain visibility impaired Premier’s ability to respond noting, “the minute the GE plant shut down in April, we should have been able to say exactly what product is produced there and what the impact would be to our providers, but we could not do that.”<sup>200</sup> Health care providers also expressed concern. Mike Schiller, Senior Director of Supply Chain with the American Hospital Association told the Majority Committee staff, “the minute Shanghai went into lockdown, there should have been a call from manufacturers explaining the situation,” noting, “quicker communication would have given hospitals more time to put conservation tactics in place.”<sup>201</sup> In response to questions from Majority Committee staff about this criticism, GE HealthCare shared a May 2022 letter from the American Hospital Association (AHA) to GE HealthCare, in which AHA wrote, “we appreciate GE’s quick action to notify its customers and the continued steps it is taking to communicate with all necessary stakeholders.”<sup>202</sup> GE HealthCare acknowledged “our customers’ frustration throughout the shortage and the impact this had on health care services.”<sup>203</sup>

**The impact:** As a result of GE Healthcare’s plant closure in Shanghai, demand for IV contrast media from other suppliers increased and resulted in widespread shortages.<sup>204</sup> According to Dr. Andrew Shuman, surgical oncologist and

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<sup>192</sup> GE HealthCare Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 16, 2023) (hereinafter “GE HealthCare Correspondence to Committee”).

<sup>193</sup> American College of Radiology Committee on Drugs and Contrast Media, *ACR Manual on Contrast Media* (2023) ([https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast\\_Media.pdf](https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf)).

<sup>194</sup> ASHP Drug Shortages Website (<https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=495>) (accessed Mar. 6, 2023) (noting Bracco discontinued certain vials in April and November 2022).

<sup>195</sup> FDA Drug Shortages Website ([https://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_ActiveIngredientDetails.cfm?AI=Iohexol%20Injection&st=d](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Iohexol%20Injection&st=d); [https://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_ActiveIngredientDetails.cfm?AI=Iodixanol%20Injection&st=r](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Iodixanol%20Injection&st=r)) (accessed Mar. 6, 2023).

<sup>196</sup> GE HealthCare Correspondence to Committee.

<sup>197</sup> ASHP Drug Shortages Website (accessed Mar. 6, 2023) (noting multiple forms of iopamidol injection is in shortage as of February 7, 2023).

<sup>198</sup> Letter from GE HealthCare to Valued Customer, *Re: GE Healthcare Contrast Media Availability* (Apr. 19, 2022).

<sup>199</sup> Interview with Premier.

<sup>200</sup> *Id.*

<sup>201</sup> American Hospital Association Briefing.

<sup>202</sup> Letter from American Hospital Association to GE HealthCare, *Re: General Electric Omnipaque Supply Disruption and Product Shortages*, (May 16, 2022) (<https://www.aha.org/lettercomment/2022-05-16-aha-ge-re-general-electric-omnipaque-supply-disruption-and-product>).

<sup>203</sup> GE HealthCare Correspondence to Committee.

<sup>204</sup> *Hospitals ration CT scans, other procedures over shortage of contrast dye*, NBC News (May 18, 2022) (<https://www.nbcnews.com/news/us-news/shortage-contrast-dye-hospitals-ration-ct-scans-procedures-rcna29379>).



ethicist, some providers were unable to rely on alternate suppliers due to the unique nature of the product resulting in a “nightmare” situation by “completely handcuffing” certain health care providers from conducting routine procedures.<sup>205</sup> In addition, Dr. Yoram Unguru, a pediatric oncologist, noted that in addition to hospitals, IV contrast supply shortages also affected outpatient radiology facilities who may not have had prioritization and rationing mechanisms in place.”<sup>206</sup> GE HealthCare told the Majority Committee staff its plant returned to full capacity in June 2022.<sup>207</sup> GE HealthCare has since taken steps to increase capacity for its contrast media manufacturing, which include expanding their API site in Norway and opening a new production line at an existing site in Ireland.<sup>208</sup> In addition, GE HealthCare said it has “added contingency supply routes from [its] Shanghai and alternative sites and increased safety stocking levels at [its] main US Distribution Center.”<sup>209</sup>

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### III. Impact on Patients, Hospitals, and Health Care Systems

