

**DRUG SHORTAGE HEALTH AND NATIONAL
SECURITY RISKS: UNDERLYING CAUSES AND
NEEDED REFORMS**

HEARING

BEFORE THE

COMMITTEE ON
HOMELAND SECURITY AND
GOVERNMENTAL AFFAIRS
UNITED STATES SENATE
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CONTENTS

Opening statements:	Page
Senator Peters	1
Senator Paul	3
Senator Lankford	16
Senator Blumenthal	19
Senator Hassan	21
Senator Johnson	23
Senator Hawley	25
Senator Rosen	28
Prepared statements:	
Senator Peters	35
Senator Paul	37

WITNESSES

WEDNESDAY, MARCH 22, 2023

Andrew Shuman, M.D., Associate Professor of Otolaryngology-Head and Neck Surgery, and Chief of the Clinical Ethics Service Center for Bioethics and Social Sciences in Medicine, University of Michigan Medical School	5
Vimala Raghavendran, Vice President Informatics Product Development, U.S. Pharmacopeia	7
Erin Fox, Pharm.D., Associate Chief Pharmacy Officer of Shared Services and Adjunct Professor, College of Pharmacy, University of Utah	9
John C. Goodman, Ph.D., President Goodman Institute for Public Policy Research	11

ALPHABETICAL LIST OF WITNESSES

Fox, Erin Pharm.D.:	
Testimony	9
Prepared statement	55
Goodman, John C. Ph.D.:	
Testimony	11
Prepared statement	63
Raghavendran, Vimala:	
Testimony	7
Prepared statement	46
Shuman, Andrew, M.D.:	
Testimony	5
Prepared statement	40

APPENDIX

Majority Staff Report	74
Statements submitted for the Record:	
Association of Clinical Oncology	115
Children's Cancer Cause	120
Healthcare Supply Chain Association	123
Responses to post-hearing questions for the Record:	
Ms. Raghavendran	126
Ms. Fox	129

DRUG SHORTAGE HEALTH AND NATIONAL SECURITY RISKS: UNDERLYING CAUSES AND NEEDED REFORMS

Wednesday, March 22, 2023

U.S. SENATE,
COMMITTEE ON HOMELAND SECURITY
AND GOVERNMENTAL AFFAIRS,
Washington, DC.

The Committee met, pursuant to notice, at 10 a.m., in room SD-562, Dirksen Senate Office Building, Hon. Gary Peters, Chairman of the Committee, presiding.

Present: Senators Peters [presiding], Hassan, Sinema, Rosen, Ossoff, Blumenthal, Paul, Johnson, Lankford, Romney, Scott, and Hawley.

OPENING STATEMENT OF SENATOR PETERS¹

Chairman PETERS. The Committee will come to order.

Today's hearing will examine ongoing and rising shortages of medications, which range from drugs used in hospitals to provide critical care and treat serious diseases like cancers, to prescription medications, and even common over-the-counter remedies to treat cold and flu symptoms.

After a winter with high cold, flu, and respiratory syncytial virus (RSV) cases, many of us have gone to the store and have seen bare shelves due to shortages of children's Tylenol and Motrin. Others have faced shortages of key prescription medications, including antibiotics.

Throughout the country, hospitals regularly experience shortages of a range of drugs needed for emergency care, for surgeries, and for other procedures. These often include sterile injectable drugs like intravenous (IV) saline solution and sodium bicarbonate needed to provide critical care, dialysis, and other lifesaving treatments. Some of these products have been in shortage for over a decade. For example, lidocaine, used to manage pain, has remained in shortage since 2011. Vancomycin, used to treat bacterial infections, has been in shortage since 2009. Even drugs needed to treat childhood and adult cancers, including some that have simply no alternative treatment, are regularly in shortage. While some shortages may only be an inconvenience, others can have devastating impacts on patient care.

¹The prepared statement of Senator Peters appears in the Appendix on page 35.

These shortages, which reached a peak of 295 individual drugs in shortage at the end of 2022, have left health care professionals grappling with limited resources to treat patients in need.

Drug shortages are certainly not new. There are a number of factors that contribute to drug shortages, including economic drivers that lead to a lack of manufacturers willing to enter or to remain in the market or invest in quality manufacturing systems, insufficient visibility into the entire supply chain for critical medications, and an overreliance on foreign and geographically concentrated sources for the materials needed to make these drugs. Taken together, these underlying causes not only present serious concerns about providing adequate care to patients, they also represent serious national security threats.

In 2019, I released a report identifying many of these national security risks, and how they contributed to drug shortages and in some cases, price hikes. My report found that nearly 80 percent of the manufacturing facilities that produce active pharmaceutical ingredients (APIs), the key ingredients that give a drug its intended effect, are located outside of the United States, and many of our APIs are sourced from either China or India.

Just months after I released that report, as the Coronavirus Disease 2019 (COVID-19) pandemic spread around the globe, we saw firsthand how our overreliance on foreign producers for medical products, along with failures to adequately prepare for a pandemic, quickly led to widespread shortages of desperately needed medications and medical supplies like personal protective equipment (PPE).

Today, I am releasing a new report, that I am holding up here, that builds on those previous findings and identifies additional recommendations to strengthen domestic manufacturing of critical drugs and limit the disruptions caused by shortages and supply chain issues.

I now move to introduce this report into the record,¹ and without objection, the report will be included in the hearing record.

My report finds that between 2021 and 2022, new drug shortages increased by nearly 30 percent, and that both the pharmaceutical industry and the Federal Government, including the Food and Drug Administration (FDA), lack the information needed to effectively detect and to prevent shortages.

Most significantly, this updated report found that our continued overreliance on foreign suppliers for the key materials needed to make critical drugs, primarily those in China, remains an unacceptable national security risk. For example, over 90 percent of generic injectable drugs used to treat serious injuries or illnesses in the United States rely on key materials from China and India, and nearly 90 percent of generic API manufacturing sites are located overseas.

My report makes several recommendations to help protect our health and our national security, including to invest in advanced manufacturing capabilities to produce critical drugs here in the United States, and require that the Food and Drug Administration and its interagency partners can get the information needed to bet-

¹The Majority Staff Report appears in the Appendix on page 74.

ter monitor supply chain vulnerabilities and to anticipate possible shortages.

I am encouraged by recent legislative and executive actions to bolster our medical supply chain resiliency. Last Congress, I helped author a bipartisan provision to increase visibility into where critical medical supplies and drugs are produced, and this Congress I am working on legislation that builds on many of the report recommendations to protect our health and national security. I look forward to working with my colleagues to advance these important measures.

Today's discussion with our panel of expert witnesses will provide even more detail about what Congress and our Federal agencies should do to address both drug shortages and the national security risks that they present, and I look forward to the conversation.

I would now like to recognize Ranking Member Paul for his opening statement.

OPENING STATEMENT OF SENATOR PAUL¹

Senator PAUL. Ever wonder why we never have shortages of iPhones or computers? What separates the drug industry from the computer or smartphone industries? Computers and smartphones, like drugs, are highly technical and globalized industries, yet there are seldom shortages in any of those industries.

However, unlike the computer, automobile, or smartphone industry, the needs addressed by the drug manufacturing industry are often a matter of life and death. This is why the decisions of policymakers and regulators are of utmost importance. Rules and regulations that inhibit the production of drugs will create pain for hospitals and patients.

The Food and Drug Administration recently identified a shortage of over 120 different drugs. Some of these drugs, such as saline, are necessary for the most basic of treatments.

These shortages are not a new phenomenon. This has been going on for quite some time. Since 2007, the FDA identified an average of over 100 separate drug shortages per year. In 2011, the FDA identified a whopping 267 drugs in short supply. Despite possessing the most innovative medical industry in the world, the United States is unable to maintain a consistent supply of the most crucial medicines. We have to understand why. We understand there is a problem and we have to understand why this is happening.

While many blame these shortages on foreign producers, so-called "greedy" pharmaceutical companies, and even hospitals, it is no coincidence that the rise in drug shortages correlates with the expanded regulatory reach of the FDA.

Drug shortages force doctors to consider rationing medicines and postponing essential procedures and force patients to needlessly suffer.

While our nation's hospitals have trouble purchasing the necessary amounts of drugs for cancer patients, heart attack victims, and those in chronic pain, these same hospitals find no such short-

¹The prepared statement of Senator Paul appears in the Appendix on page 37.

age when purchasing computers. Doctors and nurses do not have to cope with a smartphone shortage. There has to be an explanation here.

The key difference between these industries and the drug manufacturing industry is obvious. The companies producing computers and smartphones are, by comparison, left to compete with one another with little manipulation from the government, while the FDA places the heavy yoke of regulation on drug manufacturing. This is the key difference. It is the heavy hand of government.

Over 40 years ago, Milton Friedman remarked, “If you put the Federal Government in charge of the Sahara Desert, in five years there would be a shortage of sand.” While Friedman was discussing price controls and output restrictions on oil and gas production in Dubai, the same wisdom still holds for drug pricing in our country.

The drug industry is one of the most regulated markets in the economy. Output controls, such as FDA’s approval procedure for nearly every step of the manufacturing process, increase the cost of production and restrain the adaptability of manufacturers to meet shifting demands. When one company goes out of business, another one cannot ramp up without asking permission to make more of a drug. If a drug maker closes, the remaining manufacturers, which must react to increased demand, are forced to seek FDA approval to produce more than the originally approved amount or to produce quicker than the originally approved timeline. This is crazy and we should stop it.

Why does the United States embrace central planning in health care? Central planning produced shortages of even the most basic consumer goods in communist countries during the Cold War. There is a famous Soviet quip about a man entering a shop and asking the clerk, “You don’t have any meat?” The clerk says, “No, we are the store that doesn’t have any fish.” They were used to shortages. It was a common thing. It was common enough that people joked about not being able to get enough of basic items.

We should not tolerate central planning in a capitalist country for the most essential products on the market. Further abandoning the principles of basic economics, Medicare price controls, such as requiring drug companies to pay rebates to Medicare if they raise their prices too quickly, create even more barriers to entry, which prevent competitors from arising in the market. Limiting the amount of drug production and producers results in artificially high prices and drug shortages.

Americans will be healthier and live longer if their government allows innovators to provide drugs at affordable prices, and produce a strong supply. I hope this hearing will identify the regulations that impede the ability of markets to do what they do best—provide for the consumer.

I look forward to hearing our witnesses’ testimonies.

Chairman PETERS. Thank you, Senator Paul.

The practice of the Homeland Security and Governmental Affairs Committee (HSGAC) is to swear in our witnesses, so if each of our witnesses would please stand and raise your right hand.

Do you swear that the testimony you will give before this Committee will be the truth, the whole truth, and nothing but the truth, so help you, God?

Dr. SHUMAN. I do.

Ms. RAGHAVENDRAN. I do.

Ms. FOX. I do.

Mr. GOODMAN. I do.

Chairman PETERS. Thank you. You may be seated.

Our first witness is Dr. Andrew Shuman, Associate Professor of Otolaryngology—I hope that is correct; that is quite a mouthful. He is also in Head and Neck Surgery at the University of Michigan Medical School, and Chief of Clinical Ethics Service at the Center for Bioethics and Social Sciences in Medicine. Dr. Shuman is an internally recognized leader on ethical issues within his specialty, and has authored numerous publications in several leading journals in the field, including the *New England Journal of Medicine*.

Dr. Shuman, welcome to the Committee. You may proceed with your opening remarks.

TESTIMONY OF ANDREW SHUMAN, M.D.,¹ ASSOCIATE PROFESSOR OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY, AND CHIEF OF THE CLINICAL ETHICS SERVICE CENTER FOR BIOETHICS AND SOCIAL SCIENCES IN MEDICINE, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

Dr. SHUMAN. Thank you, Chairman Peters, Ranking Member Paul, and the Committee for the privilege of speaking with you today. I am a cancer surgeon and a medical ethicist, and I have a surgical practice and leadership roles at both the University of Michigan and the Veterans Affairs (VA). I am not speaking on behalf of either institution today.

My personal experience with drug shortages began 15 years ago. At the time, there was a national shortage of propofol, an anesthetic we need to perform surgery, that required anesthesiologists to improvise how to keep patients comfortable. You do not need to go to medical school to realize that patients need to stay asleep during their operation.

Since that first experience, colleagues and other hospitals have asked me to help them respond to the never-ending game of drug shortage Whack-a-Mole. My goal for the next few minutes is to share some examples from my experience trying to protect patients from the serious medical consequences of not having access to the drugs they need.

We are lucky enough to live in a country where cutting-edge research has massively reduced cancer-related deaths, but cancer drug shortages represent a tragedy that is happening in slow motion. For example, etoposide is a cancer drug that has been on the market for over 40 years and typically costs less than \$50 per vial. It is given to patients for nearly a dozen different kinds of cancer. But in 2018, due to a manufacturing delay, this drug was on shortage across the country. Which of our patients with cancer should get it? How can we prioritize between American lives? Should our limited vials go to an older woman who was just diagnosed with lung cancer? A young man who had already been successfully taking it for testicular cancer? Or a baby with neuroblastoma, an ag-

¹The prepared statement of Dr. Shuman appears in the Appendix on page 40.

gressive cancer for which this drug is recommended, but others might substitute?

Our hospital, like others across the country, struggled to make these decisions based on projected availability, which patients were already under our care, and our best guess at how many new patients would be diagnosed in the coming weeks. As a doctor who has devoted my life to fighting cancer, it is hard to express how horrible that is.

In this particular case, we had enough drug for our lung and testicular cancer patients, and our heroic pharmacist was able to scrape together enough etoposide from the bottom of the leftover vials to also treat the infant patient. But our pharmacists should not be desperately trying to squeeze out a few last drops when a life may be on the line.

While my focus is on oncology, drugs shortages impact every field of medicine. For example, Senator Paul has dedicated his professional career to preserving and restoring his patients' vision. There are eyedrops that literally keep people from going blind that cost a few dollars, but these are sometimes unavailable.

All patients affected by drug shortages deserve better. I would be remiss not to point out how the COVID pandemic has exacerbated drug shortages. My colleagues across the country have worked tirelessly over the past three years to take care of patients with COVID. We have learned quite a bit about how to conserve and ration health care resources, and try to do so equitably to ensure that diverse patient communities have access to the best care possible.

But all hospitals do not have access to the same resources. Michigan Medicine has multiple pharmacists whose full-time job is mitigating drug shortages, but not every hospital has that resource. Patients should not have better access to scarce drugs based on the hospital they go to. This is why I and my team have studied how institutions across regions can better communicate about ongoing shortages.

One key role for lawmakers is to improve drug shortage monitoring and information sharing nationwide. Information sharing is a critical component of health care emergency preparedness. We often think of important resources in terms of staff, space, and stuff. For example, in April 2020, we desperately tried to make sure we had enough ventilators—this is at the onset of the COVID pandemic—but a ventilator is just an expensive box if we do not have enough respiratory therapists to operate it. At Michigan Medicine, we had to train our medical students to help use the ventilators when we ran out of respiratory therapists.

Even if we have enough ventilators and the personnel, we still need enough hospital beds, which remain in short supply even today. Finally, the patient on that ventilator needs the proper medications to keep them sedated and comfortable, ironically the same medication, propofol, we ran out of in the operating room.

We need to diversify where our medical supplies come from, including increasing production on American soil. Companies need to disclose the reasons they cannot meet demand. Otherwise, we will not know where to focus resources.

In addition, drug pricing structures are not always reflective of their value to patients. We should incentivize companies to make

high-quality, critical-need drugs like the ones that I have mentioned, even if they have been less profitable historically.

We can all agree that sick Americans deserve access to lifesaving medications. Telling someone with cancer that they cannot receive a drug that was developed during the Johnson administration and costs less than my Uber ride from the airport is simply not acceptable.

I thank the Committee for highlighting this critical issue finding creative legislative solutions.

Chairman PETERS. Thank you, Dr. Shuman.

Our next witness is Vimala Raghavendran, who is the Vice President of Informatics Product Development at U.S. Pharmacopeia (USP), an independent, scientific, nonprofit organization focused on building trust in the supply of safe, quality medicines. She led the development of USP's Medicine Supply Map, an information platform that identifies and forecasts risk in the generic drug supply chain to help predict potential shortages.

Welcome, Ms. Raghavendran. You are welcome to the Committee and you may proceed with your opening comments.

**STATEMENT OF VIMALA RAGHAVENDRAN,¹ VICE PRESIDENT
INFORMATICS PRODUCT DEVELOPMENT, U.S. PHARMACOPEIA**

Ms. RAGHAVENDRAN. Good morning and thank you, Chairman Peters, Ranking Member Paul, and distinguished Members of the Committee for this opportunity to testify today. As you note, my name is Vimala Raghavendran, and I am Vice President for Informatics Product Development at USP. I am pleased to provide USP's perspective on the underlying causes of drug shortages and the reforms needed to improve the resiliency of our nation's medicine supply.

USP is an independent, scientific, nonprofit organization founded in 1820, when 11 physicians took action to protect patients from poor-quality medicines. Convening in the old Senate Chamber, they published a national, uniform set of guidelines for medicines called the U.S. Pharmacopeia.

A core pillar of USP's mission in the 200 or so years since then has been to help strengthen the pharmaceutical supply chain so that the medicines people rely on are available and meet quality standards.

The Federal Food, Drug, and Cosmetics Act of 1938, created the requirement that medicines sold in the United States generally must adhere to USP standards. As a result, USP standards are used in the vast majority of FDA registered facilities that make pharmaceutical finish doses and active ingredients.

Drug shortages remain a persistent threat to both public health and national security. When there is a drug shortage it means that a patient is not able to get a medicine they need to either protect their health or save their life.

Recognizing the urgent need for more insight to guide solutions, USP invested in the development of a data intelligence platform, the Medicine Supply Map. As you note, Chairman Peters, our mission is to identify, characterize, and quantify supply chain risk so

¹The prepared statement of Ms. Raghavendran appears in the Appendix on page 46.

that stakeholders can anticipate and mitigate the impact of drug shortages. We quantified over 200 factors that contribute to drug shortages in order to build our models.

Based on this work, USP has identified four types of risk that are correlated with drug shortages, many that you outlined in your opening statement. The first is geographic concentration. Our data shows that geographic concentration anywhere, including within the United States, can result in drug shortages.

The second factor is manufacturing complexity, which can take many forms. For example, the need to maintain sterility when making injectables or the need for dedicated facilities to make certain types of antibiotics.

The third factor is price. USP's analysis shows that lower-priced drugs have a higher likelihood of being in shortage. We see this particularly for older generics like sterile injectables and antibiotics. Manufacturers only receive pennies per dose for some of these drugs.

Fourth is quality. Drugs made at facilities that have a history of poor outcomes from FDA inspections are more likely to experience drug shortages, as are drugs with a history of recalls.

Given these findings, USP makes the following recommendations to Congress.

One, establish an early warning system and research center of excellence that will help assess risks in the supply chain and predict drug shortages, giving stakeholders in the public and private sector enough notice to react. USP has started working on this, as have other organizations, but more work is needed. For example, policymakers are flying blind in our understanding of U.S. reliance on other countries for critical ingredients used in the manufacture of medicines.