According to multiple physicians and pharmacists who spoke with Majority Committee staff, drug shortages have wide-ranging, and at times, devastating consequences for patients.<sup>210</sup> Hospitals generally experience the effects of drug shortages on a daily basis.<sup>211</sup> To assess the impact of drug shortages, the Majority Committee staff administered a survey for hospitals, pharmacists, and other healthcare providers to voluntarily participate and conducted interviews with healthcare providers.<sup>212</sup> Dr. Yoram Unguru, pediatric hematologist/oncologist, explained to Committee staff, “shortages are a dotted line that can be connected to deaths.” In a 2021 report, USP/Vizient found that drug shortages can “result in significant harm, including increased medication errors, delayed administration of lifesaving therapies, inferior outcomes, and patient deaths.”<sup>213</sup> A subsequent study published in 2022 and conducted in France examined the clinical impact of drug shortages on patient care and found that shortages were associated with medication errors, adverse drug reactions, and inefficiencies.<sup>214</sup>

Dr. Shuman told Majority Committee staff that the impact shortages can have on patients and health care providers is often not captured. Dr. Shuman explained, “we already have a shortage of nurses and drugs and supplies. When providers are asked to change their work flow—with less resources and fewer people—I’m not sure how to see that in the data, but there will be individual errors, one offs, and the number of [these occurrences] is probably skyrocketing.”<sup>215</sup> The selected

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<sup>205</sup> Interview with Dr. Andrew Shuman.

<sup>206</sup> Interview with Dr. Yoram Unguru.

<sup>207</sup> GE HealthCare Correspondence to Committee.

<sup>208</sup> GE HealthCare, *Preventing Future Global Shortages of Iodinated Contrast Media Requires Industry Action*, (Dec. 1, 2022) (<https://www.gehealthcare.com/insights/article/preventing-future-global-shortages-of-iodinated-contrast-media-requires-industry-action>).

<sup>209</sup> GE HealthCare Correspondence to Committee.

<sup>210</sup> See Interview with Dr. Andrew Shuman and Dr. Yoram Unguru; American Hospital Association Briefing.

<sup>211</sup> Interview with Dr. Andrew Shuman and Dr. Yoram Unguru.

<sup>212</sup> In August 2022, Majority Committee staff administered a survey through the American Hospital Association, Michigan Hospital Association, Association for Health-System Pharmacists, American Society of Clinical Oncology, and American Society of Anesthesiologists. The Majority Committee staff received nine survey responses directly from hospitals (hereinafter “Hospital Survey Responses”).

<sup>213</sup> Vizient/USP/Angels for Change Report, at 1.

<sup>214</sup> Delphine Bourneau-Martin, et al., Adverse drug reaction related to drug shortage: A retrospective study on the French National Pharmacovigilance Database, *British Journal of Clinical Pharmacology* (Sept. 16, 2022).

<sup>215</sup> Interview with Dr. Andrew Shuman.

examples below (Figure 10) are not exhaustive, but demonstrate numerous ways in which drug shortages have impacted patients, healthcare providers, and hospitals firsthand.