Two, protect critical medicines with vulnerable supply chains by investing in solutions that incentivize new and efficient manufacturing technologies that have the potential to bring manufacturing back to the United States. USP is working with FDA and other partners to facilitate the adoption of advanced manufacturing. Congress can help by making it easier for manufacturers by funding workforce development and the development of practices and methodologies that apply industry-wide. We thank Congress for the omnibus spending law passed in December 2022, that calls on the Department of Health and Human Services (HHS) to establish centers of excellence that support advanced manufacturing. That was an important step.

Finally, Congress should consider comprehensive solutions that extend beyond an exclusive focus on onshoring. Given our finding, the geographic diversity is important to a resilient medicine supply.

Again, thank you to the Committee for this opportunity for input. We welcome the prospect of serving as a resource to you as you seek solutions, and I look forward to answering any questions you have. Thank you.

Chairman PETERS. Thank you, Ms. Raghavendran, thank you so much for your comments today.

Our next witness is Dr. Erin Fox. Dr. Fox is the Associate Chief Pharmacy Officer of Shared Services and Adjunct Professor at the

University of Utah College of Pharmacy. Dr. Fox's areas of expertise include drug shortages, medication use policy, drug information, evidence-based medicine, and drug costs.

Dr. Fox, welcome to the Committee. You may proceed with your opening remarks.

TESTIMONY OF ERIN FOX, PHARM.D.,¹ ASSOCIATE CHIEF PHARMACY OFFICER OF SHARED SERVICES AND ADJUNCT PROFESSOR, COLLEGE OF PHARMACY, UNIVERSITY OF UTAH

Ms. FOX. Thank you, Chairman Peters, Ranking Member Paul, and distinguished Members of the Committee, for holding this hearing and for inviting me to participate.

I am the Associate Chief Pharmacy Officer for Shared Services at University of Utah Health, but I am not speaking on behalf of the university today. I am here to provide my perspective on drug shortages, highlight some of the problems shortages create, and offer two recommendations.

My team and I at the University of Utah Drug Information Service have tracked national drug shortages since January 2001. We receive voluntary reports from health care providers who cannot access important medicines for their patients. We confirm directly with manufacturers if there is or is not a shortage, and we post our findings to a public website that is hosted by the American Society of Health-System Pharmacists.

Our goal in providing these data is to help clinicians mitigate the effects of drug shortages, providing estimated release dates, evidence-based safety and management suggestions. Currently, we are tracking 302 active drug shortages.

Some patients have died due to drug shortages, most as a result of medication errors where substitute drugs were dosed incorrectly or an emergency product was not available. Patients also suffer when alternative drugs have worse outcomes than the drug of choice, such as patients with sepsis, who had a higher mortality rate during a shortage of norepinephrine. Shortages of chemotherapy have led to delayed treatments, delayed clinical trials for new therapies, reduced doses, and poor outcomes.

In the background, pharmacists scramble. Most health systems have one or more full-time employees devoted exclusively to shortage management, directing medication switches, and spending time tracking down scarce products.

Switching products is time-consuming and challenging in today's technologically advanced pharmacies. Switching just two drugs, for example, to be administered in syringes instead of saline bags did help us, at our organization, manage our saline shortage, but it also required us to review and manually change 700 patient treatment plans in a single day.

The cause of a specific shortage is rarely publicly available. When we investigate shortages we ask manufacturers for causes directly. We also use other available data, such as FDA inspection reports, but in most cases we cannot identify what triggered a specific shortage. Was it a quality problem? A demand increase? A

¹The prepared statement of Dr. Fox appears in the Appendix on page 55.

prioritization issue to prioritize other products? Problems accessing ingredients? Answers to these questions are important because they can give us clues about how long a shortage will last and how long a shortage will last is something that companies often do not give us.

Although we may not know what drives individual shortages, we now understand an important economic driver. There is no recognition for manufacturers that choose to invest in quality. FDA sees really clear quality differences between products and manufacturing sites, but this information is confidential and it is not available to the people making the purchases.

Buyers cannot easily see the reliability of manufacturing operations, so there is a race to the bottom for prices, the result of pressure from hospitals that are paid with capitated payments, and group purchasing organizations that contract on behalf of hospitals. For a pharmacy buyer, the differentiating factor is price.

I was part of National Academies of Sciences, Engineering, and Medicine's (NASEM) consensus committee on building resilience into the nation's medical product supply chains. Our committee provided a comprehensive set of recommendations, which I urge you to review.

I have two recommendations that build on this report today. First, we need additional transparency to develop a rating system for pharmaceutical manufacturing reliability. FDA has been working to develop quality metrics ratings, but they do not intend to make the scores publicly available. A rating system could be used by health systems that are already paying more for shortages, with employees and time spent making drug switches. Hospitals would be wise to consider paying more for reliable supply agreements, particularly in the current setting of significant health care labor shortages. Payers and accreditation bodies can also incentivize hospitals to do the same, to prevent poor patient outcomes.

Second, if the Federal Government intends to use tax credits, loans, or subsidies to strengthen supply chains, FDA's current list of critical medications is not a good starting point. Understanding which products are most at risk would allow targeted, more effective actions to prevent or mitigate shortages with limited resources available. I am concerned that without addressing the scope of the current FDA list and the scope of our analytical capabilities the government may be overlooking some critical supply chains and their vulnerabilities and opportunities to strengthen supply chains.

Thank you once again for holding this hearing and for the opportunity to share my perspective. I welcome any questions you may have.

Chairman PETERS. Thank you, Dr. Fox.

Our final witness is Dr. John Goodman. Dr. Goodman is President of the Goodman Institute for Public Policy Research. Dr. Goodman received his Ph.D. in economics from Columbia University and has taught at Columbia University, Stanford University, Dartmouth University, Southern Methodist University, and the University of Dallas. Dr. Goodman regularly writes and speaks about health policy.

Dr. Goodman, welcome to the Committee. You may proceed with your opening remarks.

**TESTIMONY OF JOHN C. GOODMAN, PH.D.,¹ PRESIDENT,
GOODMAN INSTITUTE FOR PUBLIC POLICY RESEARCH**

Mr. GOODMAN. Thank you, Senator Peters, Senator Paul, and the rest of the Committee. Thank you for having me here today.

We have shortages, especially in the market for generic drugs because, No. 1, we have price controls in the Medicare Part B program, we have price controls in the 340B program, we have unproductive output regulations, that Senator Paul so aptly described, and probably more important than those three things all combined is the fact that we have suppressed in this market normal market forces that eliminate shortages everywhere else in the economy.

If the manufacturer of a generic drug finds a way to make that drug more reliable, more consistent, safer, even more efficacious, better at curing diseases, the manufacturer cannot communicate this information to the buyers of the drug. Therefore, he cannot profit by making these changes.

What has happened in this market is the FDA imposes on the market a vision that all generics are the same, the only difference among them is price, and that is the only difference that is allowed to be communicated. The principle here is that if you force buyers and sellers to compete on price and price alone, you are going to get a race to the bottom on every other feature of the product, and that is what is happening in this market.

If I could compare it to another market, if there is a wine in surplus and the price goes down, Walmart buys it and stocks it. If there is a shortage of a wine and the price goes up, Walmart may not buy it at all. In Dallas, Texas, when I go to Sam's Club, I know I am going to pay the lowest price in all of Dallas, but they may not have the wine I want. If I go to a boutique wine shop, on the other hand, I may pay \$1 or \$2 more, but they will have the wine I want. What we are doing is we are forcing, in the generic drug market, the Walmart approach to every other product.

Now, this report that you all have put out today I think it is really good on problems, better than I could have done in my testimony. It mentions a few things I have already mentioned. It says that in this market people are competing on price alone, that there is a race to the bottom on every other feature of the product. It compares the market for brand drugs to the market for generics. All that is really good.

But when we come to the solutions there is one thing that is missing, and that is the observation that the reason why the generic market works the way it does is because we do not allow it to work in any other way.

Let me conclude by a reference to Senator Paul's reference to other markets, including the automobile market. The battery in an electric car has parts that, in principle, come from 25 different countries. We do not send inspectors off to those 25 countries to see what is happening elsewhere around the world. We looked at Tesla. If the battery does not work, we blame Tesla and we do not buy the car, and that is the kind of model that we need to about in reforming the market for generic drugs.

Thank you.

¹The prepared statement of Dr. Goodman appears in the Appendix on page 63.

Chairman PETERS. Thank you, Dr. Goodman.

The Defense Logistics Agency (DLA) basically buys its medication for the U.S. military from the same commercial market that gets its raw materials from foreign and geographically concentrated sources. Ms. Raghavendran, how at risk is the United States, for example, if another pandemic or a major earthquake, flood, or other natural disaster hits where these drugs are sourced?

Ms. RAGHAVENDRAN. Thank you, Chairman Peters, for that question, and also again for the opportunity to be here today. Our analysis suggests there is significant reliance on foreign sources when you look at finished dose forms and active pharmaceutical ingredients, and more for the latter than the former.

There are some blind spots in this picture, though, which I will explain. When you examine facility and product registration counts we see that the concentration is predominantly in India, lesser extent in Europe, and then followed by China. But what we have to keep in mind is that these are counts of facilities and product registrations. What it does not take into account is volume. The volume could be concentrated in one facility among many, and we do not know that picture.

Where we are flying completely blind is in our understanding of where the key raw chemicals that go into making the active ingredient come from. We have some anecdotal evidence but we really have no systematic understanding.

Chairman PETERS. Thank you.

Dr. Fox, the Defense Department (DOD) told my staff that with the exception of just three drugs, the DLA is not able to assess with certainty whether any of the other drugs it purchases rely solely on sources from either China or India. Given this blind spot, as was mentioned in the previous comments, what would happen to veterans, to military personnel, and to the U.S. health care system at large if these raw materials, including those sourced from China and India, simply became unavailable?

Ms. FOX. We would have significant shortages, and that is a little bit about what we have today where the DOD and our military are relying on the same commercial market as hospitals.

Chairman PETERS. The report that I released today and that Dr. Goodman referenced finds that our lack of supply chain visibility is basically a national security risk, and it persists at a time when active shortages that we are seeing today are actually on the rise. The COVID-19 pandemic only exacerbated this problem.

Dr. Fox, the FDA created the Essential Medicines list in 2020, but in your testimony you note that this list should not be the starting point for determining which drug supply chains are most vulnerable because, "it is not comprehensive for essential medical care," quoting your testimony today. Why is this so, and what should the Federal Government be doing differently?

Ms. FOX. Thank you for that question. The government really needs to assess which products truly have a vulnerable supply chain. As my colleague mentioned, there may be very concentrated sources of key starting materials. It could look like we have a broad supply chain with maybe five to six manufacturers of something, but if each one of those companies was relying on a single key starting material that is only available in China or India, we sim-

ply do not know that. We need to do more work to truly assess where the key vulnerabilities are.

FDA's essential medications list was not developed for that purpose, and in fact it includes medications like filgrastim, that has a very hardened manufacturing process, where they could basically operate off the grid without any water, without any power, and they would still be producing filgrastim.

We really need to target the true vulnerable products.

Chairman PETERS. Dr. Shuman, we have data on drug shortages but data on the impact of these shortages, especially on patient care, is unfortunately very limited. For example, a 2010 shortage resulted in pediatric Hodgkin's lymphoma patients receiving medication substitutions that unfortunately turned out to be less effective as well as increasing complications for the delivery of that drug.

If you could please, for the Committee, describe the impact that you have seen from your work at the University of Michigan Medical School and what Congress should be aware of that is not right now being captured by just looking at the data.

Dr. SHUMAN. Thank you for that question, Senator. You are absolutely right. One of the challenges of drug shortages is that it requires hospitals to essentially MacGyver different treatment opportunities and regimens, which is not necessarily evidence-or data-based.

As an example, the Hodgkin's lymphoma drug was not available, and as a result, very well-meaning oncologists switched to a different chemotherapeutic drug. The analogy that I will use is when you are baking you have a list of ingredients and you need that list to be exactly what it is in order to have an end product. When you make a substitution and you do not necessarily know how well that is going to work, the problem is you are not going to end up with a dry cake. You are going to end up with a child whose cancer has not been cured. That is a prescient example of where we are and where we have been going.

I can speak more about impact on VA and current at your discretion, sir.

Chairman PETERS. We will do that, but my final question to you, as we look at these drug shortages clearly it has a big impact on a major medical center like the University of Michigan. But talk to me about the impact of smaller, less-resourced hospitals, which is the majority of hospitals out there around the country.

Dr. SHUMAN. You are absolutely right, sir. The major issue here is the disparities that exist. At major institutions we have more staff and resources in order to anticipate and mitigate shortages, to make sure that we have enough product, conserve it, obtain it from other sources. Smaller institutions simply do not have that. What that creates is situations in which smaller hospitals may not know what the supply may look like elsewhere. They may be making rationing decisions that are not necessarily consonant with national guidelines or with what hospitals down the street are doing.

For example, when we are short on a medication at Michigan Medicine I have absolutely no idea what that supply looks like or what the workflow looks like at hospitals across the State. That begets disparities. That treats people unfairly, whether that is poor

people in Detroit or whether that people in a rural hospital in northern Michigan. They are suffering in ways that we cannot even necessarily know.

Chairman PETERS. Thank you. Ranking Member Paul, you are recognized for your questions.

Senator PAUL. Thank you. I think one of the problems we face in health care policy is that people think it is unique. We have this unique problem. We have a shortage here, and so what are the peculiarities to health care policy? There may be some answers but many of the answers, and probably the most important answers, are economic answers. Do price controls work and do price controls lead to shortages? Yes. Obviously they do.

Some people say the Soviet Union was defeated, and they really were not defeated, in a big pitched military battle. They were defeated because they could not determine the price of bread. If you set the price too high, the bread rots on the shelves. If you set the price too low, there is no bread. If you set the bread too high, there is a black market. These are just things that happen with price controls.

In capitalism, the signal that is given to everybody who manufactures something is the price, and the price is where supply meets demand. It is a mathematical function. But it is also something that no one person can figure out. None of us are smart enough or have enough knowledge or bandwidth to figure this out. So 330 million Americans, but really billions of people worldwide, are interacting, and that is how we determine the price of things.

If doxycycline, which has been around forever—it was used in acne and also still for infections and things—is in shortage and in low price, as soon as it becomes in shortage the price will rise. In true capitalism, price rises and they will make more of it. But if you keep the price the same and there is a shortage, it just gets worse and worse and worse, and people leave the marketplace because you are keeping the price suppressed.

There is no moral price. There is no right price. The Soviets or socialists or people who think they know what is best for people try to determine the moral price of things. There is only the price where supply meets demand if you want goods to be distributed, so you have to allow prices to go up and down. In essence, probably all of these problems are fixed by freeing up prices, and they have to go up and down fast.

Dr. Shuman mentioned, which is true, we have to get the information back. Everybody is saying we have to get the information back. How come we do not tell Walmart to do that? That is the real question here. How come Walmart does it automatically? You scan something, you buy a chair at Walmart, or you buy food at Walmart, it goes into the computer in Bentonville, they are reading it. I always joke because as I check out somebody in Bentonville is already putting it on a truck, and it is going to be there an hour later.

There is no reason medicine should not work that way. But we have this mistaken notion that keep the prices low, suppress the prices, and then somehow we will do good for people, we will help poor people. What it has done is it destroys the market.

We also have regulations such that we essentially shut things down. I think the baby formula fiasco was a great example. It is not even prescription, really, but the FDA oversees this. There was some question, and still is a question to this day, whether the bacteria that the children unfortunately died from had anything to do with the plant. They did a Deoxyribonucleic acid (DNA) analysis on it. It was a different bacteria, and yet we shut the plant down.

To combine the problems and make it worse, we would not let in any of the imported stuff. It is like they do not put iron in it in Europe. You can debate how much iron should be in formula, and 10 different experts can tell you how much iron should be in formula, but for goodness sakes, would it not be better to have some formula than no formula?

But we do not allow international competition. We should do that in drugs as well. If we had international competition it helps to keep our prices down, but it also would help to keep the supply up as well. But these are things we have talked about for decades, and actually many in my party have opposed allowing the reimportation or allowing you to shop internationally. I think that would help, but you have to free up prices.

If we only look at the back end where we say, “Oh, we are going to come in and we are going to tell government and tell hospitals how to look at things,” that is one way of looking at it, but it is like you do not even have to do that. Free up prices and then people will make pricing decisions. The prices go up automatically and more of the stuff gets produced. We will not have to have like government figure out how to institute capitalism. We just have to get government as much out of the way and allow more capitalism.

Another thing we could do—and I will direct this question to Dr. Goodman—is the patient has to encounter the price for the pricing system to work. If you have a deductible of \$10, you do not encounter the price, you do not care what. You get heart surgery and it costs \$3 million and your toothpaste costs \$42. Why? Because they can and you do not care. The patient has to care. You have to connect the patient to the price.

One of the things we do in our country is we limit how much you can put into a health savings account. We also limit who can get them. Health savings account (HSA) is basically capitalism. These are people encountering, at least for their first set of dollars, seeing the price, understanding the price, and making decisions on price.

One of the proposals I have had is instead of only having 10 percent of the public allowed to have it legally, let everybody that has insurance, or does not have insurance, have an HSA. Everybody has kids with crooked teeth, and now they all have beautiful teeth but it cost a fortune. But it would be nice to be tax-deductible for everybody. Even if you have a low-deductible policy, why should you not be allowed to have an HSA?

I guess the question to you, Dr. Goodman, is getting the patient or the consumer connected to the price important in this? Would HSAs be part of reform?

Mr. GOODMAN. Absolutely. If you think about aspirin, when I go to the store I see Bayer aspirin and I see other brands. I identify with a brand. Bayer assures me that its product is good and I trust

them. When I get a generic drug I do not know where it came from. I do not know what country it was produced in.

The only thing I would add to your analysis of price controls is what we have done is we have created a market where you can only compete on price. You cannot compete on reliability. Reliability is a valuable thing. The brand companies invest in reliability, so their drug will be there when the demand is there.

In the generic market, if the only thing that matters is price, you do not care about reliability. You just want the lowest price possible, and that is what is happening.

Senator PAUL. Even in the generic market when we have shortages are not they limited in raising their prices, at least to government and to most insurance policies. If I am selling you doxycycline and I make it generically, the hospital has sort of got a fixed price, Medicare has a fixed price, insurance has a fixed price. Is it not pretty hard, as there becomes a shortage, to really even have price competition?

Mr. GOODMAN. As I said in the beginning, we have price controls in the Medicare Part B program, at least what the doctor can get, and in the 340B program we have price controls.

In general, people can pay more for a generic drug but no one does because, again, we have a race to the bottom. We have no competition on reliability, consistency, safety, or even the efficacy of the drug, and half the time, or more than half the time, you do not even know where the drug came from. If we could just make the generic market work as well as the brand market works, we would have huge improvement.

Senator PAUL. I have one question but I will come back to it.

Chairman PETERS. Very good.

Senator Lankford, you are recognized for your questions.

OPENING STATEMENT OF SENATOR LANKFORD

Senator LANKFORD. Senator Lankford is looking up his notes, running in from the last hearing, trying to be able to get set. You all, thank you. Many of us are running back and forth to multiple hearings today, and interestingly enough, a lot of conversation on the Hill about drugs in general.

One of my questions is, let me set a scenario in front of us. Russia invades Ukraine, and so immediately the United States cuts off Russian companies and American companies based in Russia shut down.

China invades Taiwan. The United States says we are not going to do business with China right now. Ten thousand some-odd number of our active ingredients are coming out of China. What happens that next day? Yes, John.

Mr. GOODMAN. Three years ago, almost to this day, China threatened to cut us off. We were complaining about COVID and they said if you keep complaining we will just cutoff your drugs. Now, it is not in their self-interest to do it, but China has a lot of power over our drug market, and we know that they care about things other than maximizing profit.

Senator LANKFORD. Anyone else want to jump in on the conversation? Go ahead.

Ms. FOX. Thank you for that question, and I would say that that is one of the reasons why we need more transparency to identify exactly which products we are relying on China for and which ones we might have some diversification in. We also do not have any idea about the key starting materials that China is holding, so that would be very important to investigate.

Senator LANKFORD. Go ahead.

Ms. RAGHAVENDRAN. Yes, just to add a little bit to what Erin Fox said, I particularly want to emphasize that there is anecdotal evidence that we rely on China for the key raw chemicals that go into making our pharmaceuticals. That might be true. We just do not know because we have not done the systematic analysis.

Senator LANKFORD. OK. Did you want to mention something on that as well? Go ahead.

Dr. SHUMAN. Sure. I appreciate the question. I will answer with a specific example. This past year, one plant in Shanghai that produced a contrast material that is used for radiological scans across the board, went down, and literally overnight, half of the U.S. supply of contrast for radiologic scans was unavailable.

I work in the VA system. This impacts veterans literally overnight, where we needed to make decisions about whether we were going to allow some scans to be done to evaluate someone's cancer to treat someone's heart disease. Veterans deserve better, and we should not be reliant on a supply chain that is that tenuous.

Senator LANKFORD. Where are the next sources? What countries, what agencies, what entities, what drug companies are actually stepping up into this and saying, "We are bringing the manufacturing back here. We understand that we are vulnerable at this, and so we are actually doing something about it"?

Mr. GOODMAN. It is my understanding that the brand companies, who also use overseas suppliers, mainly use Europe and maybe Puerto Rico, but I think most of our brand drugs are not produced in China or India. The China and India production is there because of the race to the bottom and competing on price alone. If all you care about is price, you go to the place in the world where you can get price the lowest, and those are two countries where you can do that.

Senator LANKFORD. But that is also where the generic active ingredients are coming out of.

Mr. GOODMAN. Yes.

Senator LANKFORD. What other countries or entities? I know Saudi Arabia and United Arab Emirates (UAE) are rapidly accelerating drug manufacturing and trying to be able to do some of the things to set up a process for that. There are other countries that are trying to engage in it. But I do not hear a lot of the race, just trying to figure out how we do low-cost alternatives in other places, because those low-cost alternatives, in many of the older drugs, are the only option and the only place that it is there. It may be new technology and new innovation for one type, but for older technology, and antibiotics and such, it is very different.

Mr. GOODMAN. Mark Cuban told me the other day that he is building a manufacturing plant right here in the United States, and he sells generic drugs. For him to be successful I think he has

to be able to advertise and convince the buyers that his product is reliable, consistent, safe, efficacious.

This goes back to what Dr. Paul asked me, he is selling directly to the consumer. They do not even accept third-party payment. Maybe that manufacturer-to-consumer model is going to work better than everything else we have been experiencing.

Senator LANKFORD. It cannot work worse than the pharmacy benefit manager (PBM) model that we currently have.

Mr. GOODMAN. I agree with that.

Senator LANKFORD. OK. Does anyone else want to make a comment on that? Other places?

Ms. RAGHAVENDRAN. Senator, I do want to talk a little bit about the promise of pharmaceutical continuous manufacturing. These are sort of novel approaches to manufacturing that hold great promise in terms of bringing or medicine supply onshore. It might make sense, particularly for certain critical medicines that we rely on as patients.

Pharmaceutical continuous manufacturing can be scaled up rapidly. It has lower production costs. It has a smaller environmental footprint. But we need to make it easier for manufacturers to enter the market. Remember here we are talking about drugs where manufacturers are getting paid pennies per unit, and so we need to make it easier for them by funding things like workforce development. People in this country do not know how to work with these new technologies necessarily. They are new. We need to build out industry-wide best practices, methodologies.

Congress has actually funded legislation. The omnibus spending law actually addresses this point. I look forward to where that goes and it is a great first step.

Senator LANKFORD. We have found ways to be able to push a lot of the manufacturing out of Puerto Rico that was well-known for having a lot of the drug manufacturing, and push it out of the United States in multiple other areas. We currently are one of the worst countries in the world for research and development (R&D), based on our current tax policy. It literally punishes companies for doing R&D here.

We currently are getting out of the manufacturing tax policy, where for manufacturing it was, up until this past year, that you could actually get a full expensing for that. Now that full expensing has gone away, and we are actually punishing people for doing manufacturing here.

If we do not fix our tax policy and incentivize manufacturing to actually be here rather than punishing people to do manufacturing here, and if we do not reduce some of the hoops to actually do the manufacturing, or allow innovation, like what you have talked about on this, to be able to do directly from manufacturer and other ways you can get around some of the PBMs, we are in trouble. But currently there is very little incentive to be able to onshore things based on our tax policy and our regulatory environment, when we desperately need it.

When I ask people about how quickly can we get drugs out of China, to be able to do this and just get access to it, they talk in decades, not in year. That is not a good scenario for us right now

with currently a growing hostile threat from the Chinese. Thank you.

Chairman PETERS. Thank you, Senator Lankford.

Senator Blumenthal, you are recognized for your questions.

OPENING STATEMENT OF SENATOR BLUMENTHAL

Senator BLUMENTHAL. Thank you, Mr. Chairman. Thank you for having this hearing on a problem that really has been longstanding. Dr. Schuman, you refer to the shortages of propofol 15 years ago. I was absolutely astonished in visiting some of our hospitals 12, 15 years ago, to discover the shortage of anesthetics like that one. This problem has been around for a long time.

In the greatest country in the history of the world, capable of providing the greatest health care on the planet, we seem to be unable to provide enough of these basic medicines, anesthetics. This is not kind of the advanced care, cancer treatment that no doubt you are using in the course of your oncology practice. This is the workhorse medicine. Why is it that anesthetics are in short supply? Are they still now—I should ask that question first—and why was it then, and why is it now, if that is still the case?

Dr. SHUMAN. Thank you for that question, and I agree completely. The problem here is many of these sterile injectable drugs are, frankly, very complicated to make, and when companies are making pennies on the dollar per unit, it is very hard to incentivize their production, for many of the reasons that have been brought up earlier.

The issue with propofol 15 years ago was that there were contaminants within the drug. It was a mold and glass shards, I believe, were in the medication, which, again, you do not need to know much to know is a problem. That became another problem yet again during the early COVID pandemic when we were struggling to keep people on ventilators comfortable, for exactly that reason.

The broader problem here involves generic sterile injectables and the complexity of their production and the lack of sufficient incentive for companies to be able to make them, especially on short.

Senator BLUMENTHAL. Is there still a shortage of anesthetics?

Dr. SHUMAN. Yes. A number of different drugs, and I believe Dr. Fox can add more details to that. But the short answer is yes.

Senator BLUMENTHAL. But presumably the contaminant issue has been resolved. Is it still the very tiny margins of profit that are a disincentive to these companies to make this workhorse medicine?

Dr. SHUMAN. The short answer is yes. The process of making these is also quite complicated in terms of the facilities that are utilized. For example, propofol is in a lipid solution which is much more at risk for contamination than many others. But I will defer to Dr. Fox and others for more details.

Senator BLUMENTHAL. I know you are an oncologist, not an economist, so I will ask the question first and then turn to others who can speak on the economics. But I suspect, as a lawyer and a non-economist, a non-doctor, there is something wrong here when anesthetics, workhorse medicine, needed by every single hospital in the country, somehow are not responding to demand signals or the de-

mand signals are not working. Why is it that we are not seeing more production? We all believe in capitalism. I am a strong supporter of capitalism, but in this situation why is it not working?

Mr. GOODMAN. Suppose I tell you, as a manufacturer, if you pay me a dollar more I will overinvest in capacity, and we will not have any shortages, and I will meet your demand. I, under the current rules, cannot do that. I can only compete on price. If you can only compete on price, it is a race to the bottom on everything else, including reliability of supply. It is that simple.

Senator BLUMENTHAL. Take Senator Paul's analogy, bread. Someone is going to produce more bread if there is more demand, the price will rise, and the demand will be met.

Mr. GOODMAN. But suppose the grocery store owner, like the pharmacist, is compelled to sell you the lowest-priced bread that comes his way, then the quality of bread would go through the floor. That is what is happening here. It is not the quality. It is the reliability, safety—

Senator BLUMENTHAL. But these are all reliable, safe anesthetics. They are not selling snake oil.

Mr. GOODMAN. No. But the manufacturing process is not reliable. Compare that to brand-name drugs.

Senator BLUMENTHAL. Someone would make a more reliable process. To take a different analogy, if you are in a company that puts satellites in space and they do not make it into space, they are not reliable, you are not going to get paid. A product that cannot be delivered will not be relied on and they will turn to another manufacturer. I do not understand.

Mr. GOODMAN. The FDA does not allow me to charge you a little bit more for reliable supply. It forces me to compete only on price. If I am competing only on price then sometimes I am going to run out of product or I will not be able to meet demand. But that is the only way I can compete.

Senator BLUMENTHAL. You are blaming it on the FDA.

Mr. GOODMAN. Yes.

Senator BLUMENTHAL. OK. Let us take the next.

Ms. FOX. Sure. Unlike an iPhone or anything else we buy at Walmart, we do not have the information about how good is the quality. We do not have a rating system. We have no way to differentiate between the products.

Your example about the anesthetics, they are still in short supply, in part because there are usually only one or two companies making those drugs, and also there is really no incentive for one company to do a better job. If one company did do a better job we have no way of knowing that. Unlike other things we buy, we have no rating system and no way to do that.

I will tell you, unlike other products, people's lives are at stake. It is not just a matter of maybe not buying peanut butter today or not buying a tire. It is having to decide to use a lower-quality product or a product that we know will not work as well, just because we do not have the access to it in our hospitals.

Senator BLUMENTHAL. I am out of time, but I am also, so far, unsatisfied that we have really identified what the actionable policy should be here. I cannot blame it all on the FDA. I am sorry. There have to be other reasons, and I think Dr. Shuman suggests

in his testimony whether it is bringing some of the supply chain back to this country, producing more here. I do not think that you can just blame it on the FDA. Thank you.

Chairman PETERS. Thank you, Senator Blumenthal.

Senator HASSAN, you are recognized for your questions.

OPENING STATEMENT OF SENATOR HASSAN

Senator HASSAN. Thank you very much, Mr. Chair and Ranking Member Paul, for holding this hearing, and to our witnesses, thank you all for your insights and the important work that you do.

Look, my office, like I think all of our offices, frequently hears from constituents about the challenges they are facing to fill prescriptions and purchase over-the-counter medications that their families use on a daily basis. I am really glad we are holding this hearing.

I want to start with a question to you, Dr. Shuman. In 2017, the FDA reported that 80 percent of active ingredients used in medicines were manufactured in China and India. This manufacturing monopoly is one of the root causes of the drug shortage, and relying on China for active ingredients is a national security and public health risk.

Dr. Shuman, how can the United States shore up domestic drug manufacturing and better protect our supply chains from potential conflicts with China?

Dr. SHUMAN. Thank you for your question, and thank you for your advocacy on this issue. I completely agree with you that this is a national security concern and it is something that we need to deal with. I think incentivizing production on American soil is critical. The devil is, of course, in the details of what that looks like.

But I would consider drug manufacturing to be critical infrastructure. If we have crumbling bridges, we fix them. If we do not have medications that we need, we build the factors and we incentivize companies, whether it is public-private partnerships or other types of arrangements, to make the critical drugs, that are quite expensive to make, on American soil.

Senator HASSAN. Thank you.

Ms. Fox, I want to turn to you. The FDA maintains a list of essential medications and medical devices that is intended to inform which supply chains are most critical to support. That is a really important baseline. However, some medications like Adderall and some children's medicines are not on the FDA's Essential Medicines list. Many Americans need these medications, and the FDA and other entities need to do a better job of managing these particular supply chains, as you discussed in your testimony.

What can the FDA and other organizations do to identify and then prioritize addressing supply chain vulnerabilities for drugs that are not on the Essential Medicines list?

Ms. FOX. Thank you so much for that question. We really do need to address transparency. We absolutely need to get more information about the true vulnerabilities, exactly where we are missing information, where the key starting materials are coming from. We cannot focus our efforts on every drug, so with limited resources we need to really drill down to which products are most vulnerable.

FDA's Essential Medicines list was actually not intended to identify those that are most vulnerable. It was really kind of targeted toward taking care of patients in an acute pandemic, honestly. That list, we really do need to revise it and identify those items that are most critically relying on products that we really cannot get.

Senator HASSAN. OK. Thank you.

To Ms. Raghavendran, the U.S. Pharmacopeia Medicine Supply Map collects and analyzes data from across the world to pinpoint drug manufacturing supply chain vulnerabilities. This map can help prevent shortages and ensure quality. How could FDA use this the Medicine Supply Map or similar data to better address vulnerabilities in the medical supply chain?

Ms. RAGHAVENDRAN. Senator, thank you for the question. We have seen many applications of data intelligence, like the Medicine Supply Map. We think there is value not just to the FDA but also within the private sector. On a day-to-day basis it is in the private sector that the supply chain is managed, and it is the stakeholders in the private sector that are responsible for getting medicines to patients when they need it. The FDA drug shortages team also uses information such as this to manage drug shortages.

The ways you can use it, so for example, if you are manufacturer it would be great to know that your competitor might have a drug shortage, because then you can ramp up your production to meet that demand. On the other end of the spectrum, if you are a hospital it is really good to know what are the critical medicines that are going to likely have a shortage because then you can plan for it. You can either contract with additional suppliers, and if the shortage were to actually happen you have time to prepare. I mean, Dr. Shuman and Dr. Fox can talk about how, when that shortage happens, hospitals staff are scrambling to figure out alternate treatment protocols and so forth.

Senator HASSAN. I appreciate that hospitals and private manufacturers may want to use this data, but I also think it is really essential that the FDA and the United States government use this data too, so it can be looking at the whole map, not just an individual region's particular experience, and really begin to plan and make sure, again, that we are treating this as the critical kind of infrastructure that it is.

Quickly, in my remaining time I want to start with a question to Ms. Fox and Dr. Shuman, because earlier this month I introduced a bill with Ranking Member Paul to get more generic drugs to market faster. Under current law, FDA may reject an application for a generic drug without telling the generic drug manufacturer what part of the formula was wrong, which can ultimately lead to really time-consuming delays. By simply telling a generic drug manufacturer what adjustments they need to make, our bipartisan bill would help improve the generic market approval process and lower drug prices overall.

Are there other aspects of FDA's generic approval process that could be improved and help more generics make it to the market in a more timely way? And we will start with you, Ms. Fox.

Ms. FOX. Thank you for that question. I think when we think about the generic drug approval process we know that FDA does

prioritize products that are in shortage, and so those do get bumped up to the top of the list, which is great. But I think it is also really important to understand which companies are set to do a good job, which companies are investing in their quality manufacturing, and those products should potentially also get priority. Why should we approve a product from a factory that is old and crumbling and is likely to have all of its medicines recalled because they are contaminated?

Senator HASSAN. Also why should we slow a company down by not telling them where they are off.

Dr. Shuman, quickly, would you like to comment on that process as well?

Dr. SHUMAN. I completely agree. I will say that as an institution we have no idea what that quality looks like, and if legislation can clarify for buyers, either hospitals or preferred provider organization (PPOs) or others, whether or not the product we are buying is of higher quality and is, thus, more reliable, it would go a long way. I would argue that the market would pay more for that if we were able to clarify that we are paying for a higher-quality product.

Senator HASSAN. Thank you very much, and thank you, Mr. Chair.

Chairman PETERS. Thank you, Senator Hassan.

Senator Johnson, you are recognized for your questions.

OPENING STATEMENT OF SENATOR JOHNSON

Senator JOHNSON. Thank you, Mr. Chairman. As Chairman of this Committee in February 2020, at the very start of the pandemic I held a roundtable with former Center for Disease Control and Prevention (CDC) Director, Julie Gerberding, and former FDA Commissioner, Scott Gottlieb. The main takeaway from that roundtable was that we do not produce the precursor chemicals, we do not produce the API.

That was more than three years ago. We have spent trillions of dollars. I think we misspent many of those trillions of dollars. I am not sure we even spent a dime addressing that problem that we pointed out in February 2020. Again, if you want to point the finger of blame at somebody, point the finger of blame at Congress, that spent trillions of dollars, a trillion-dollar infrastructure bill, a China bill that made sure we could make chips, but we did nothing in terms of precursor chemicals and the API.

Dr. Goodman, I want to talk a little bit about generics and the completely unlevel playing field. I think what certainly was revealed during our, and I would say miserably failed response to COVID, is we not only ignored but we sabotaged the use and the research into cheap, widely available, generally safe generic drugs. There were a host of them, that some doctors were using. I certainly referred people that called me to these doctors, I was amazed at some of the results.

But what was revealed is that the playing field, generics versus expensive patentable drugs, was completely tilted in the favor of randomized controlled trials—and let us face it, there is not the dollars available in generic drugs to do randomized controlled trials. All of a sudden observational studies were put to the side,

like they were not valid, when in many cases the doctors I have talked to, that might have the greatest validity.

Can you kind of speak to that unlevel playing field between patentable drugs and cheap generic? I will call them molecules because some of these are just miracle molecules. For example, Nobel Prize-winning drugs that have been trashed by our FDA.

Mr. GOODMAN. The first point I want to make is that when you have a pandemic that you do not know anything about, and it is new, and we really do not know what to do with it, you want experimentation. You want to know what doctors in New York are doing, in California. You want them to communicate with each other.

Senator JOHNSON. That was not allowed, was it?

Mr. GOODMAN. It was strongly discouraged.

Senator JOHNSON. That information was shut down. It was censored. But the doctors that had the courage and compassion to treat patients were vilified, including from this dais. They were vilified.

Mr. GOODMAN. I agree. Now compare that to what has happened with cancer drugs. Maybe half the cancer drugs these days are off label, so how did that happen? It is because of doctors experimenting and communicating with each other and writing in medical journals.

Let me make a second point about randomized controlled trials. For years and years and years we thought this was the way to do it. You have this group, they take the pill, this group takes a placebo, and then you compare them, and if there is not a significant difference you do not allow the drug on the market.