**Figure 10. Examples of Impact of Drug Shortages on Patients, Hospitals, and Health Systems**

Impact	Example
Patient Transfers	Dr. Unguru relayed examples to Majority Committee staff of patients that in the event smaller hospitals were unable to provide needed medications, attempts were made to secure required medications, which included transferring patients to other facilities. Dr. Unguru noted, “there are huge justice and ethics issues: patients who show up to a [larger and well-resourced hospitals] may get drugs sooner than patients who either by chance or proximity, are required to seek care at a less well-resourced hospital. It is not fair or equitable. We do not want people’s outcomes based upon luck of where they live or other factors that should not factor into whether a patient receives care.” <sup>216</sup>
Alternate Treatments	Of the nine hospitals that responded to the Majority Committee staff survey, every hospital reported having to use substitute treatments due to shortages. Although alternate treatments may appear as an adequate substitute, changing drug products can affect the way health care providers prepare medication, which can carry negative effects. For example, Eric Warren, Clinical Coordinator of Pharmacy for Munson Medical Center in Michigan stated that shortages of injectable sedatives, like lorazepam, affected alcohol withdrawal protocols to the point where nurses had to provide oral tablets instead of injectables, which presented a number of difficulties, including patient compliance and a longer release time. <sup>217</sup> The FDA provides dosage and administration guidelines for drug products, but it does not provide guidelines on substituting different drug products. <sup>218</sup>
Medication Errors	The introduction of therapeutic alternatives poses a huge impact to patient care as it can result in medication errors due to alternate product concentrations or providers who are not familiar with substitute products, among other challenges. <sup>219</sup> A recent study found that a disruption of Heparin supply from Hurricane Maria resulted in a 152 percent increase in medication error rates for Heparin and a 114 percent increase in medication error rates for its substitute drug, enoxaparin. <sup>220</sup> Further, the study concluded that “mitigation strategies assumed to be effective, such as relying on substitute medications, may be unsafe and require precautions.” <sup>221</sup>
Lack of Alternative Treatment	Shortages of children’s oncology drugs can present devastating consequences. Dr. Yoram Unguru explained the difficulty in not being able to adequately substitute pediatric chemotherapy treatments: “if amoxicillin is short, I can prescribe penicillin. But I cannot do that [in pediatric oncology cases]. It is very rare to be able to switch treatments and we are very nervous to make substitutions in the absence of data. Pediatric chemotherapy agents work in concert with one another and if you are missing one drug, we don’t know what the outcome will be. It’s similar to baking a cake, if you have flour and sugar, but no eggs, your cake is not going to turn out very well.” <sup>222</sup>
Delayed Treatment	If products are unavailable due to a shortage and there is no substitute, patients are forced to wait to receive treatment. For example, the IV contrast shortage, delayed diagnostic assessments for patients. <sup>223</sup> In some cases, Dr. Unguru pointed out that cancer patients do not have the luxury of waiting and must go with a different regime that might be a lesser alternative both in terms of evidence-base and clinical outcome. <sup>224</sup>

<sup>216</sup> Interview with Dr. Yoram Unguru.

<sup>217</sup> American Hospital Association Briefing.

<sup>218</sup> Park Dissertation, Boston University, at 85.

<sup>219</sup> Hospital Survey Responses.

<sup>220</sup> Park Dissertation, Boston University, at 4.

<sup>221</sup> *Id.*

<sup>222</sup> Interview with Dr. Yoram Unguru.

<sup>223</sup> American Hospital Association Briefing.

<sup>224</sup> Interview with Dr. Yoram Unguru.

Impact	Example
	Drs. Unguru and Shuman noted that they often experience ethical dilemmas when shortages arise and a decision about a patient’s care must be made, such as whether to keep a long-time patient on a chemotherapy agent or give the limited supply of the treatment to a new patient. <sup>225</sup>
Workforce Shortages	With a baseline shortages of health care workers, limited staffing makes it difficult to respond to shortages. Many well-resourced hospitals have dedicated staff whose only job is monitor the market and to respond to drug shortages. <sup>226</sup> Hospitals with fewer resources do not have this luxury.
Increased Costs and Waste	Hospitals reported experiencing increased costs as a direct result of drug shortages due to off-contract purchasing, more expensive medication substitutes, waste, and labor hours needed to manage shortages and mitigate the impact on patient care. Some hospitals estimated that drug shortages increased spending anywhere from \$500 thousand to \$1 million per year. <sup>227</sup>

Without a central repository for providers to learn about potential shortages, providers find out about shortages through a number of ways, including GPOs, distributors, professional connections, or social media.<sup>228</sup> With regard to allocating product during shortages, Dr. Shuman told the Majority Committee staff, “the pandemic taught us that we need an ‘eyes on’ approach to scarce resource allocation,” but “there is a tension between what is good stewardship—determining when to allocate versus ration supplies.”<sup>229</sup> The Administration’s 100-day supply report found, there is no “mechanism to ensure appropriate allocation of essential drugs during acute shortages.”<sup>230</sup>

#### IV. Challenges in Predicting, Preventing, and Mitigating Drug Shortages

Federal efforts to mitigate shortages and expand supply chain visibility have been largely reactive instead of predictive.<sup>231</sup> Departments and agencies told Majority Committee staff that they rely on the FDA to identify vulnerabilities in the medical supply chain; however, the FDA has limited visibility into both the up and downstream supply chain.<sup>232</sup> DHS added that that they “collaborate with ASPR and FDA on critical infrastructure and supply chain resilience, including information-sharing with HHS in its role as the lead federal agency for [public health and medical services].”<sup>233</sup> ASPR told the Majority Committee Staff that it has a partnership with the FDA to identify vulnerabilities in the pharmaceutical supply chain and is prioritizing critical drugs.<sup>234</sup> While the FDA developed an Essential Medicines list in 2020, the agency is currently unable to assess the percentage of life-

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<sup>225</sup> Interview with Dr. Andrew Shuman and Dr. Yoram Unguru.

<sup>226</sup> *Id.*; American Hospital Association Briefing.

<sup>227</sup> Hospital Survey Responses.

<sup>228</sup> Interview with Dr. Yoram Unguru.

<sup>229</sup> Interview with Dr. Andrew Shuman.

<sup>230</sup> White House 100-Day Supply Chain Review, at 219.

<sup>231</sup> Interview with Dr. Stephen Schondelmeyer.

<sup>232</sup> *See* DOD, DHS, and ASPR Responses; Department of Homeland Security, Briefing with Senate Committee on Homeland Security and Governmental Affairs Majority Staff (Aug. 31, 2022).

<sup>233</sup> Department of Homeland Security Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023)

<sup>234</sup> Administration for Strategic Preparedness and Response (ASPR) Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 17, 2023).

supporting and life-sustaining medications that have fewer than three manufacturers or rely on only one API supplier because the FDA does not have a list of life-supporting and life-sustaining drugs.<sup>235</sup>

Over the years, the FDA gradually received increased authorities that have allowed the agency to receive more information and in turn, better prevent and mitigate potential shortages.<sup>236</sup> For example, in 2012, Congress mandated that manufacturers notify the FDA of a “permanent discontinuance or interruption in manufacturing” that is likely to lead to a meaningful disruption in supply.<sup>237</sup> The FDA Reauthorization Act of 2017 (FDARA) directed the FDA to prioritize the review of generic drug applications for products on FDA’s drug shortage list.<sup>238</sup> In 2020, Section 3112 of the Coronavirus Aid, Relief, and Economic Security (CARES) Act expanded drug listing and reporting requirements to include API suppliers and required certain manufacturers maintain and implement risk management plans.<sup>239</sup> In addition, Congress required that manufacturers submit the amount of product produced at each facility to the FDA. Additional measures in the Consolidated Appropriations Act of 2023, including extending expiration dates for drugs in short supply and strengthening requirements for foreign establishments that produce products for the U.S. to register with the FDA, also aimed to mitigate shortages.<sup>240</sup>

Executive action throughout the past two administrations has also aimed to bolster supply chain resiliency. For example, in 2020, President Trump issued Executive Order 13944, which required the FDA to develop a list of “Essential Medicines, Medical Countermeasures, and Critical Inputs.”<sup>241</sup> In 2021, President Biden issued Executive Orders 14001 and 14017, which has prompted interagency collaboration and included a 100-day supply chain review for pharmaceuticals and APIs and a report by HHS on “supply chains for the public health and biological preparedness industrial base.”<sup>242</sup>

While these efforts by Congress and the Executive Branch will help mitigate potential shortages, recent data indicates drug shortages are currently increasing and the underlying causes of these shortages have yet to be addressed. The FDA reported preventing a record number of 317 shortages in 2021.<sup>243</sup> However, both new and active drug shortages are back on the rise with 160 new

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<sup>235</sup> FDA Response.

<sup>236</sup> See, e.g., Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115; Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-144, Title VII (hereinafter “FDASIA of 2012”); Coronavirus Aid, Relief, and Economic Security Act of 2020, Pub. L. No. 116-136 (hereinafter “CARES Act of 2020”); Food and Drug Administration, *Report to Congress: Drug Shortages for Calendar Years 2020 and 2021*.

<sup>237</sup> FDASIA of 2012, Sec. 1001.

<sup>238</sup> Food and Drug Reauthorization Act of 2017, Pub. L. No. 115-52, Sec. 801.

<sup>239</sup> CARES Act of 2020, Sec. 3112.

<sup>240</sup> Consolidated Appropriations Act of 2023, Pub. L. 117-328, Sec. 2511 and 2512.

<sup>241</sup> Exec. Order No. 13944, 85 Fed. Reg. 49929 (Aug. 6, 2020).