But over time people noticed that over here in the people who are taking the drug, even though the group as a whole was not significantly different from the placebo group, some people did remarkably well. Then it dawned on people, well look, maybe it has something to do with the DNA of the patients, and once you understand that you begin to realize that these controlled trials do not tell you all you need to know. Some people may respond well to a drug and other people may not. We simply have to recognize that.

I am in favor of doctors being able to experiment. If something is working with a patient, let the patient and the doctor do it and let us not censor anything that is not coming out of the CDC.

Senator JOHNSON. You mentioned there is a pretty high percentage of drugs that are prescribed off label. Correct? Do you have a number off the top of your head?

Mr. GOODMAN. No, but I think for cancer it is half of them.

Senator JOHNSON. I have heard something like 20 percent of all drugs, 20 to 30 percent, are described as off label. By the way, that is called the practice of medicine. That is how we actually advance medicine, OK, as opposed to a dictate coming from doctors in these agencies that do not practice medicine. That has been a real problem.

Let us talk a little bit about the revolving door between our Federal health agencies, and I would call it the capture by Big Pharma of our Federal health agencies. The two individuals I just spoke of, that testified before our Committee in a roundtable in February 2020, one of them is now a director of Pfizer. Talk about how harm-

ful that is in terms of the public trust and the public getting correct, honest, transparent information from our Federal Government.

Mr. GOODMAN. All I can say is there is an economic literature on the economics of regulation, and going all the way back to the ICC, one of our first regulatory agencies, right up through the end of the last century, many studies showed that regulatory capture often happens, maybe not 100 percent capture, but the regulatory agencies tend to do the bidding of the industry they regulate. This is well known, whether it is taxicabs or railroads or trucking, this has happened over and over again. It is definitely a problem.

Senator JOHNSON. Have our Federal health agencies been transparent and honest during this pandemic, in general?

Mr. GOODMAN. No, and I think I read an expose in The New York Times just the other day where people who worked in the CDC said they were not transparent and were angry that they could not speak for the public.

Senator JOHNSON. I would agree with that. I have written over 50 oversight letters. I have gotten mostly non-response responses when I have gotten any response whatsoever.

I just came from a Finance Committee hearing. We had Secretary Becerra in front of us. Through court-ordered Freedom of Information Act (FOIA), about 4,000 pages of HHS documents were released a lot of Anthony Fauci, Francis Collins emails. Those were heavily redacted through FOIA. Congress is not subject to those redactions. Together with Senator Paul and I think Senator Hawley and two other of my colleagues we wrote a letter.

There is a law that says if five of us write a letter, those documents shall be turned over to us. They have not been. In the combination process we targeted 400 pages. They did not turn them over to us but they did allow us to read 50 pages at a time in a reading room. We could not take copies; took notes.

It has been over a year since the last 50 pages have not been turned over to us, a year, 50 pages, heavily redacted. I asked Secretary Becerra to commit to turning those last 50 pages over to us. I certainly hope he does. But again, that just proves, one example of how the agencies simply have not been transparent and honest with the American public, and the American public has a right to know.

Chairman PETERS. Thank you, Senator Johnson.

Senator Hawley, you are recognized for your questions.

OPENING STATEMENT OF SENATOR HAWLEY

Senator HAWLEY. Thank you very much, Mr. Chairman. Thanks for holding this important hearing on this critical subject. Thanks to all the witnesses for being here.

I just have to say, I think we are suffering from an increased market concentration here in the United States with the pharmaceutical companies, combined with over-reliance on foreign nations and foreign industry abroad. When you put those two things together it is disastrous. It is disastrous not just for our industry, though that is absolutely true, it is disastrous for everyday consumers.

This is one of the reasons, let us take a drug that we have not yet talked about but that millions of people, 34 million at least, people in this country rely on every day, and that is insulin. We have three companies in this country that produce insulin, and yet the cost of it, which has not substantially changed in terms of manufacturing over the last century—insulin has been around forever—the cost of it has just exploded.

Now why is that? I would submit to you one of the reasons is market concentration. This is one of the reasons, by the way, I have introduced legislation that would cap the cost of insulin on a monthly basis at \$25. I think that Americans should not be paying more out of pocket than that, and I do not think that these monopolies ought to be ripping off consumers in order to pad their own profits.

For the same reason I am very concerned about over-reliance on China, in particular. I would just notice, I want to get into some of these statistics, that our over-reliance on China when it comes to these drugs has really exploded since the turn of the century, since 1999, 2000, 2001. What happened around that time? We gave China most favored nation status on a permanent basis. We brought China into the World Trade Organization (WTO) and gave them full access to the international trade market. Disastrous mistake. They weaponized it. They have taken our industry. They have taken control, in many cases, of manufacturing, including some of this drug market. It is really exceptional. I think this ought to be a wake-up call that it is time to change course.

Ms. Raghavendran, let me start with you. Your Medicine Supply Map, which Senator Hassan mentioned a second ago, I think is great and really shows just how dependent on foreign manufacturers we have become. Just looking at the manufacturing locations associated with active API drug master files (DMFs), if I am reading it correctly, and correct me if I am wrong, fully 60 percent, as of 2021, 60 percent were based either in India or in China, and the United States accounts for just 10 percent. What caught my attention is the change in the last 20 years.

I mean, here again, in 2000, India contributed 20 percent of active API files. That percentage tripled by 2021, to 62 percent. In 2000, China contributed just four percent of active API files. That share increased sixfold by 2021, to 23 percent. By contrast, what happened in this country, in 2000, the United States contributed 15 percent of active API, but in 2021, just four percent. Europe, really, I mean, 49 percent they contributed in 2000, only seven percent by 2021. I mean, that is really astounding.

Let me just ask you, do you think that being overexposed to China and India—and, of course, we know that China supplies India with 80 percent of its API, India being the world's largest producer of generic drugs—do you think being overexposed to China has major implications for our national security?

Ms. RAGHAVENDRAN. Senator Hawley, thank you for the question. I am not a national security expert. I am a drug shortages expert. What I can tell you is that we see four different types of risk for drug shortage. Geographic concentration is one of them. But there are other factors. There is low prices, there is manufacturing complexity, and there is quality failures. When we design solutions

we have to look at the whole picture, and, it is a multifaceted problem.

Senator HAWLEY. Let me ask you about the U.S.-China Commission's recommendation. They recommended that the United States, and I am quoting them now, "maximize the production of such goods"—meaning drug precursors and other critical medical supplies—"maximize the production of such goods domestically or as appropriate from trusted countries." Do you agree with that recommendation?

Ms. RAGHAVENDRAN. Senator, I think the specifics matter, and I would be happy to get back to you with a statement for the records, but USP does not have a position on that.

Senator HAWLEY. Dr. Shuman, let me ask you because in your written testimony you mentioned the Shanghai plant example. You brought it up again, I think, to Senator Blumenthal, what a dramatic impact that had on your practice and your patients at the VA, and of course not just yours but at VA hospitals nationwide.

Give me your view on this. Just tell us about, for your patients, the people that you serve, what does our over-reliance and exposure to foreign adversaries—China is a foreign adversary—what does that mean, practically, for them in moments of crisis and moments of danger and situations like we had with COVID and may have in the future, should we be in a kinetic conflict with China?

Dr. SHUMAN. Thank you for your question and thank you for your advocacy on this really important issue. I confess I know much more about surgical anatomy than the geopolitical situation that we are talking about. But what I will say is when I am talking to my patients, frankly, whether it is a veteran or someone at a private hospital, they do not necessarily care where the drug is coming from or what is going on other than the fact that they do not have it.

That is how I feel as well, as a doctor, as an ethicist, as somebody with administrative oversight of drug shortage manage. What we are dealing with is a situation in which doctors, patients are truly handcuffed by the seemingly unpredictable nature of these drug shortages. This is a perfect example where one single factory going down dramatically impacted our supply.

There is absolutely no doubt that we are vulnerable, as a Nation, but also as individual patients and doctors to this issue, and I am so thankful that this Committee is facing this head-on and that we can hopefully bring the supply back to American soil in a way that will allow us to be more reliable.

Senator HAWLEY. Let me just ask before my time expires, Dr. Fox, last week the Committee held a hearing on cybersecurity risks in the health care sector, and I was particularly concerned about risks to rural health care. Let me ask you about that in this context, drug shortages and their effect on rural communities. Do drug shortages, do you know, disproportionately affect rural hospitals, rural communities? Should we be concerned about that?

Ms. FOX. Yes, I do, in part because those rural communities often do not have full resources like academic medical centers, like I and Dr. Shuman work at. They are disparately impacted.

To your past line of questioning, I do want to say that private companies are choosing to invest in China and manufacture there,

and yet they do not reveal where they are making their products. It is not a requirement for those companies to reveal which products are made in China, which products are made in India, which products are made in the United States. Without that information we really are vulnerable.

Senator HAWLEY. That is a great point, and I hope something that this Committee can work on.

Thank you, Mr. Chairman.

Chairman PETERS. Thank you, Senator Hawley.

Senator Rosen, you are recognized for your questions.

OPENING STATEMENT OF SENATOR ROSEN

Senator ROSEN. Thank you, Chairman Peters, Ranking Member Paul, and thank all of you for being here today and your testimony because this hearing and finding solutions not only matters to patients, to ourselves, to our own budgets, people's kitchen-table budget, what they pay, their access, rural and urban, but I would say it is also not just our national security but our economy. The implications, personal and nationwide, worldwide, have a huge impact.

We have to figure out what those incentives are. We are going to build on what some of my colleagues have said, to increase pharmaceutical independence because we know 80 percent of the key ingredients, they come from overseas, China and India. I am not going to say what my colleagues have already said, but like others on the Committee, I, of course, am concerned about this over-reliance and the risk it posts, again, to families, to the ones we love, and their health care and their ability to get it, and our national security as well.

Last Congress, I worked with Senator Tim Scott to introduce the Made in America Act. It is bipartisan legislation to create a tax credit for pharmaceutical manufacturers to operate in certain distressed communities across the United States, creating good-paying jobs and retaking control of our drug supply chain. I am pleased that a number of the FDA-related provisions of our bill were passed into law as part of the fiscal year 2023 omnibus. If we are serious about this, I do agree we need to do a better job bringing lifesaving drugs here.

Dr. Fox, a core pillar of the Made in America Act was to increase collaboration between FDA's drug shortage staff and the Office of Compliance. Both are mission critical—we know that—in helping to prevent these shortages and monitoring supply chains.

How should the FDA be thinking about implementing this provision and linking these two important offices together? What can we do there?

Ms. FOX. Thank you so much for that question, Senator Rosen. Those two offices do work together closely, but usually it is only during a drug shortage. Outside of that they do not often work together. Certainly you could envision, if Congress is able to change the labeling laws to require drug companies to disclose where products are made, perhaps where their sources are made, perhaps the Office of Compliance could work much closer together with FDA to try to enforce that.

Senator ROSEN. To get a better bill of materials, if you will.

Ms. FOX. Yes.

Senator ROSEN. Do you have any other incentives you might like us to try to do while we work on being sure that we can build this collaboration?

Ms. FOX. I think it is important to think about how we do need private industry to make changes, especially to their quality, and if we are also going to ask them to do a little bit more work to reveal their sources of where they are manufacturing drugs.

The societal benefits are much greater than any benefit the manufacturers could get, so I think we need to structure incentives appropriately. But certainly with the Office of Compliance and FDA working closer together we could probably get there.

Senator ROSEN. Yes, I think it is good to have transparency, that is for sure. We want to think about some other ways that we can potentiate this, and how we support our nonprofit pharmaceutical industry as well. That is another big component. Tapping these drug shortages, increasing the access, of course, to critical medications, I do not have to tell any of you it is an all-of-the-above approach. There is not just one thing that is going to fix it. It is going to be many little things perhaps.

Without the need to maximize profits, shareholders, nonprofits, maybe they can focus on lower prices to stabilize supply, lower costs, and again, improve access across the country. It is all about saving people's lives in the long run, right?

I am pleased when the omnibus was signed into law, legislation that I co-wrote with Senator Romney to direct the Government Accountability Office (GAO) to study the impact of nonprofit generic drug companies, that they would have on lowering these drug costs, addressing the drug shortages, and accelerating the development of new drugs. Some of my colleagues have already asked questions to that.

But what I want to ask, I guess I will keep picking on you, Dr. Fox. Today we have such a great panel and not enough time for every question. But how can the nonprofit pharmaceutical model, how can that help to mitigate the shortages, particularly given its focus on maximizing access to lifesaving medication, particularly in those underserved areas, urban and, of course, rural?

Ms. FOX. Thank you so much for that question. I am very familiar with one of the nonprofit drug companies, which is Civica Rx, which is based in Utah. I do serve as a volunteer on their advisory board. That company is really focused on making high-quality medications inside the United States. They have a factor that is almost ready in Virginia. They are also partnering with a company to make the active pharmaceutical ingredients in the United States as well, with Phlow. That was a little bit of the money spent during COVID. You guys actually gave some to Phlow for that.

These nonprofit pharmaceutical companies are able to make high-quality products, focus in on building better facilities, building a more resilient supply. The way that Civica works is that our hospital has to make a long-term commitment to buy a certain amount of product, and what that does is that allows the nonprofit company to know exactly how much to make. They are not in a guessing game of being in a price war with somebody. We have com-

mitted to buy that product. Those reliable supply agreements really do help shore up the overall supply chain.

Senator ROSEN. That is terrific, and thank you again, all, for being here. At the end of the day, it is about the health of the ones we love, the availability, the accessibility, the affordability, and we need to bring that back here. Thank you.

Chairman PETERS. Thank you, Senator Rosen.

Ranking Member Paul has a few closing questions.

Senator PAUL. I think it has been a good discussion. Everybody seems to agree there is a problem. That is a good starting point. But like most of the discussions, I agree somewhat with Senator Blumenthal, the description of the problem is much easier than the actual availability of the answer.

All four of you have said that there is a lack of incentives that lead to shortages, so what are incentives? Allowing the price to rise or moving price controls so prices can rise for a generic, particularly when they become the only one. When there is a shortage of supply you have to allow the price to rise.

Some have said, there is a race to the bottom on prices. Maybe prices are more elastic on the downward side than they are on the upward. There are not many regulations saying that you cannot lower your price, but there are a lot of regulations that say you cannot raise your price.

What happens is, you think about, Medicaid and Medicare are at least half, if not more than half. Their prices are stuck. If you have a shortage of doxycycline, the price needs to go up. The price will not go up for Medicare and Medicaid. But private insurance is pretty sticky too. The contracts are long-term and they have made long-term contracts. The gas stations, the prices go up and down every day, so they can meet supply and demand. That is the answer. You have to allow prices to go up and down. It is sticky prices, inelastic prices, that cause shortages.

Now you say you want other incentives. What else can we do? There are two other ways you could help companies. You could either subsidize them or give them a tax break. People on our side of the aisle tend, most of the time, not to be in favor of subsidies because if you give a subsidy to somebody that is not any good at something you have squandered your subsidy. If you give them a tax break, they only get it if they are good at it, because you only get to deduct your profit. If you do not make a profit, the tax break does not do you anything.

Now we did, once upon a time, have huge tax breaks in Puerto Rico. It was a 100 percent tax credit. If this body wants more American and closer-to-home production, reinstitute the Puerto Rico tax break.

But I would go one step further, and I agree with Senator Rosen. We have a bill that would take the opportunity zones that have designed as poverty areas in our country, and there is a bunch of them in every State. We would say to the pharmaceutical industry, we are not just going to give you what the last tax bill did, we are going to go further because really, they have not worked that well. I am all for them.

I call them economic freedom zones. I have been talking about them for five or six years. Jack Kemp talked about them 20 years

ago. They never have really worked because the incentives have not been good enough or have been too difficult to get the incentives. Let us make them bigger, either a tax credit like we used to have or lower or abolish the income taxes, let us make it immediate, and let us let them start doing it, because they have not moved because the incentive is not enough. We could have more domestic production.

The only thing I will finish with is I think we have to be careful, as a country, not to have irrational anger toward China. Look, I have been talking about COVID coming from the lab for two years. I am not an apologist for China. But at the same time I do not want to end trade with China. It was mentioned here—you end trade with China, you want to see shortages, you are going to see a catastrophe. We cannot overnight do that.

Should we encourage more production here? Yes. Let us have more production here, but let us do not be irrational in our anger toward China such that we disconnect and have no trade. Both of our countries have grown wealthy because we have traded, and we should be wary of that before we go further.

But I think it was a great panel and I hope people will take to heart that everybody believes we need more incentives. We have to figure out how those incentives can be put into action.

Thank you all for coming.

Chairman PETERS. Thank you, Ranking Member Paul.

I think this is an important issue that we have to really drill down on, so a little bit more clarification on it, and picking up on the questions that Ranking Member Paul has. When he says that we have sticky prices that cannot go up, that is because they are contracts, Medicare contracts and others, which is part of capitalism. If you are a really big customer you will negotiate for a price—that is pure capitalism—and then you lock into a contract to do that, which is part of the market. But is that the reason why we are seeing shortages is because we have big customers locking in contracts for a price?

I am a little concerned. In fact, in our report, fludarabine was a drug that had a shortage here, and I see once it was in shortage it was less than \$300 a vial, but all of a sudden the manufacturer raised it to \$2,736 per vial. Especially if you only have one manufacturer making a drug you own that market and the price could go right through the ceiling as well.

Talk to us a little bit about price controls. Dr. Goodman talks about price controls. Are there price controls by the FDA or are these contracts that folks who are big customers are entering into in order to have some control over the prices that consumers pay? That is usually a good way to make sure consumers are not gouged is by having a long-term contract.

Any of you can answer that. Dr. Fox, you are shaking your head.

Ms. FOX. Thanks, Senator Peter. I will say that you are exactly right with the contracting. The reason why hospitals cannot pay 10 times the amount for a drug next week is because we will still only get paid our capitated rate that has been locked in for years. The insurance and the way that we pay for health care in this country really does not allow for prices to change every day, like at the gas station.

Chairman PETERS. Anybody else? Dr. Goodman.

Mr. GOODMAN. Again, I am going to sound like I am repeating myself. This is in the report that you all put together, which I think is a very good description of the problem. What your own report says is this is a market where people compete only on price. I just want to say again, if buyers and sellers only compete on price and nothing else we are going to get a race to the bottom of all the other features of the product, including reliability. What I mean by reliability is, the product is there when you need it, and if you sacrifice reliability you are going to have shortages.

If I could just take Mark Cuban's plant, for example, what could you all do to make sure that Mark Cuban is successful with his U.S.-based plant? You can allow him to say, "Look, the FDA can come by my plant any day of the week, at the drop of the hat, no prior announcement, and inspect my facility. That does not happen in India. It does not happen in China. I am held to a higher safety standard than those guys overseas. Furthermore, I am going to invest in reliability, so when you come to"—what does he call it? Cost Plus Drugs—"when you come to Cost Plus Drugs online it is going to be there when you need it."

If he could say those kinds of things to his consumers he would be competing in the right way.

Chairman PETERS. You are saying the FDA is preventing companies from saying—

Mr. GOODMAN. Yes.

Chairman PETERS. Is that accurate? Dr. Shuman, you cannot assess the quality of a drug? There is not information, because the FDA just simply does not allow you to have the information?