<sup>242</sup> Exec. Order No. 14001, 86 Fed. Reg. 7219 (Jan. 21, 2021); Exec. Order No. 14017, 86 Fed. Reg. 11849 (Feb. 24, 2021); White House). In February 2022, the Biden Administration released its *Plan to Revitalize American Manufacturing and Secure Critical Supply Chains*, which among other initiatives, called for the establishment of a “Defense Production Act Investment Program to build and expand the health resources industrial base.” See White House, *The Biden-Harris Plan to Revitalize American Manufacturing and Secure Critical Supply Chains in 2022* (Feb. 24, 2022) (<https://www.whitehouse.gov/briefing-room/statements-releases/2022/02/24/the-biden-harris-plan-to-revitalize-american-manufacturing-and-secure-critical-supply-chains-in-2022/>).

<sup>243</sup> Food and Drug Administration, *Report to Congress: Drug Shortages for Calendar Year 2021*, at 3.

shortages and a record 295 active drug shortages recorded in 2022.<sup>244</sup> For the reasons detailed throughout the section, the federal government is still not well positioned to predict and mitigate potential shortages before they become widespread.

### A. Data Shortfalls

As discussed in Section II above, no federal agency or private industry partner has end-to-end visibility into the entire U.S. pharmaceutical supply chain. Several federal agencies are engaged in efforts to improve supply chain visibility, such as the FDA’s effort to map key starting materials and drug master files, ASPR’s partnership with distributors to track critical medical products through its Supply Chain Control Tower program, and DOD’s private sector partnership to track and map the pharmaceutical supply chain. The private sector has also heavily invested in efforts to improve upstream supply chain visibility through medical supply chain mapping, but these too appear to have been independent efforts. Some of these efforts include U.S. Pharmacopeia’s Medicine Supply Map and the University of Minnesota’s Resilient Drug Supply Project.<sup>245</sup> While these efforts are critical to bolstering supply chain visibility and monitoring potential bottlenecks to better identify risks and potential shortages, the Majority Committee staff found that efforts among the agencies and industry generally lack centralized coordination.

Multiple individuals and organizations interviewed by the Majority Committee staff raised concern with the FDA’s data management and analytical capabilities.<sup>246</sup> Premier told Committee staff, “FDA is data rich, but information poor,” and has not collated the significant amount of data it has into useful information.<sup>247</sup> In contrast, Premier stated that it is able to “see market shifts earlier than FDA” by examining market demand signals and fill rates (what hospitals ordered versus what they received).<sup>248</sup> AAM expressed concern that the FDA—even with the information it currently has—does not have the ability to evaluate and predict shortages.<sup>249</sup>

In a briefing with the Majority Committee staff, the FDA acknowledged its data shortfalls. While there are still a number of gaps in the FDA’s supply chain visibility, certain data the FDA

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<sup>244</sup> American Society of Health-System Pharmacists, Drug Shortage Statistics (<https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics?loginreturnUrl=SSOCheckOnly>) (accessed Mar. 19, 2023). According to ASHP’s data, FY 2021 recorded the lowest number of new drug shortages (114) since 2006 (70).

<sup>245</sup> U.S. Pharmacopeia, Increasing visibility to strengthen supply chain preparedness (<https://www.usp.org/supply-chain/medicine-supply-map>) (accessed Mar. 19, 2023); Mary Van Beusekom, *RDSP maps medicine supply to US to predict, prevent shortages (part 2 of 2)*, University of Minnesota, Center for Infectious Disease Research and Policy Newsletter (Apr. 18, 2022) (<https://www.cidrap.umn.edu/rdsp-maps-medicine-supply-us-predict-prevent-shortages-part-2-2>).

<sup>246</sup> Interviews with Dr. Erin Fox, Dr. Stephen Schondelmeyer, Association for Accessible Medicines, and Premier.

<sup>247</sup> Interview with Premier.

<sup>248</sup> *Id.* (noting during the COVID-19 pandemic, Premier tracked hospital fill rates for 250 drug products to determine potential areas of concern if a fill rate fell below 80 percent).