Dr. SHUMAN. I cannot answer the regulatory question. I would defer to Dr. Fox. I will say we, as individual doctors and institutions, do not have any way of gauging quality, and the answer for that, I believe Dr. Fox—

Chairman PETERS. Dr. Fox?

Ms. FOX. Thank you. That is true. Because there is no requirement for any company to list which company even made the drug, where it was made, sources of raw material, there is no way to assess which company has a good quality record and which company has a bad quality record.

Chairman PETERS. That is a lack of transparency. That is not the FDA saying you cannot say that.

Ms. FOX. No. FDA cannot share that information. FDA has the information but legally they cannot share.

Chairman PETERS. They have the information about all these drugs?

Ms. FOX. Most of it.

Chairman PETERS. But they are just not sharing it.

Ms. FOX. Correct. Congress could change the labeling law to require drug companies to disclose that, and they could also change the law to allow the FDA to disclose that. But right now the companies decide what is confidential.

Chairman PETERS. Yet even a lot of the companies do not know where some of this stuff comes from, is my understanding. Is that correct?

Ms. RAGHAVENDRAN. Chairman Peters, just to add some color to what Dr. Fox shared, when we analyze labels, only three percent of labels actually listed who the active ingredient manufacturer is. There is very little information in the public domain about who makes these drugs.

Chairman PETERS. But does the company know? The company knows and the FDA knows, you are telling me? Or we do not know because that is just not really tracked?

Ms. RAGHAVENDRAN. The finish dose manufacturer that purchases the active ingredient will know who the active ingredient—

Chairman PETERS. Oh, so they will know. Do they provide that information to the FDA, and the FDA is just not telling anybody?

Ms. RAGHAVENDRAN. Yes, Senator, I would have the FDA has certain confidentiality requirements that bind them.

Chairman PETERS. Also the report shows that there are multiple layers of manufacturing processes that could also create false appearance that there is actually diversity in the suppliers, and all of you have touched on this. I think there were 12 FDA-approved manufacturers, fludarabine, which is the one I mentioned here earlier, a critical drug for treating childhood and adult cancers. But only a handful of those approved are actually supplying the drug.

It looks like there is a lot of diversity but there really is not. There are just a couple of companies out there? That is lack of transparency? Talk to me about that, why that is a problem. Dr. Fox.

Ms. FOX. Yes, that is exactly right. I can look, and it looks like there are maybe six or seven suppliers of this product. No problem if we have a shortage because the other companies might be able to make up the difference. But when all of those companies are actually getting their product from just one or two sources, then we have a false sense of security. All of that information in your report, which is fantastic, is really not publicly available to anyone at a hospital to do that level of research.

Chairman PETERS. But it is available to the FDA. They have all of that information.

Ms. FOX. It is but I do not believe that they can access it well. A lot of that information is buried in portable document format (PDFs). They can change. They only get the information once a year as a snapshot in time.

Chairman PETERS. Any other comments?

We have to dive into these issues. We are going to be talking to all of you more than just what we can cover here. With all that is happening today as well as votes occurring right now, which is my Committee is now all gone, except for me, as they run to vote.

But I look forward to working with you, each and every one of you, as we look for some solutions. There is no question that identifying a problem always is easier than identifying solutions, but this Committee is about solutions and we would need your expertise to help us sort this out so that we can deal with this problem.

I want to thank all of you for joining us today and offering very important testimony. The testimony received today and findings identified in my report that we put out today certainly point to the need for reforms, and I intend to work with my colleagues and will

introduce legislation to address the underlying causes of these shortages as we seek out appropriate solutions to what are clearly major problems.

The hearing record will remain open for 15 days, until 5 p.m. on April 6th, for the submission of statements and questions for the record. Thank you again. This hearing is now adjourned.

[Whereupon, at 12:26 p.m., the hearing was adjourned.]

A P P E N D I X

**Chairman Peters Opening Statement As Prepared for Delivery
Full Committee Hearing: Drug Shortage Health and National Security Risks: Underlying
Causes and Needed Reforms
March 22, 2023**

Today's hearing will examine ongoing and rising shortages of medications, which range from drugs used in hospitals to provide critical care and treat serious diseases like cancers, to prescription medications, and even common over-the-counter remedies to treat cold and flu symptoms.

After a winter with high cold, flu and RSV cases, many of us have gone to the store and seen bare shelves due to shortages of children's Tylenol and Motrin. Others have faced shortages of key prescription medications, including antibiotics.

Throughout the country, hospitals regularly experience shortages of a range of drugs needed for emergency care, surgeries, and other procedures. These often include sterile injectable drugs like IV saline solution and sodium bicarbonate needed to provide critical care, dialysis, and other life-saving treatments. Some of these products have been in shortage for over a decade. For example, lidocaine, used to manage pain, has remained in shortage since 2011.

Vancomycin, used to treat bacterial infections, has been in shortage since 2009. Even drugs needed to treat childhood and adult cancers, including some that have no alternative treatment, are regularly in shortage. While some shortages may only be an inconvenience, others can have devastating impacts on patient care.

These shortages, which reached a peak of 295 individual drugs in shortage, at the end of 2022, have left health care professionals grappling with limited resources to treat patients in need.

Drug shortages are not new. There are a number of factors that contribute to drug shortages, including economic drivers that lead to a lack of manufacturers willing to enter or remain in the market or invest in quality manufacturing systems, insufficient visibility into the entire supply chain for critical medications, and an overreliance on foreign and geographically concentrated sources for the materials needed to make these drugs.

Taken together, these underlying causes not only present serious concerns about providing adequate care to patients, they also represent serious national security risks.

In 2019, I released a report identifying many of these national security risks, and how they contributed to drug shortages and in some cases, price hikes.

My report found that nearly 80 percent of the manufacturing facilities that produce active pharmaceutical ingredients, or APIs, the key ingredients that give a drug its intended effect, are located outside of the U.S., and many of our APIs are sourced from China and India.

Just months after I released that report, as the COVID-19 pandemic spread around the globe, we saw firsthand how our overreliance on foreign producers for medical products, along with

failures to adequately prepare for a pandemic, quickly led to widespread shortages of desperately needed medications and medical supplies like personal protective equipment.

Today, I am releasing a new report that builds on those previous findings, and identifies additional recommendations to strengthen domestic manufacturing of critical drugs and limit the disruptions caused by shortages and supply chain issues.

My report finds that between 2021 and 2022, new drug shortages increased by nearly 30 percent, and that both the pharmaceutical industry and the federal government, including the Food and Drug Administration, lack the information needed to effectively detect and prevent shortages.

Most significantly, this updated report found that our continued overreliance on foreign suppliers for the key materials needed to make critical drugs, primarily those in China, remains an unacceptable national security risk.

For example, over 90 percent of generic injectable drugs used to treat serious injuries or illnesses in the U.S. rely on key materials from China and India, and nearly 90 percent of generic API manufacturing sites are located overseas.

My report makes several recommendations to help protect our health and national security, including to invest in advanced manufacturing capabilities to produce critical drugs here in the U.S., and require that the FDA and its interagency partners can get the information needed to better monitor supply chain vulnerabilities and anticipate possible shortages.

I am encouraged by recent legislative and executive actions to bolster our medical supply chain resiliency. Last Congress, I helped author a bipartisan provision to increase visibility into where critical medical supplies and drugs are produced, and this Congress, I am working on legislation that builds on many of the report recommendations to protect our health and national security. I look forward to working with my colleagues to advance these important measures.

Today's discussion with our panel of expert witnesses will provide even more detail about what Congress and our federal agencies should do to address both drug shortages and the national security risks they pose.

Senator Rand Paul**Opening Statement for HSGAC Hearing on “Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms”**

Ever wonder why we never have shortages of iPhones or computers? What separates the drug industry from the computer or smartphone industries? Computers and smartphones, like drugs, are highly technical and globalized industries, yet there are seldom shortages in any of those industries.

However, unlike the computer, automobile, or smartphone industry, the needs addressed by the drug manufacturing industry are often a matter of life and death.

This is why the decisions of policy makers and regulators are of utmost importance. Rules and regulations that inhibit the production of drugs will create pain for hospitals and patients.

The Food and Drug Administration recently identified a shortage of over 120 different drugs. Some of these drugs, such as saline, are necessary for the most basic of treatments.

These shortages are not a new phenomenon. Since 2007, the FDA identified an average of over 100 separate drug shortages per year. In 2011, the FDA identified a whopping 267 drugs in short supply. Despite possessing the most innovative medical industry in the world, the U.S. is unable to maintain a consistent supply of the most crucial medicines.

While many blame these shortages on foreign producers, so-called “greedy” pharmaceutical companies, and even hospitals, it is no coincidence that the rise in drug shortages correlates with the expanded regulatory reach of the FDA.

Drug shortages force doctors to consider rationing medicines and postponing essential procedures and force patients to needlessly suffer.

While our nation’s hospitals have trouble purchasing the necessary amounts of drugs for cancer patients, heart attack victims, and those in

chronic pain, these same hospitals find no such shortage when purchasing computers. Doctors and nurses do not have to cope with a smartphone shortage.

The key difference between these industries and the drug manufacturing industry is obvious. The companies producing computers and smartphones are, by comparison, left to compete with one another with little manipulation from government, while the FDA places the heavy yoke of regulation on drug manufacturing.

Over 40 years ago, Milton Friedman remarked, “If you put the federal government in charge of the Sahara Dessert, in five years there’d be a shortage of sand.” While Friedman was discussing price controls and output restrictions on oil and gas production in Dubai, the same wisdom still holds for the drug industry.

The drug industry is one of the most regulated markets in the economy. Output controls, such as FDAs approval procedure for nearly every step of the manufacturing process, increase the cost of production and restrain the adaptability of manufacturers to meet shifting demands. For example, if a drug maker closes, the remaining manufacturers, which must react to increased demand, are forced to seek FDA approval to produce more than the originally approved amount or to produce quicker than the originally approved timeline.

Why does the United States embrace central planning in healthcare? Central planning produced shortages of even the most basic consumer goods in communist countries during the Cold War. There is a famous Soviet quip about a man entering a shop and asking the clerk, “You don’t have any meat?” The clerk says, “No, here we don’t have any fish. The shop that doesn’t have any meat is across the street.”

We should not tolerate central planning in a capitalist country for the most essential products on the market. Further abandoning the principles of basic economics, CMS price controls, such as requiring drug companies to pay rebates to Medicare if they raise their prices too quickly, create even more barriers to entry, which prevent competitors

from arising in the market. Limiting the amount of drug producers results in artificially high prices and drug shortages.

Americans will be healthier and live longer if their government allows innovators to provide better drugs, at affordable prices, and produce a strong supply. I hope this hearing will identify the regulations that impede the ability of markets to do what they do best – provide for the consumer. I look forward to hearing our witnesses' testimonies.



Drug Shortage Health and National Security Risks:

Underlying Causes and Needed Reforms

Statement for the Record: 22 March 2023

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I would like to thank Chairman Peters, Ranking Member Paul, and the distinguished Members of the Committee for holding this hearing and for the privilege of speaking with you. My name is Dr. Andy Shuman, and I am a cancer surgeon and medical ethicist. I have a surgical practice and leadership roles at both the University of Michigan Hospital System and the Veterans Affairs Ann Arbor Healthcare System. Please note that I am not speaking on behalf of either institution today.

My personal experience with drug shortages began fifteen years ago during a routine surgical case. At the time, there was a national [propofol shortage](#), an anesthetic we need to perform surgery, that required anesthesiologists to improvise how to keep patients safe and comfortable during their procedure. And you do not need to be a cancer surgeon to realize how important it is that patients remain asleep during their operation.

Since that first experience, colleagues and other hospitals have continuously asked me to help them respond to the never-ending game of drug shortage whack-a-mole. Hundreds of drug shortages affect our country each year. Drug shortages have wide-ranging, and at times, devastating consequences for patients. My goal for next few minutes is to share some examples from my experience trying to protect patients from the terrible consequences of not having access to the drugs they need.

Almost [two million](#) Americans are diagnosed with cancer each year. We are lucky enough to live in a country where cutting-edge research has massively reduced cancer-related deaths. But cancer drug shortages represent a [tragedy happening in slow motion](#).

For example, [etoposide](#) is a cancer drug that has been on the market for over 40 years and typically costs less than \$50 per vial. It is given to patients for nearly a dozen different types

of cancer. But in 2018 due to manufacturing delays, [etoposide was on shortage](#) at hospitals across the country. This left us in an awful position. Which of our patients with cancer should receive this potentially lifesaving drug? How can we prioritize between American lives? Should our limited vials go to an older woman who was just diagnosed with lung cancer? To a young man who had already been successfully taking it for his testicular cancer? Or a baby with neuroblastoma, an aggressive cancer for which this drug is part of the standard of care, but others might work too despite limited studies?

Our hospital, [like other hospitals across the country](#), struggled to make these decisions based on the drug's projected availability, which patients were already under our care, and our best guess at how many new patients would be diagnosed in the coming weeks. We could not spread our limited supplies across all the patients that needed it. As a doctor who has devoted my life to fighting cancer, it is hard to express how [horrible it is](#) to face this kind of tragedy. In this case, after we offered the patients with lung and testicular cancer our limited supplies, a heroic pharmacist was able to scrape together enough etoposide from the bottom of the leftover vials to also treat our infant patient. But our pharmacists should not be desperately trying to squeeze out a few last drops when a life might be on the line.

Another ongoing shortage involves injectable anesthetic drugs such as lidocaine, which are used for everything from epidurals during labor, to dental procedures, to the cancer surgeries I perform every week. This shortage is one that has not received quite as much media attention because, in many cases, alternative drugs and doses are available. But often, these alternates [require more clinical work](#), and [increase the risk for errors](#). Many of these products come in a vial that is ready to use, but sometimes the alternative product may need to be made

by a pharmacist, or mixed right before use. We already have a shortage of [nurses](#) and supplies. For clinicians who are perpetually overworked and understaffed, these additional tasks also increase the risk of inadvertent errors in dosing or administration.

The role of geopolitics and our reliance on foreign products is a major cause of such drug shortages. For example, last year, a GE plant in Shanghai [stopped making the contrast](#) used for many radiology tests, literally [threatening half of the country's supply](#), including that which [VA hospitals](#) relied upon. At that time, we had no idea how soon another shipment would come in or when the factory would reopen, leading to decisions such as whether to [prioritize scans for cancer](#), or for [heart disease](#). No American who proudly served our country should be told that they cannot have a necessary medical test because a single foreign factory stopped production.

While cancer patients not being able to get treatment is heartbreaking, drug shortages impact almost every field of medicine. For example, Senator Paul has dedicated his professional career to preserving and restoring his patients' vision. There are [eyedrops](#) that literally keep people from going blind that cost a few dollars a month. But these miracle drops are sometimes completely unavailable. Professional organizations of eye doctors have [pleaded for help](#). Some patients with glaucoma [require additional surgeries](#) that would be avoidable if they had these drops. These patients also deserve better.

And I would be remiss not to bring up how the COVID pandemic has [exacerbated drug shortages in our country](#). My colleagues and I have worked tirelessly over the past three years to take care of patients with COVID. We have also learned quite a bit about how to [conserve and ration health resources](#), doing so [equitably](#) by making sure that that diverse patient

communities have access to the best care possible. We know that supporting clinicians in making tough decisions with clear objective criteria can help limit subjectivity and variance between doctors [to ensure decisions are consistent and fair](#).

But all hospitals do not have access to the same resources. Michigan Medicine has multiple pharmacists focusing on predicting, mitigating and avoiding drug shortages. Some smaller hospitals are not so lucky. Patients should not have better access to scarce drugs than other people across the state purely based on which hospital they use, particularly because access is driven by differences in demographics and health disparities. This is why I and my team [have studied](#) how institutions across regions and states can better communicate about ongoing drug shortages, such as prioritization approaches, patient volumes, and existing supplies to *predict* drug shortages, and in so doing, better *prepare* for them. One key role for lawmakers is to improve drug shortage monitoring and information sharing nation-wide.

Information sharing is a critical component of [health care emergency preparedness](#), where we often think of important resources in terms of staff, space and stuff. For example, in April 2020, we desperately tried to make sure we had enough ventilators and were relieved when we believed we had secured a sufficient supply. But a ventilator is just an expensive metal box if we do not have enough respiratory therapists to operate it. At Michigan Medicine, we had to [train our medical students](#) to help use the ventilators when we ran out of respiratory therapists. And, even if we have enough ventilators and the personnel, we still need enough hospital beds, which remain in short supply even [today](#). Finally, the patient on the ventilator [needs the proper medications to keep them sedated and comfortable](#) ... ironically the same medication, propofol, that began my passion for fighting drug shortages so many years ago.

We know what causes drug shortages. [FDA](#) issued a roadmap in 2019 demonstrating the root causes and potential solutions to this problem. This Committee issued a [detailed report](#) as well. Americans are too dependent upon drugs and drug precursors from abroad. We need to diversify where these supplies come from, including increasing production on American soil. If there are shortages, we need companies to disclose the reasons why – otherwise we will not know where to focus resources. In addition, drug pricing structures [are not always reflective of their value](#) to patients. We should incentivize and/or subsidize companies to make high-quality, critical-need drugs like the ones I have mentioned, even if they have been less profitable. My fellow witnesses today are experts in the supply side and pharmacy approaches, and I welcome their further wisdom and advice.

We can all agree that sick Americans deserve access to life-saving medications. Telling someone with cancer that they cannot receive a drug that was developed during the Johnson administration and costs less than my Uber ride from the airport is not acceptable. I thank the Committee for highlighting this critical issue and the importance of finding creative legislative solutions.

Statement of the U.S. Pharmacopeia

Submitted to the Senate Homeland Security and Governmental Affairs Committee

**For the Hearing “Drug Shortage Health and National Security Risks:
Underlying Causes and Needed Reforms”**

March 20, 2023

The United States Pharmacopeia (USP) is pleased to submit the following statement for the record on the hearing “Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms.”

USP is an independent, scientific, global non-profit organization founded in 1820 when eleven physicians took action to protect patients from poor-quality medicines. Convening in the old U.S. Senate Chamber, they published a national, uniform set of guidelines for medicines called the U.S. Pharmacopeia.

A core pillar of USP’s work is to help strengthen the global supply chain so that the medicines, dietary supplements, and foods that people rely on for their health are available when needed and meet quality standards as expected and required.

The Federal Food, Drug, and Cosmetics Act of 1938 created the statutory requirement that medicines sold in the United States generally must adhere to USP’s public quality standards to help ensure the quality of medicines and the safety of patients. USP standards are developed by nearly 800 scientific and healthcare experts who volunteer their time on USP’s standard-setting committees, which also include over 200 U.S. Food and Drug Administration (FDA) government liaisons. In these and other ways, USP works closely with the FDA, other government agencies and across health and science communities to develop USP standards (over 6,000 today) that are enforced by the FDA.

In addition to our work on standards, USP is an active participant in many public-private partnerships on supply chain-related issues. This includes work with the FDA, the Administration for Strategic Preparedness and Response (ASPR), and the Biomedical Advanced Research and Development Authority (BARDA). USP also engages with the World Health Organization and the Pan American Health Organization as an officially recognized non-state actor and hosts the USP-APEC (Asia-Pacific Economic Cooperation) Center of Excellence for Securing Medical Product Quality through the Supply Chain, under the sponsorship of the FDA.

USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.¹

¹ USP’s governing bodies, in addition to the Council of the Convention, include its Board of Trustees and Council of Experts.

Assessing and Addressing Supply-Side Vulnerabilities Is Essential to Reducing Drug Shortages

Vulnerabilities in supply chains manifest as shortages when supply is unable to meet demand, which may be due to demand spikes, supply disruptions, or both. Currently, there is little insight available into supply-side risk for medicines and the ingredients necessary to manufacture them that could help guide effective decision-making. For example, a simple factory count is an insufficient gauge of actual production volume, and the task is even harder when it comes to taking inventory of raw materials for drugs. Before a crisis, companies and the government need a better understanding and mapping of their full supply chains to identify potential vulnerabilities.

Neither a single government agency nor any industry entity has a complete view of upstream supply. This lack of clarity contributes to a limited understanding of the risks affecting the U.S. medicines supply. This could lead to ineffective deployment of resources to reduce drug shortages and improve medicines supply chain resiliency by failing to account for the upstream root causes of many shortages.

The U.S. pharmaceutical supply chain will be more resilient and reliable for patients if Congress targets its efforts at drugs at long-term risk of shortage due to structural weaknesses in their upstream supply chains. The identification of upstream supply chain risks can enable regulator and industry action to reduce medicine supply disruptions by informing risk mitigation strategies, public and private investment, as well as policy reforms that build more resilience. A holistic approach to address medicines supply chain vulnerabilities – that encompasses both demand and supply-side indicators – can help inform medicines supply chain resiliency efforts to improve their design and effectiveness.

Recognizing the urgent public health need for better supply chain intelligence, USP has invested in the development and continuous improvement of a data intelligence platform, the *Medicine Supply Map* (www.usp.org/medicinesupplymap), to:

1. Help identify, characterize and quantify vulnerabilities in the upstream pharmaceutical supply chain;
2. Deliver insights that can guide risk mitigation strategies and investments; and
3. Help inform policy changes that advance supply chain resilience.

The *Medicine Supply Map* uses multiple sources of information to identify the worldwide sites of pharmaceutical ingredient and finished dose medicine manufacturing. More than 40 datasets from USP, FDA, the Centers for Medicare & Medicaid Services, European Medicines Agency, World Health Organization and private sector sources are utilized by the *Medicine Supply Map* platform. These data are enriched with information about risk drivers such as price and ingredients and covers 92 percent of FDA-approved generic prescription drugs. Notably, the *Medicine Supply Map* includes over 250 million aggregated datapoints to evaluate indicators of drug shortage risk, including geographic concentration, manufacturing complexity, price, and quality. The model is also informed by insights on the use of USP quality standards in over 80 percent of FDA-registered finished dose and active pharmaceutical ingredient (API) manufacturing facilities.



Insights from USP's *Medicine Supply Map*: Risk Categories Driving Drug Shortages

Using the *Medicine Supply Map*, USP has identified, characterized, and quantified factors that contribute to the vulnerability of the U.S. medicines supply chain. USP identified over 200 potential drivers of drug shortages and quantified their contributions to drug shortages. Four risk categories were found to be correlated with drug shortages, which singularly or in combination can increase a medication's risk for shortage:

1. **Low prices:** Drug products with low prices, common in older drug products, have a higher risk of drug shortage.
2. **Manufacturing complexity:** Drugs with higher manufacturing complexity, such as sterile injectables, are more vulnerable to shortage. Examples of manufacturing complexity include the need for dedicated facilities for certain product categories (e.g., certain antibiotics) and complex chemical synthesis of the active ingredient.
3. **Geographic concentration:** Drugs with greater geographic concentration of API and/or finished dose manufacturing are more susceptible to shortages.
4. **Quality concerns:** Quality failures, accounted for in the *Medicine Supply Map* as outcomes of FDA inspections and a history of recalls, predict increased vulnerability to drug shortages.

These four risk factors are often interrelated, and, in combination, can exacerbate economic challenges for manufacturers of low-margin drug products and impact business decisions about whether to continue manufacturing some drug products. For example, manufacturing complexity increases the cost to manufacture a medicine, which, when combined with low prices of certain drug products, can yield a margin that is unsustainable. To improve margins, industry has sought to reduce manufacturing costs by concentrating production in lower-cost geographies. This concentration creates a range of vulnerabilities. Moreover, the low price/low margin dynamic impedes industry's ability to create manufacturing redundancies and may lead to underinvestment in quality management systems. To increase resiliency, it is important to account for these dynamics. We should incentivize geographic diversity of manufacturing, facility redundancies, and continuously improved quality management.

Lower-priced drugs

Lower-priced drugs have a higher likelihood of being in shortage. The association between pricing and drug shortages is well documented. For instance, Root Cause 1 in the 2019 FDA report "Drug Shortages: Root Causes and Potential Solutions" was the "lack of incentives for manufacturers to produce less profitable drugs." In that same report, FDA analyzed 163 drugs regulated by the Center for Drug Evaluation and Research (CDER) that went into shortage between 2013 and 2017, and found that "[w]hen compared with all marketed drugs with the same dosage form during the same period, including both generics and brands, the prices of the shortage drugs were at the 36th percentile of prices, while the prices of injectables that were in shortage were at the 33rd percentile and oral products in shortage were at the 46th percentile."² Lower price and margin drug products offer limited incentives for manufacturers to stay in or enter the market. The fact that lower-priced drugs have more availability issues should be evaluated within the context of quality and supply chain vulnerability.

² FDA. 2019. Drug Shortages: Root Causes and Potential Solutions. Available at: <https://www.fda.gov/media/131130/download>.



USP *Medicine Supply Map* analysis shows low price is a significant risk factor for antimicrobial shortages, the impacts of which we very recently experienced. During the winter of 2022-2023, with multiple respiratory viruses circulating, drug shortages were experienced among certain antimicrobial drug products. Previously, in the summer of 2022, USP's *Medicine Supply Map* found that antibacterial drug products were 42 percent more likely to be in shortage than the average drug product. Out of the 128 antibacterial drug products approved in the U.S., 20 were in shortage (15.6 percent compared to 10.9 percent for all drug products).³

Manufacturing complexity

There are numerous ways to assess the complexity of pharmaceutical manufacturing, including the type and variation of dosage forms, the number of underlying ingredients and key starting materials, the expertise needed to synthesize the molecule, storage requirements, and the size and molecular structure of the active pharmaceutical ingredient. USP *Medicine Supply Map* analysis shows that the injectable dosage form and certain specifics of the manufacturing and API synthesis processes are predictive of drug shortages. Injectables are particularly vulnerable to supply chain disruptions when compared to solid oral dose medications. Injectable medicines often undergo a manufacturing process called lyophilization, which is expensive and complex, and therefore medicines made with this process have lower supply chain resilience. The complexity of the chemical synthesis of the API was also found to be correlated to drug shortages.

As an example, while not currently in shortage, vincristine sulfate injection, which is used for the treatment of cancer, remains highly vulnerable to shortage. This drug requires plant-based starting materials that can be difficult and expensive to obtain. Moreover, its cytotoxic active ingredient is hazardous, expensive to manufacture and requires dedicated facilities. Manufacturers of vincristine sulfate injection also cannot take advantage of economies of scale due to the low dose/strength of the drug and the low total API needed.

Geographic concentration

USP's *Medicine Supply Map* data show that geographic concentration anywhere – including within the U.S. – increases the risk of drug shortage. While the globalization of the supply chain has generally facilitated access to medicines at a lower cost, it poses the risk of unreliable supply following sudden or unexpected shocks in specific locations, followed by a lack of understanding of what might be impacted because the mapping of where products are made is complex and incomplete. Geographic concentration of the medicines supply chain is generally an outcome of specialization and pricing pressure and can result in drug shortages when a variety of issues occur, including natural disasters (e.g., earthquakes, hurricanes), trade wars, domestic or geopolitical strife, or pandemics such as COVID-19.

In March 2021, nearly three-quarters of FDA-registered API manufacturing facilities and approximately half of all FDA-registered finished dosage form (FDF) manufacturing facilities were located outside of the U.S. Within the generic drug market, 87 percent of FDA-registered

³ Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map analysis | Quality Matters | U.S. Pharmacopeia Blog.



API facilities and 63 percent of FDA-registered FDF facilities were located outside of the U.S. While instructive, these figures do not account for the volume produced within these facilities.⁴

USP used the *Medicine Supply Map* to assess U.S. dependence on foreign API. USP leveraged machine learning techniques, including Natural Language Processing, on data from FDA, information from non-U.S. regulatory agencies and its own proprietary insights to map manufacturing locations associated with approximately 90 percent of active API Drug Master Files (DMFs) around the world. DMFs are submitted to FDA by companies when they intend to supply drug ingredients to another company without disclosing proprietary information. FDA publishes the names of companies filing the DMFs. While DMFs are commonly utilized in the generics industry, some manufacturers may choose to make their own API or not use a DMF. Nevertheless, this mapping provided a picture of U.S. reliance on foreign API sources at the end of 2021. The USP *Medicine Supply Map* analysis counted the number of active API DMFs by location:

- India: 48%
- Europe: 22%
- China: 13%
- U.S.: 10%
- Other: 7%

USP *Medicine Supply Map* insights also show how U.S. reliance on foreign API sources has changed over time. In 2021, India contributed 62 percent of active API DMFs filed that year, up from 20 percent of currently active DMFs that were filed in 2000. This increase is consistent with India's well-publicized national ambition to enhance API manufacturing capabilities. Meanwhile, Europe's contribution declined from 49 percent of active API DMFs filed in 2000 to 7 percent filed in 2021. The U.S. likewise contributed a lower percentage in 2021: 4 percent. China contributed 23 percent of new API DMFs filed in 2021. USP data suggest that China produces a wide variety of APIs for medicines marketed in the U.S.

Understanding this data could give leaders an opportunity to prepare for a potential disruption caused by a shock event, such as an emerging public health, political, or trade crisis. Questions remain from the current analysis, however, when thinking about facets of U.S. reliance on foreign API manufacturers. For example, USP's analysis does not take volume into account, and it is not clear if certain DMF holders are responsible for larger volumes of drugs compared to competitors. Importantly, we also do not understand U.S. reliance on other countries for key ingredients that are used in the manufacture of API.

Quality concerns

USP underscores that medicines supply chain resilience and medicines quality are inextricably linked; issues with medicines quality can threaten medicines supply chain resilience, and medicines supply chain failures, vulnerabilities and disruptions can lead to medicines quality issues, increasing the risk of substandard and falsified medicines. It is well documented that quality issues remain a primary contributor to drug and medical product shortages.

⁴ The White House. Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017 2021 [cited 2021 August 20]; Available from: <https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf>



USP *Medicine Supply Map* analysis found that poor FDA inspection outcomes at a facility and products with a history of recalls were correlated with a higher likelihood of shortage. This is consistent with FDA's findings: for example, of the 163 drugs that went into shortage between 2013 and 2017, the FDA found that 62 percent went into shortage due to quality issues.⁵ Root Cause 2 outlined in FDA's 2019 drug shortages report suggested that the market does not recognize and reward manufacturers for mature quality management systems.

Using Data to Guide Policy Reforms and Investments

Leveraging a comprehensive set of data – including upstream and supply-side risk indicators and factors – to guide potential policy reforms and investments will reduce drug shortages and improve supply chain resiliency. Improved visibility into and analysis of the vulnerabilities of the upstream medicines supply chain can help target potential policy reforms and inform U.S. government investments to enhance resilience.

Additional Data and Insights Are Needed to Guide Policy Reforms

Policymakers, manufacturers, wholesalers, and hospitals could benefit from intelligence to help size and scope geographic concentration and other types of risk, but some supply chain risk information is either not available or is considered confidential.

To address these challenges, USP proposes that the Committee consider the establishment of and investment in a public-private partnership to build an early warning system for the pharmaceutical supply chain. A "centers of excellence" model could be an appropriate construct for such a partnership, although other models could be effective as well. The USP *Medicine Supply Map* could be utilized in a variety of collaborative models that could include:

- Monitoring the pharmaceutical supply chain for disruptions, shortages and quality issues;
- Coordinating among the Department of Health and Human Services, Department of Commerce, Department of Defense, Department of Veterans Affairs, other federal and state agencies, allied trading partners, academic research institutions, non-profits and private sector entities to identify, assess and respond to supply chain challenges;
- Building predictive capabilities to inform stakeholders, including the U.S. Government, manufacturers, wholesalers and hospitals, of the risk of supply chain disruption with enough notice that mitigative action can be taken;
- Informing decisions made by the Strategic National Stockpile on medicines to include; and
- Periodically issuing public recommendations and reports on ways to prevent supply chain disruptions, shortages and quality issues.

Better Understanding of the Vulnerability of Key Starting Materials and Excipients Is Needed

There is very limited understanding today within the government or in the private sector about where many of the key ingredients used in the manufacturing of pharmaceuticals are made. Pharmaceutical supply chain data collection and analysis should be expanded to include key starting materials (KSM) and inactive ingredients known as excipients.

⁵ *Ibid.*



The U.S. needs better intelligence regarding which KSMs are commonly used in commercial synthesis; where KSMs are made and at what volume; and whether there are alternative KSMs and synthetic pathways. USP has initiated some methodologies to start this mapping, but more work is needed.

Additional visibility into the excipients supply chain is also needed, including where critical excipients are made and at what volume. Despite being called “inactive” ingredients, excipients play a critical role in drug development, delivery, effectiveness, and stability. Excipients comprise up to 90 percent of a medicine’s volume and serve important functions, including as binders, disintegrants, coatings, preservatives, colors and flavorings. As such, breakdowns of critical excipient supply chains can have significant downstream effects. For example, magnesium stearate is included in 32,060 drug products according to NIH DailyMed, including those to treat high cholesterol, high blood pressure, diabetes, and bacterial infections.⁶

Excipients are sourced from suppliers around the world and are used for more than just the manufacture of medicines. The reliance of the pharmaceutical industry on the global excipients supply chain presents challenges for supply chain resiliency as well as quality and regulatory oversight. Quality issues and shortages of excipients have contributed to supply chain disruptions. Critically, the impact of excipient quality failures extends beyond supply chain disruptions and drug recalls to include patient health impacts. A lack of awareness remains about how many and which drug shortages have been caused by shortages of or quality issues associated with excipients and which excipients are most vulnerable to quality issues and supply chain disruptions. Overall medicines supply chain vulnerabilities that apply to finished products, including geographic concentration, price, political and geopolitical considerations, sole/limited suppliers and climate vulnerabilities also apply to the excipients supply chain.

Incentives Are Needed to Promote Geographic Variation of Medicines Manufacturing

To minimize or prevent the occurrence of drug shortages due to disruptions, USP encourages diversifying the supply chain and building redundancies into the system. Similar to the way back-up systems work, perturbations in one part of the supply chain could be addressed or mitigated by scaling production in another, redundant part. The goal should be geographically diversified supply chains, as geographically concentration anywhere – even within the U.S. – is problematic and comprises a significant risk factor for drug shortages. For example, the recent Chapter 7 bankruptcy of a U.S.-based generic drug manufacturer had ripple effects on the production of certain medicines on the FDA Essential Medicines List, including levofloxacin oral/ IV (the company had 100 percent market share of ophthalmic form); adenosine injection (the company had 38 percent market share); and mycophenolate mofetil oral/ suspension (the company had 47 percent market of the injectable form).⁷

USP encourages policymakers to consider a range of reforms to foster geographic diversification of manufacturing facilities to reduce the risk of shortages that may occur from disruptions. These disruptions can occur globally, such as due to the COVID-19 pandemic, or locally, such as due to a natural disaster or political unrest. Policy reforms can include exploring economic or other incentive measures to support supply chain resiliency that will encourage geographic diversification of manufacturing facilities.

⁶ Wosinska, M. and R. Conti. Comments on the draft harmonized system code list of critical supply chains. November 7, 2022. Available at: <https://www.brookings.edu/opinions/comments-on-the-draft-harmonized-system-code-list-of-critical-supply-chains/>.

⁷ End Drug Shortages Alliance. 2023. “Supply chain disruption due to manufacturer closure: Akorn Pharmaceuticals ceases operations.” Available at: <https://www.enddrugshortages.com/files/Akorn-Pharmaceuticals-ceases-operations.pdf>.



U.S. government investment in domestic production of prioritized API is an important element of a comprehensive effort to enhance medicines supply chain resiliency. Economic incentives to help foster an environment conducive to more private sector medicine manufacturing in the U.S. should also be evaluated.

Stockpiling Decisions Should Factor in Medicines Supply Chain Vulnerability

The Strategic National Stockpile (SNS) is critical to the nation's response to public health threats to protect the American public. The composition of the products in national stockpiles should be continually reviewed and modified to address the most likely shortages of the included products. The list of pharmaceuticals to include in the stockpile should be informed by supply and demand side analysis, as described previously.

Additional Investments and Incentives Are Needed to Overcome Barriers to Adoption of Advanced Manufacturing Technologies (AMT)

Manufacturers have long produced pharmaceuticals using a method known as "batch manufacturing." Advances in manufacturing technologies – collectively referred to as advanced manufacturing technologies (AMT) – could help to strengthen supply chain resilience, but significant hurdles must be addressed to foster broader adoption.

Traditional batch manufacturing will remain an essential pillar of global medicine manufacturing strength, and any discussion related to onshoring must consider existing capacity for batch manufacturing. Recent studies suggest up to 50 percent of manufacturing capacity in the U.S. is not utilized.⁸ Implementing market-based incentives that encourage utilization of this excess domestic capacity would enhance the resilience of the U.S. medicines supply chain.

At the same time, AMT, including pharmaceutical continuous manufacturing (PCM), can be phased into unutilized manufacturing sites in some cases. PCM can provide efficiencies for many medicines and their ingredients and could facilitate expansion of domestic manufacturing in the U.S., particularly for the manufacture of critical medicines.

PCM is highly automated and involves a continuous flow of materials in a single facility, from inputs to process outputs, such as an active pharmaceutical ingredient or finished drug product. It can enable flexibility and efficiency, lower production costs, cut the environmental footprint, accelerate production and scale-up in response to emergencies and reduce potential quality issues through real-time monitoring. In contrast, in traditional batch manufacturing, the raw materials that are eventually transformed into the final product (e.g., a tablet) are processed in different machines at different times and potentially in different locations. This process naturally requires many starts and stops in manufacturing.

Continuous manufacturing provides a set of technologies that can help bring manufacturing back to U.S. soil and may allow economies that are new to pharmaceutical manufacturing to establish production plants of quality medicines and APIs. However, substantial challenges stand in the way of broader adoption of PCM. These obstacles can include knowledge about the areas where PCM use could be the most impactful and how to best implement it; workforce capacity challenges with an industry-wide shortage of PCM expertise; considerable capital and

⁸ Sardella, Anthony. Sep 2022. <https://wustl.app.box.com/s/32e1w52bajp6z22qf4vioti78997uk>



start-up costs associated with establishment of new facilities; lack of clarity on the return on investment; and ongoing uncertainties regarding regulatory reviews and approvals of medicines made with PCM around the world.