<sup>249</sup> Interview with Association for Accessible Medicines. GAO identified these same concerns almost a decade ago in a 2014 report that found that FDA did not conduct “routine analyses of [its drug shortage] data to proactively identify and evaluate the risks of drug shortages.” In that report, GAO recommended that FDA conduct periodic analyses to assess and proactively identify risk factors for potential drug shortages. This recommendation remains open as FDA has yet to fully comply. Government Accountability Office, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, at 2 (GAO-14-194) (Feb. 10, 2014).

receives, such as upstream supply chain information included in new drug applications, is not provided or stored in a manner that is useful to provide adequate visibility into the supply chain.<sup>250</sup> The FDA told Committee staff that the agency has not been able to successfully map out the upstream supply chain or engage in predictive modeling “due to limitations in the way the data is submitted and maintained.” For example, while the FDA receives information on the key starting materials and other excipients used in the drug manufacturing process through these data submissions, the FDA is unable to utilize this information in analyses because it is “unstructured” and “buried in PDFs within individual applications.”<sup>251</sup> The FDA told Majority Committee staff they are currently “trying to find a way to extract this information across applications” and last year started building a key starting material database and a database of sites listed in drug master files so the information can be used for analytical purposes.<sup>252</sup> According to the FDA, “even with this data, there is no guarantee [the agency] can be predictive due to other limitations on the data FDA has access to.”<sup>253</sup>

In March 2020, the FDA received new authority to collect annual information from registered drug manufacturers on the amount of certain drugs they produce for commercial distribution.<sup>254</sup> However, the agency is still in the process of issuing final guidance for industry on these amount reporting requirements. The FDA attributed the delay of implementation to the need to first identify the information to be submitted, and then build the IT infrastructure to receive amount reporting. Finally, the FDA had to “develop training and technical guidance” to instruct registrants on how to submit the reports. According to the FDA, few manufacturers have started providing such amount reporting and the FDA anticipates industry is waiting for final FDA guidance.<sup>255</sup>

To date, FDA has received 19% of listed drugs submitted amount information for CY 2020 and 16% submitted amount information for CY 2021. As a result, the FDA is still not yet fully able to estimate potential reliance on foreign sources based on amount reporting (e.g., to assess how much product each registered manufacturer is producing from each source).<sup>256</sup> Even with the amount data reported, the FDA will not be able to “connect the dots” in the supply chain to identify which manufacturers are relying on which API source(s) and how much material they source from each API or KSM supplier because section 510(j)(3) of the Federal Food, Drug, and Cosmetic Act does not require registrants to submit information about their suppliers or how reliant they are on each

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<sup>250</sup> Food and Drug Administration, Briefing with Senate Committee on Homeland Security and Governmental Affairs Majority Staff (Feb. 15, 2023) (hereinafter “FDA Briefing”). FDA received upstream supply chain information via drug applications and drug master files (DMFs). Industry submits this information to FDA electronically in separate submissions in an electronic gateway and in the form of PDF or word documents. Within these submissions are multiple sections (e.g. raw materials, etc.) and within each section are additional documents.

<sup>251</sup> *Id.*

<sup>252</sup> *Id.*

<sup>253</sup> Food and Drug Administration Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

<sup>254</sup> Section 510(j)(3) of the Federal Food, Drug, and Cosmetic Act as added by the CARES Act, Sec. 3112(e).

<sup>255</sup> FDA Briefing.

<sup>256</sup> *Id.* FDA told the Majority Committee staff, “the timelines proposed in the FDA’s October 2021 draft guidance for submitting the required annual reports were only recommendations and not binding on industry.” Food and Drug Administration Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 15, 2023).

supplier.<sup>257</sup> Additionally, since it is only reported annually, the data will only provide the FDA with a “snapshot in time,” not a “real time” view into the pharmaceutical supply chain.

Insufficient information sharing among industry partners also “limits the ability to predict and prevent shortages, making it more difficult to track product allocations.”<sup>258</sup> The FDA is constrained by statutory requirements and agreements with companies on what information they are able to share with federal partners.<sup>259</sup> As a result, limited data sharing among key federal and industry partners hinders efforts to increase end to end supply chain visibility and thoroughly assess risks.<sup>260</sup> ASPR explained, the inability to easily share information between federal agencies limits potential analyses that can be performed with the FDA, noting, “the federal government does not currently gather all production volume data in a manner that would facilitate easy understanding of supply chain limitations, and commercial software produces limited results based on incomplete data sets.”<sup>261</sup> DOD added that in addition to these constraints, “[the] FDA’s data are not complete since some suppliers change their sources frequently for various business reasons. Tracking those changes has been challenging for [the] FDA.”<sup>262</sup> Insufficient information sharing among industry partners also “limits the ability to predict and prevent shortages, making it more difficult to track product allocations.”<sup>263</sup>