USP is working with partners to address PCM knowledge gaps through educational programs; the creation of an online continuous manufacturing Knowledge Center in collaboration with the National Institute for Pharmaceutical Technology and Education (NIPTE) and funded by FDA; and the launch of a flow chemistry research and development (R&D) laboratory to investigate novel routes of synthesis for API using PCM and develop new analytical techniques to help ensure product quality. To build upon these efforts, USP supports the authorization of appropriations to fund workforce training on AMT.

USP is currently engaging with a broad group of stakeholders, including academic research centers and manufacturers, to identify and articulate appropriate standards and practices that will help make advanced manufacturing more accessible and achievable for industry uptake.

However, not all drug manufacturers have the financial resources necessary to invest in AMT; this is especially true for manufacturers of low-margin drug products. Addressing these economic and market factors will be fundamental to fostering broader uptake of these promising advanced manufacturing technologies for lower margin medicines.

Conclusion

USP thanks the Committee for this hearing and for the bipartisan, careful consideration of the underlying causes of drug shortages and needed policy reforms to improve medicines supply chain resilience. We look forward to working with the Committee and Congress to seek solutions that will ensure that the U.S. medicines supply chain will be more resilient and reliable for patients.

Senate Committee on Homeland Security and
Governmental Affairs

Hearing on: “Drug Shortage Health and National Security
Risks: Underlying Causes and Needed Reforms”

Statement for the Record

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Thank you, Chairman Peters, Ranking Member Paul, and distinguished Members of the Committee, for holding this hearing and for the invitation to participate in this important discussion this morning. My name is Erin Fox, and I am the Associate Chief Pharmacy Officer for Shared Services at University of Utah Health. I am not speaking on behalf of the University. I am here today to provide my perspective on drug shortages.

Background

My team and I at the University of Utah Drug Information Service have tracked national drug shortages since January 2001. We receive voluntary reports from healthcare providers across the United States (US) and we confirm directly with the manufacturer if there is or is not a shortfall of the particular presentation they sell. We post our findings to a public website that is hosted by the American Society of Health-System Pharmacists (www.ashp.org).¹ Specifically, we note which products are available as well as which products are not. We also try to list reasons for the shortage, the expected duration of the shortage, and evidence-based alternatives and safety recommendations. This information is different than the information on FDA's drug shortage website because FDA cannot provide recommendations for alternatives, even though FDA does consider substitutes when making their own market-wide shortage determinations. Our goal in providing these data is to help clinicians mitigate the effects of drug shortages on their patients and to assist clinicians with planning by providing estimated resupply dates and management suggestions.

Drug shortages are frequent. When we began tracking shortages in 2001, we identified 120 new shortages. In 2011, we saw a peak of new shortages at 267, and in 2022, we saw a total of 160 new shortages.¹ However, just because a shortage begins in one calendar year does not mean that it resolves the same calendar year or even the next year. Many shortages last for years. Since 2018, we have been tracking over 200 active and ongoing shortages. For many months in that timeframe, there were over 250 active and ongoing shortages, and [at the end of 2022](#), we were monitoring 295 active and ongoing shortages.¹

The most common type of drug in short supply is a generic injectable drug used in hospitals and clinics. Some current examples include local anesthetics such as lidocaine with epinephrine, steroids such as dexamethasone, and older chemotherapy agents such as cytarabine or dacarbazine. Because of shortages, patients and hospitals routinely cannot access the most basic and essential prescription medications.²

Causes

The cause of a specific shortage is rarely known to the public. Manufacturers are not required to publicly provide specific reasons for shortages, and we typically do not identify a reason for at least half of the shortages we track. My team asks manufacturers directly for causes and uses available FDA data and press reports to infer causes, but frequently we are unable to understand what triggered the shortage. Was it a manufacturing quality problem? A demand increase? Business decision to prioritize other products? Problems accessing ingredients? Answers to these questions can give us clues about how long a shortage will last. A

manufacturing problem takes much longer to resolve than a shipping delay. For 2022 shortages, my team could identify the reason for only 44% of them.¹

Because drug manufacturers are not required to provide a public explanation for shortages, the best data are those summarized by FDA, which does have access to manufacturers' immediate reasons for shortages. FDA's Drug Shortages Task Force published a [report](#) in 2019 identifying supply disruptions as the key reason for shortages and economic forces as the root cause of those disruptions.³

First, the Task Force found that there are few incentives for manufacturers to produce difficult to make generic injectable drugs that have low profit margins. The low prices for some of these products are due to a "[race to the bottom](#)"—the result of pressure from hospitals that are paid for most hospital stays with capitated payments and group purchasing organizations (GPOs) that contract on behalf of hospitals.⁴ Manufacturers cannot be expected to produce products at a loss.

Second, even if a new supplier would like to enter the market, there are [significant regulatory hurdles](#) to receive FDA approval for a product.³ Even more challenging is building new manufacturing operations, partly due to regulatory hurdles and anecdotally, partly due to the lack of readily available capital for funding such investments for low margin generics in the US.

Third, there is no recognition for manufacturers that choose to invest in quality. FDA sees [clear quality differences](#) between products and manufacturing sites, but this information is confidential.⁵ Sixty-two percent of shortages between 2013 and 2017 were due to manufacturing or quality problems based on the most current aggregate data from FDA that outlines reasons.⁶

Lack of Transparency

Purchasing medications is different from other products as there is no requirement for the manufacturer to publicly disclose which company made the product and where the product was made.⁷ Currently, price is the only differentiating factor for pharmacy buyers.

Buyers can also have skewed views about a product's potential availability or the true number of manufacturers. For example, a purchaser using [DailyMed](#)⁸ may see listings for 5 to 6 products. However, contract manufacturing means that one company can make a medication for multiple other companies who then put their label on the product. The true manufacturers are not known as there is no requirement to disclose this information. Market share information is also not publicly available. This means that when a shortage occurs for just one supplier, buyers can have a false sense of security about a product's availability. The situation may look like just one supplier is out of a product, but 4 to 5 others are available. However, if contract manufacturers are making the product for several companies, there may only be 2 manufacturers. Further, they cannot see that one of those products has a much larger market share than others. The public information about shortages is insufficient to buyers. This lack of information prevents making timely decisions and plans to mitigate patient impact during a shortage.

Buyers also have no information about quality when making purchasing decisions. FDA provides notices of quality issues, but most forms are highly redacted. It's impossible for a buyer to know which products are made in a particular facility. Even if we could map products to facilities, it would be difficult for purchasers or GPOs to act on that information and avoid purchases from companies with poor compliance reports. Unlike in European inspection reports, FDA's inspection reports list observations, without an indication as to how serious of a problem that observation is or what FDA recommends to remedy that observation.

Our ability to act on FDA's compliance records is also complicated by the fact that FDA is unable to hold the line on Good Manufacturing Practices (GMPs).⁹ FDA exercises [regulatory flexibility to mitigate the impact of shortages](#), in some cases allowing injections to remain on the market [despite containing particles](#).¹⁰ Healthcare professionals are instructed to use a filter in these cases. This regulatory flexibility has unintended consequences. Quoting from a 2013 [paper](#)⁹ by Janet Woodcock and Marta Wosinska *"The FDA's need to use regulatory flexibility on behalf of patients to avert and mitigate shortages could have unintended long-term consequences when coupled with the market's lack of reward for quality. Economic models predict that, in the face of the seeming intertemporal inconsistency created by dual FDA objectives, quality investments would be lower than if the FDA could use preemptive enforcement without regard for disruptions in medically necessary products. This dynamic may further reinforce the economic incentives to minimize quality investments given the nature of competition (based on price, not quality)."*

What would be helpful to us is a rating system that would consolidate all the relevant compliance information in a way that is easy to interpret. FDA been working to develop such quality metrics system, but they do not intend to make the scores publicly available.¹⁰

Shortages Affect Patients

Shortages adversely impact patients, healthcare professionals, and health systems. An entire generation of clinicians [has never practiced during a time without shortages](#). A survey from 2018 noted that 95% of medicine, anesthesiology, and emergency medicine residents have had to manage shortages, often on a daily basis, with little or no training on how to manage these situations.¹²

The true number of patients harmed by shortages is difficult to quantify as there is no national reporting system. But some examples have been documented. For example, in 2011, at least [15 patients died](#) due to drug shortages, most as a result of medication errors where substitute drugs were dosed incorrectly or an emergency product was not available.¹³ Patients also suffer when alternative drugs have worse outcomes than the drug of choice, such as patients with sepsis who had a [higher mortality rate](#) during a shortage of norepinephrine.¹⁴ [Shortages of chemotherapy](#) have led to delayed treatments, delayed clinical trials for new therapies, reduced doses, and poor outcomes.¹⁵

Shortages Affect Hospital Operations

Hospitals have invested in technology such as barcode scanning, electronic health records, and automated dispensing cabinets to improve patient safety, but these systems require stable supplies of drugs. Switching products is time-consuming and challenging, especially when faced with ongoing labor shortages. For example, after Hurricane Maria devastated Puerto Rico, disrupting the operations of a key saline manufacturer, creating a critical shortage of saline, our health system went to great lengths to conserve supplies of saline bags and administer some drugs in syringes.¹⁶ Switching just 2 drugs to be administered in syringes instead of saline bags required review and changes to 700 patient treatment plans in a single day. Because of these challenges, most health systems have one or more full-time employees devoted exclusively to shortage management.

Recommendations

Patients and hospitals need access to routine supplies of medications. I was part of the National Academies of Sciences, Engineering, and Medicine's (NASEM) [consensus committee](#) on building resilience into the nation's medical product supply chains.¹⁷ Our committee's report provides comprehensive recommendations to build resilience and security into the supply chain, and improve the drug shortage problem. I urge you to review it.

I would like to put forward to the Committee two recommendations that build on the NASEM report.

First, in line with the NASEM report, the most important step towards resolving the problem addressing shortages is requiring additional transparency to allow for rating systems for pharmaceuticals. Ratings systems with checks from accreditation agencies would set the stage, perhaps for payers to shift hospitals to preferentially purchase products from manufacturers with higher quality and less chance of shortages.

Health systems will need to use a rating system and pay more for products from manufacturers that meet all quality standards and are able to offer more reliable supplies. Health systems are already paying more for shortages with employees and time spent making drug switches. Hospitals would be wise to consider paying more for reliable supply agreements than to spend money on staff dealing with shortages, particularly in the current setting of significant healthcare labor shortages. Payers can also incentivize hospitals to do the same to prevent poor patient outcomes and associated higher health spending.

Second, to the extent that the Federal Government intends to strengthen specific supply chains through tax credits, loans or subsidies, the government would be wise to reassess¹⁸ which drug supply chains are most vulnerable because FDA's current list of critical medications¹⁹ may not be a good starting point. In particular, that list was developed in response to a 2020 Executive Order²⁰ focusing on "outbreaks of emerging infectious diseases and chemical, biological, radiological, and nuclear (CBRN) threats." A 2021 Executive Order²¹ directed vulnerability assessments for supply chains to include "extreme weather events, terrorist attacks, geopolitical and economic competition, and other conditions" but using the existing FDA list.

FDA's list of essential medicines should not be the starting point for identifying critical medicines that may need their supply chains strengthened because it is not comprehensive for essential medical care and in many cases the selections do not make sense from a clinical perspective or resource allocation perspective. It is also critical that the government supplement any updates to the list with supply-side analytics to identify vulnerabilities. For example, filgrastim is included on the list, however former FDA Commissioner Scott Gottlieb has provided significant details about how Amgen has hardened their filgrastim manufacturing to avoid any potential shortfalls no matter the threat.²² While filgrastim is an essential medication, its supply chain does not need strengthening. The government should seek to have a comprehensive view, not only focusing on finished dosage forms (FDF) and active pharmaceutical ingredients (API) but also on excipients and key starting materials. FDA has information on FDF and API, but not key starting materials and excipients. Without such data, we cannot know the true extent of vulnerability and target strengthening measures. From a clinical perspective, essential products like chemotherapy used in curative regimens (bleomycin, vinblastine, cisplatin) are not included on FDA's list, and all have had significant shortages in the past.

Adjusting the essential medicines list and expanding the government's analytical capabilities is important because we need both to assess the risk to supply chains, be it single source of raw material or manufacturing site, or products solely produced in countries we have tenuous relationships with. Understanding which products are most at risk would allow targeted, more effective actions to prevent or mitigate shortages with limited resources. I am concerned that without addressing the scope of the FDA list and the scope of our analytical capabilities, the government may be overlooking some critical supply chains and their vulnerabilities and opportunities to strengthen supply chains.

Thank you once again for holding this hearing and for the opportunity to share my perspective on how shortages impact patient care, healthcare professionals, and health systems. I look forward to learning more and participating in ongoing discussions on this critically important issue. I welcome any questions you may have.

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63

Why Are There Drug Shortages?

by

John C. Goodman

Testimony before

The U.S. Senate Committee on Homeland Security and
Governmental Affairs

Wednesday, March 22, 2023,

Hearing on “Drug Shortage Health and National Security
Risks: Underlying Causes and Needed Reforms.”

Why Are There Drug Shortages?

by

John C. Goodman¹

Jenny Morrill, a Kinston, New York, mother and former arts administrator, had been battling ovarian cancer since 2007. When she went for her chemotherapy treatment in June 2011, the nurse greeted her with good news and bad news. The good news: she was responding well to the drug Doxil. The bad news: the hospital had no more Doxil to give her. Morrill was not alone. By November 2011, the plant that produced the drug completely shut down, leaving 7,000 US patients without access to its life-saving properties.²

Doxil is not the only drug that patients have faced trouble getting. The problem has been escalating for many years. (See the Figure below.) Some patients have died as a result.³ Others are trying to get by on inferior substitute therapies.

¹ Dr. Goodman is president of the Goodman Institute for Public Policy Research.

² Roni Caryn Rabin, "Drug Scarcity's Dire Cost, and Some Ways to Cope," *New York Times*, December 12, 2011, <http://www.nytimes.com/2011/12/13/health/policy/the-personal-price-paid-for-shortages-of-doxil-and-other-drugs.html>.

³ See for example, Andrew M. Seaman, "Drug Shortage in 2011 Tied to Increased Deaths," *Reuters Health*, March 21, 2017,

Nearly all thirty of the most frequently used emergency department drugs experienced shortages from 2006-2019, exacerbating patient harm “due to the time-sensitive nature of acute care.”⁴

Today, between 186 and 308 drugs have shortages.⁵ 2022 shortages include saline, a drug potentially needed by almost every patient who gets admitted to the hospital.⁶ Almost all of the drugs in short supply, by the way, are generics.

Reacting to shortages of key medications for the flu, ear infections and sore throats during the wake of COVID-19, pediatric infectious disease specialist Dr. Stacene Maroushek of Hennepin Healthcare in Minnesota said: “In my 25 years of being a pediatrician, I’ve never seen anything like this. I have seen families who just aren’t getting a break. They have one

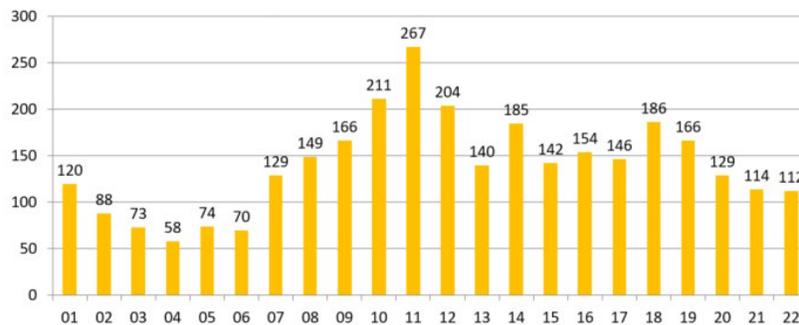
⁴ Lin MP, Vargas-Torres C, Shin-Kim J, Tin J, Fox E. “Nearly all thirty most frequently used emergency department drugs experienced shortages from 2006-2019.” *Am J Emerg Med.* 2022 Mar;53:135-139. doi: 10.1016/j.ajem.2021.12.064.

⁵ The number depends on how you count them. See Drugs.com “Current Drug Shortages,” <https://www.drugs.com/drug-shortages/> and Food and Drug Administration, “Current and Resolved Drug Shortages and Discontinuations Reported to FDA,” <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>,” (accessed November 23, 2022). See also David R. Henderson and Charles L. Hooper, “Are Some Drug Prices Too Low?” *Goodman Institute Brief Analysis No. 133*, January 13, 2020, <https://www.goodmaninstitute.org/wp-content/uploads/2020/10/BA-133-Are-Some-Drug-Prices-Too-Low-1-13-20web.pdf>.

⁶ Judy Packer-Tursman, “U.S. Drug Shortages Put People With Life-Threatening Illness At Risk,” *United Press International*, September 16, 2022, https://www.upi.com/Health_News/2022/09/16/drug-shortages-lorazepam-cancer/6681663190912/.

viral illness after another. And now there's the secondary effect of ear infections and pneumonia that are prompting amoxicillin shortages."⁷

Reported Drug Shortages



Source: American Society of Health-System Pharmacists, "Drug Shortages Statistics," <https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics> (accessed November 23, 2022)

Note: Each column represents the number of new shortages identified during that year.

In one 2011 survey, nine in ten anesthesiologists reported

⁷ Brenda Goodman and Raenu Charles, "Shortages of antivirals, antibiotics compound stress of a rough season for viral illnesses in kids," CNN, November 22, 2022, <https://www.cnn.com/2022/11/22/health/drug-shortages-tamiflu-amoxicillin-albuterol>.

experiencing a shortage of at least one anesthesia drug.⁸ Another survey found that more than 40 percent of the thirty-four generic oncology drugs on the market were in short supply.⁹ There are no reliable substitutes for most of these drugs. Most are generic injectable medications that have been on the market a long time and are commonly used in hospitals, emergency rooms, and cancer treatment centers. The American Hospital Association reported in 2011 that virtually all the community hospitals it surveyed had experienced a drug shortage in the previous six months. Two-thirds of hospitals had experienced a shortage of cancer drugs; 88 percent were short on pain medications; and 95 percent were lacking anesthesia drugs needed for surgery.¹⁰

Hospitals respond in a variety of ways, including delaying treatment, giving patients less effective drugs, and providing a different course of treatment than the one recommended.

⁸ "Survey Reveals 90 Percent of Anesthesiologists Experiencing Drug Shortages of Anesthetics," Press Release, American Society of Anesthesiologists, May 9, 2011, <http://www.asahq.org/For-the-Public-and-Media/Press-Room/ASA-News/Survey-Reveals-90-Percent-of-Anesthesiologists-Experiencing-Drug-Shortages-of-Anesthetics.aspx>.

⁹ Ezekiel Emanuel, "Shortchanging Cancer Patients," *New York Times*, August 6, 2011, <http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html>.