## **B. Domestic Manufacturing Capacity and Technology Limitations**

Senator Peters’ 2019 report found that domestic pharmaceutical manufacturing is declining and the U.S. was losing its ability to independently manufacture generic antibiotics.<sup>264</sup> According to the Biden Administration’s 100 Day Supply Report, the U.S. does not have domestic production capacity for many generic antibiotics.<sup>265</sup> ASPR has also reported that the U.S. workforce “lags behind international competitors in the number of students pursuing STEM-related degrees” necessary for pharmaceutical manufacturing roles and has a “shortage of trained workers for all educational levels, both in research and factory.”<sup>266</sup> The lack of robust domestic manufacturing capacity and diversification of suppliers for critical generic drugs prone to shortage, leaves the U.S. vulnerable to a variety of threats.

While investments in advanced manufacturing technologies, such as continuous manufacturing, have the potential to develop cost-effective, efficient, and sustainable domestic manufacturing capabilities, generic manufacturers generally do not have the resources to invest in developing these technologies, especially for low-profit margin generic drug products.<sup>267</sup> Investment in continuous

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<sup>257</sup> Section 510(j)(3) of the Federal Food, Drug, and Cosmetic Act as added by the CARES Act, Section 3112(e).

<sup>258</sup> ASPR, ARMI, and NextFAB Report, at 20.

<sup>259</sup> 21 U.S.C. § 331(j); 18 U.S.C. §§ 1905-1909; *see also* FDA Briefing.

<sup>260</sup> ASPR Supply Chain and Industrial Analysis Report, at 3; *see also* ASPR, ARMI, and NextFAB Report, at 20.

<sup>261</sup> ASPR Supply Chain and Industrial Analysis Report, at 3.

<sup>262</sup> DOD Response.

<sup>263</sup> ASPR, ARMI, and NextFAB Report, at 20.

<sup>264</sup> HSGAC Minority Staff Report, *A Price Too High*, at 5.

<sup>265</sup> White House 100-Day Supply Chain Review, at 231.

<sup>266</sup> ASPR, ARMI, and NextFAB Report, at 18; ASPR Supply Chain and Industrial Analysis Report, at 7.

<sup>267</sup> ASPR, ARMI, and NextFAB Report, at 18; *see also* Government Accountability Office, *Drug Manufacturing: FDA Should Fully Assess Its Efforts to Encourage Innovation*, at 26 (GAO-23-105650) (Mar. 2023) (hereinafter “2023

manufacturing could also shorten lead times for producing drugs, which currently take anywhere from several days to a month or more for API manufacturing. It then takes several days to weeks to manufacture finished doses through batch manufacturing because all the steps and testing must be independently completed before a batch is released.<sup>268</sup> According to GAO, continuous manufacturing can produce “finished drug products in days as opposed to traditional batch manufacturing that can take months.”<sup>269</sup>

Recent legislative and executive actions aim to bolster developments and private public partnerships in advanced manufacturing technologies. With funding from the CARES Act of 2020 and the American Rescue Plan Act of 2021, federal agencies have started to make significant investments in domestic manufacturing capacity and capabilities.<sup>270</sup> For example, in May 2020, the Biomedical and Advanced Research and Development Authority (BARDA) launched its Pharmaceutical Manufacturing in America Initiative to expand domestic manufacturing capabilities for vaccine production and raw materials needed to manufacturing life-saving drugs.<sup>271</sup> The Consolidated Appropriations Act of 2023 authorized FDA’s Emerging Technology Program (aimed to improve collaboration with industry and academics during the development of innovative manufacturing approaches) and National Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing (which provides grants to certain higher education institutions to invest in advanced pharmaceutical manufacturing technologies).<sup>272</sup> In March 2023, ASPR established the “Industrial Base Management and Supply Chain Office . . . to ensure that critical supplies are manufactured in the United States.”<sup>273</sup> However, more action is needed, particularly with regard to drug products that are not listed on the FDA’s Essential Medicines List, but regularly experience shortages.

In its *Essential Medicines Supply Chain and Manufacturing Resilience Assessment Report*, ASPR acknowledged that “there is [ ] a gap in government funding for supporting technologies through the transition from development in academic laboratories to commercial-scale production.”<sup>274</sup> GAO recently examined the FDA’s advanced manufacturing initiatives and identified shortfalls in assessing the programs’ progress because the FDA had not “documented and finalized performance

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GAO Report on Drug Manufacturing”) (explaining “[g]eneric companies’ adoption of advanced manufacturing could potentially have a large effect on drug manufacturing and ease shortages. However, shorter exclusivity periods and smaller profit margins, among other reasons, make it harder for generic companies to make the business case for adopting advanced manufacturing technologies”).

<sup>268</sup> White House 100-Day Supply Chain Review, at 212.

<sup>269</sup> 2023 GAO Report on Drug Manufacturing, at 7 (noting, “according to FDA the use of automated monitoring that occurs in continuous manufacturing may help avoid supply disruptions, because such monitoring can detect manufacturing equipment failures before they occur [and] monitoring can also enable product quality to be precisely controlled, thereby reducing the quality issues that may trigger drug shortages”).

<sup>270</sup> Administration for Strategic Preparedness and Response, *Report to Congress on Investments in Domestic Drug Manufacturing* (Jan. 2023) (on file with Committee).

<sup>271</sup> Biomedical and Advanced Research and Development Authority, *Pharmaceutical Manufacturing in America* (<https://medicalcountermeasures.gov/barda/influenza-and-emerging-infectious-diseases/coronavirus/pharmaceutical-manufacturing-in-america/>) (accessed Mar. 19, 2023).

<sup>272</sup> Consolidated Appropriations Act of 2023, Pub. L. 117-328, Sec. 3203 and 3204.

<sup>273</sup> Department of Health and Human Services, Administration for Strategic Preparedness and Response, *Justification of Estimates for Appropriations Committee Fiscal Year 2024* (undated).

<sup>274</sup> ASPR, ARMI, and NextFAB Report, at 18.



goals.”<sup>275</sup> GAO also highlighted high barriers for generic manufacturers to use advanced manufacturing technologies due to smaller profit margins and need to manufacture multiple products on one production line.<sup>276</sup> While ASPR implemented a new Innovation and Industrial Base Expansion Program (IBx) in September 2020 to address medical supply chain vulnerabilities and bolster public health preparedness, GAO found in April 2022 that the department had “not fully assessed the workforce skills and competencies needed to support the mission and goals of the office, nor has it developed strategies to address those needs.”<sup>277</sup>

## V. Conclusion

As identified throughout the report, drug shortages continue to present serious health and national security risks. These risks carry devastating, yet avoidable consequences for all Americans, including our military. The COVID-19 pandemic and recent confluence of respiratory viruses this past winter illustrates the importance of predicting, preventing, and mitigating potential supply chain vulnerabilities before they result in shortages.

To date, federal and industry efforts to prevent and mitigate drug shortages remain insufficient. With multiple underlying causes, the federal government must consider an array of reforms to address the key drivers of drug shortages. Specifically, the federal government must centralize efforts to obtain end-to-end supply chain visibility. It must better coordinate with industry and interagency partners to preemptively identify vulnerabilities and chokepoints for critical drug products and the key starting materials and APIs and needed to make them.

Ultimately, Congress must act to ensure the federal government improves data capabilities and more effectively invests in advanced manufacturing technologies for critical generic drug products (and their key inputs) and to promote diversification of suppliers through onshoring and nearshoring in a cost-effective and sustainable way. Congress should also require DOD, DHS, and HHS to jointly engage in routine supply chain risk assessments to identify potential national security concerns. Until the federal government and industry strengthen efforts to jointly assess and address their underlying causes, drug shortages will remain a consistent health and national security risk.

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<sup>275</sup> 2023 GAO Report on Drug Manufacturing, at 1.

<sup>276</sup> *Id.* at 26.

<sup>277</sup> Government Accountability Office, *COVID-19: Current and Future Federal Preparedness Requires Fixes to Improve Health Data and Address Improper Payments*, at 35 (GAO-22-105397) (Apr. 2022).