¹⁰ Scott Gottlieb, "Drug Shortages: Why They Happen and What They Mean" (Statement before the Senate Finance Committee, United States Senate), December 7, 2011. See also Edmund Haislmaier, Ensuring Americans' Access to Pharmaceuticals: A Primer and Road Map for Policymakers, *The Heritage Foundation Backgrounder No. 3545*, October 20, 2020, <https://www.heritage.org/sites/default/files/2020-10/BG3545.pdf>.

Indeed, about 82 percent of hospitals surveyed reported at least occasionally delaying a treatment because of a drug in short supply.

According to Ezekiel Emanuel in 2011 (who in addition to being White House adviser was also an oncologist), only about 10 percent of shortages were due to a lack of raw materials needed to manufacture the drugs. A more important source of the problem is government policy.

Problem: Unwise Output Regulations: The Food and Drug Administration (FDA) attempts to ensure that drug manufacturing processes and facilities meet its quality standards by instituting a zero-tolerance policy. By way of enforcement, the agency levies fines and forces manufacturers to retool both domestic and foreign facilities. They use a binary (pass/fail) system that does not reward companies that exceed minimum required standards, nor accounts for whether a facility is using best practices to anticipate and minimize the occurrence of production problems. Regulations not only slow the production at particular facilities, they make it difficult for competitors to take up the slack. If a shortage develops because the FDA shuts down a competitor's plant, for example, a manufacturer must seek FDA approval to increase output and alter its production timetable. This slows down adjustments in production.

Problem: Medicare Part B Price Controls. Some drugs that are administered by physicians—such as chemotherapy drugs or anesthesia during surgery—are paid for through Medicare Part B. Government price controls prevent the prices of these drugs from adjusting in response to shortages, increases in manufacturing costs, or increases in demand. Normally, the market price of a product rises when it is in short supply, attracting competing manufacturers. However, Medicare discourages this response.

Medicare Part B allows health care providers, such as doctors and hospitals, to charge a small percent over the drug’s “average selling price” to cover the cost of administering the drug. However, that “average selling price” is calculated across all manufacturers and is based on historical prices.

So, if one manufacturer sees a shortage developing, that manufacturer can legally raise the price of its drug. But since the health care providers that purchase it will purchase it at a loss, they won’t want to purchase it. As a result, the shortage won’t be averted.¹¹

Problem: Inability To Compete on Any Product Dimension Other Than Price. Regulations also limit the ability of drug makers to communicate improvements in safety, reliability or

¹¹ Gottlieb, “Drug Shortages.” See also David R. Henderson and Charles L. Hooper, “Are Some Drug Prices Too Low?” *Goodman Institute Brief Analysis No. 133*, January 13, 2020, <https://www.goodmaninstitute.org/wp-content/uploads/2020/10/BA-133-Are-Some-Drug-Prices-Too-Low-1-13-20web.pdf>.

efficacy to potential customers. These regulations remove the economic incentives to solve problems the way they would be solved in any normal market. As a result of these and other regulations, firms cannot recoup investments they make, including improving the reliability of supply.¹²

At the same time, the pharmacists who fill the prescriptions are implicitly or explicitly required to fill them with the generic that has the lowest price. The result: There is no competition on any other product feature other than price.

When buyers and sellers are forced to compete on price alone, there will be a race to the bottom on every other product dimension.

Contrast what happens in the market for regulated generics with what happens in the largely unregulated market for aspirin. Because aspirin is sold directly to consumers (rather than through a pharmacist middleman), there can be different prices for different brands and producer reputation matters to many consumers.

I can't remember when there has been a shortage of aspirin or any other over-the-counter pain relief drug.

¹² Gottlieb, "Drug Shortages." See also David R. Henderson and Charles L. Hooper, "Sometimes Drug Prices Are Too Low," *The Wall Street Journal*, October 31, 2019, https://www.wsj.com/articles/sometimes-drug-prices-are-too-low-11572561325?mod=article_inline.

Problem: 340B Price Controls. The federal 340B drug rebate program also contributes to shortages. This program allows hospitals and clinics treating low-income and uninsured patients to dispense drugs purchased at a discount from drug manufacturers but still receive reimbursement from the federal government at full prices. According to one analysis:

Hospitals love this profitable arrangement. But the 340B hospital pricing law relies on self-policing. A Government Accountability Office audit found that the rules are so unclear that hospitals must use their own judgment about whether they qualify for full reimbursement. In principle, that means that *any hospital* can apply for the discounts.

As a *New York Times* expose explains:¹³

Thanks to 340B, Richmond Community Hospital can buy a vial of Keytruda, a cancer drug, at the discounted price of \$3,444... But the hospital charges the private insurer Blue Cross Blue Shield more than seven times that price — \$25,425, according to a price list that hospitals are required to publish. That is nearly \$22,000 profit on a single vial.

How is that done? A nonprofit chain (Bon Secours) links a hospital in a poor neighborhood (to qualify for the program) with clinics in wealthier neighborhoods, where patients with generous private insurance receive expensive drugs.

¹³ Katie Thomas and Jessica Silver-Greenberg, "How a Hospital Chain Used a Poor Neighborhood to Turn Huge Profits," *New York Times*, Updated Sept. 27, 2022

Meanwhile, services provided in the poor neighborhood have deteriorated over time.

As the years passed, Bon Secours began stripping the hospital's services, including the I.C.U. The unit had only five beds.... Ringed by public housing projects, Richmond Community consists of little more than a strapped emergency room and a psychiatric ward. It does not have kidney or lung specialists, or a maternity ward. Its magnetic resonance imaging machine frequently breaks... Standard tools like an otoscope, a device used to inspect the ear canal, are often hard to come by.

Hospitals and clinics have gained from these discounts – \$6 billion in 2015. But there appears to be no gain for either patients or taxpayers. According to a study in the *New England Journal of Medicine*, there is no clear evidence of “expanded care or lower mortality among low-income patients.” Taxpayers haven’t gained, because the government still pays the full price for the drugs. Effectively, there’s a financial transfer from drug companies to hospitals and clinics with little benefit to anyone else.¹⁴

¹⁴ David R. Henderson and Charles L. Hooper, “Are Some Drug Prices Too Low?” *Goodman Institute Brief Analysis No. 133*, January 13, 2020, <https://www.goodmaninstitute.org/wp-content/uploads/2020/10/BA-133-Are-Some-Drug-Prices-Too-Low-1-13-20web.pdf>.

Additional resources:

David R. Henderson and Charles L. Hooper, *Are Some Drug Prices Too Low?* Goodman Institute Brief Analyses No. 133, January 13, 2020. <https://www.goodmaninstitute.org/wp-content/uploads/2020/01/BA-133-Are-Some-Drug-Prices-Too-Low-1-13-20.pdf>

David R. Henderson and Charles L. Hooper, *Why Are Drug Prices So High?* Goodman Institute Brief Analyses No. 117, January 10, 2017. <https://www.goodmaninstitute.org/wp-content/uploads/2017/01/BA-117.pdf>



Table of Contents

EXECUTIVE SUMMARY	3
FINDINGS OF FACT.....	5
RECOMMENDATIONS	6
I. Drug Shortages Continue to Pose Health and National Security Risks	8
II. Underlying Causes Remain the Same as in 2019.....	11
A. Economic Drivers	12
1. Lack of Incentives and Market Exits.....	13
2. Lack of Investment in Quality Systems.....	16
3. Market Consolidation and Contracting Practices.....	19
B. Concentrated Geographic Reliance and Insufficient Supply Chain Visibility	21
C. Increased Demand.....	27
D. Logistical and Regulatory Challenges.....	30
E. Natural Disasters and Biological Incidents	30
III. Impact on Patients, Hospitals, and Health Care Systems.....	33
IV. Challenges in Predicting, Preventing, and Mitigating Drug Shortages	35
A. Data Shortfalls.....	37
B. Domestic Manufacturing Capacity and Technology Limitations	39
V. Conclusion.....	41

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.

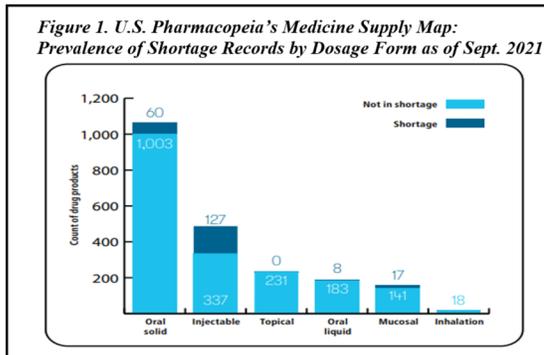
4. **The FDA should take steps to ensure its supply chain data can be used to monitor supply chain vulnerabilities and conduct predictive modeling:** The FDA should prioritize its development of a key starting material database and improve coordination with interagency and industry partners to assess 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.¹

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.² 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.³



¹ 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.

² 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”).

³ *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.⁴ 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.⁵

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).⁶ 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.⁷ Over fifteen basic critical care drugs—the majority of which are injectable products—have remained in shortage for over a decade.⁸ See Figure 2.

Figure 2. Drug Products in Shortage for Over a Decade⁹

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.

⁴ 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”).

⁵ 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”).

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

⁷ *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>).

⁸ *Id.* at 9.

⁹ 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.¹⁰ 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.”¹¹ 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.¹² 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.”¹³

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.”¹⁴ 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.”¹⁵ 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.”¹⁶

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.”¹⁷ Dr. Erin Fox, Associate Chief Pharmacy Officer at the University of Utah, leads the collection of drug shortage data for ASHP. Dr.

¹⁰ *Id.*

¹¹ 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).

¹² 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”).

¹³ 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).

¹⁴ 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).

¹⁵ *Id.*

¹⁶ 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).

¹⁷ 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.¹⁸ Lidocaine injections have low profit margins (generally costing less than 10 cents per unit) and high manufacturing complexities (requiring a sterile environment).¹⁹ 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.²⁰

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.²¹ 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.²² 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.”²³

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.²⁴ USP’s analysis of actual drug shortages recorded by the FDA and ASHP assessed over 200 factors potentially contributing to drug shortages and

¹⁸ 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”).

¹⁹ 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*”).

²⁰ USP Briefing.

²¹ HSGAC Minority Staff Report, *A Price Too High*.

²² 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”).

²³ EY Report for Healthcare Distribution Alliance, at 7.

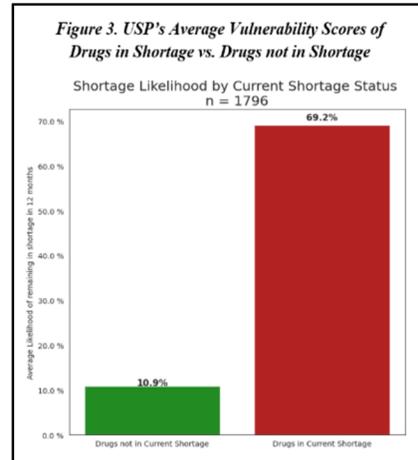
²⁴ USP Briefing.

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.²⁵

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.²⁶

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.²⁷ 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.²⁸ 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.²⁹ According to the FDA, of the drugs that went into shortage between 2013 and 2017,



²⁵ *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”).

²⁶ ASHP Drug Shortages Website (accessed Mar. 19, 2023).

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

²⁸ 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); see also ASPR Supply Chain and Industrial Analysis Report, at 7.

²⁹ 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.³⁰

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.³¹ 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.³² 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.³³ 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 1980.³⁴

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.”³⁵ 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.³⁶ The case studies below demonstrate the impact of limited suppliers and manufacturers exiting the marketplace on a lifesaving drug product.

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

³⁰ FDA Drug Shortages Report, at 5.

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

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

³³ FDA Drug Shortages Report, at 21.

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

³⁵ 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”).

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

VINCRIStINE

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 1987.³⁷

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.³⁸ Of the nine companies that received FDA approval to market vincristine (including the branded manufacturer), seven have discontinued the product.³⁹ There are currently two approved manufacturers, Hospira and Teva, but only Hospira is actively making vincristine for the U.S. market.⁴⁰ Vincristine currently costs anywhere from \$12 to \$26 per unit.⁴¹ According to USP, Vincristine currently has a vulnerability score of 53.2 percent based on low profit margins, high manufacturing complexities, and geographic concentration.⁴² 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.⁴³ 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.⁴⁴

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.⁴⁵ 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.⁴⁶ Teva told the Majority Committee staff it exhausted the last of its Vincasar PFS inventory in February 2023.⁴⁷ 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.

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

³⁸ 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>).

³⁹ 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).

⁴⁰ National Library of Medicine, *DailyMed, Vincristine* (<https://daily.med.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").

⁴¹ *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*.

⁴² USP Briefing and Medicine Supply Map Presentation.

⁴³ *Id.*

⁴⁴ USP Briefing.

⁴⁵ 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").

⁴⁶ *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>).

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

BACILLUS CALMETTE-GUERIN (BCG)

What is it? Bacillus Calmette-Guerin (BCG) live is an immunotherapy biologic drug used to treat bladder cancer.⁴⁸ The FDA first approved BCG live in 1976, and two manufacturers subsequently filed for approval to manufacture additional biologics beginning in 1989.⁴⁹ Since 2000, no additional manufacturers have entered the market. A 50 mg dose of BCG live may cost anywhere between \$180 and \$190.⁵⁰

What is the concern? BCG live has been in shortage since 2019 due to an increase in “global demand” for the product.⁵¹ 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.⁵² 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.⁵³ 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.⁵⁴ 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.⁵⁵ 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.⁵⁶

⁴⁸ Cleveland Clinic, Bacillus Calmette-Guerin (BCG) Treatment

(<https://my.clevelandclinic.org/health/treatments/17908-bacillus-calmette-guerin-bcg-treatment>) (accessed Mar. 1, 2023).

⁴⁹ 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).

⁵⁰ 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”).

⁵¹ 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).

⁵² *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.aunet.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).

⁵³ *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>).

⁵⁴ 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).

⁵⁵ End Drug Shortages Alliance, *Implications of the National BCG Drug Shortages* (Feb. 2023)

(https://www.enddrugshortages.com/files/BCG_White_Paper.pdf).

⁵⁶ 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.⁵⁷ 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.⁵⁸ 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.”⁵⁹ 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.⁶⁰ The FDA found that between 2013 and 2017, over 60 percent of drugs that experienced shortages were because of quality issues.⁶¹ 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.”⁶²

Oftentimes, generic drug manufacturers operate at full capacity and therefore are not able to adequately respond to manufacturing disruptions or increases in demand.⁶³ 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

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

⁵⁸ *Id.*

⁵⁹ 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”).

⁶⁰ 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).

⁶¹ FDA Drug Shortages Report, at 111.

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

⁶³ 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.⁶⁴ 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.⁶⁵ 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.

PROPOFOL

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.⁶⁶

What is the concern? Propofol is currently in shortage, according to ASHP.⁶⁷ 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.⁶⁸

As one example, in 2009 the FDA issued a warning letter to Teva due to quality problems at their Irvine, California manufacturing facility.⁶⁹ Teva did not resume production of the product until 2011.⁷⁰ 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.”⁷¹ In March 2022, Teva announced it would stop supplying propofol.⁷² In the summer of 2022, Hospira issued a voluntary recall for one lot of propofol after observing particulates in two vials.⁷³ A combination of a market exits, manufacturing

⁶⁴ ASPR, ARMI, and NextFAB Report, at 16, 18.

⁶⁵ Park Dissertation, Boston University at 5, 90.

⁶⁶ 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*.

⁶⁷ 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”).

⁶⁸ USP Briefing and Presentation.

⁶⁹ 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>).

⁷⁰ *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>).

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

⁷² FDA Drug Shortages Website (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).

⁷³ 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.⁷⁴ While ASHP's drug shortage list includes propofol, the FDA's drug shortage website does not currently list this product as being in shortage.

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 2022.⁷⁵ 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."⁷⁶

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.⁷⁷ 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.⁷⁸

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

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

⁷⁵ 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>).

⁷⁶ 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").

⁷⁷ 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>).

⁷⁸ 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.⁷⁹ To achieve this, the FDA has proposed a Quality Management Maturity (QMM) rating system for manufacturing facilities.⁸⁰ 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.”⁸¹ After conducting two pilot programs on the initiative, the FDA’s Advisory Committee voted unanimously in favor of establishing a QMM program.⁸² 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.”⁸³

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.⁸⁴ As of 2018, the four largest Group Purchasing Organizations (GPOs) accounted for 90 percent of the medical supply market.⁸⁵ According to the FDA, “GPOs account for over \$100 billion of the drugs purchased in this country in a given year.”⁸⁶ The distributor market is also heavily consolidated with three distributors representing approximately 80 percent of the market.⁸⁷

For nearly a decade, government watchdogs, federal agencies, and researchers have raised concerns about the effect of contracting practices on drug shortages.⁸⁸ 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.”⁸⁹ The FDA and ASPR raised similar concerns suggesting that GPOs market

⁷⁹ FDA Quality Management Maturity White Paper, at 3.

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

⁸¹ *Id.*, at 3.

⁸² *Id.*, at 4.

⁸³ 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.”

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

⁸⁵ 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>).

⁸⁶ FDA Quality Management Maturity White Paper, at 9.

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

⁸⁸ 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.

⁸⁹ 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.⁹⁰ 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.”⁹¹

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.⁹² 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.⁹³ 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.⁹⁴ It has been in shortage since November 2021, despite having at least six suppliers.⁹⁵ 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.⁹⁶

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.⁹⁷ 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

⁹⁰ ASPR, ARMI, and NextFAB Report, at 20; FDA Drug Shortages Report, at 6.

⁹¹ 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”).

⁹² 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).

⁹³ 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”).

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

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

⁹⁶ 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”).

⁹⁷ Interview with Association for Accessible Medicines.

comes to critical drugs.”⁹⁸ 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.⁹⁹ 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.¹⁰⁰

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.¹⁰¹

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.”¹⁰² 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.¹⁰³ Foreign government investments, mainly from China and India, also heavily subsidized pharmaceutical manufacturing, offering lower costs, skilled workers, and a less stringent regulatory environment.¹⁰⁴ A 2011 FDA report estimated the cost of API manufacturing in India was 15 to 40 percent less than in the United States.¹⁰⁵ 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.¹⁰⁶

⁹⁸ Interview with Vizient.

⁹⁹ 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).

¹⁰⁰ Interview with Healthcare Distribution Alliance.

¹⁰¹ ASPR Supply Chain and Industrial Analysis Report, at 6.

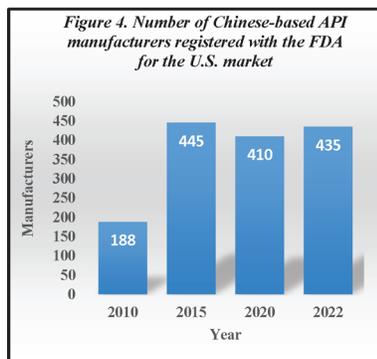
¹⁰² DHS Response; *see also* Department of Defense, Office of Inspector General, *Evaluation of the Department of Defense’s Mitigation of Foreign Suppliers in the Pharmaceutical Supply Chain* (DODIG-2021-126) (Sept. 20, 2021) (hereinafter “DOD IG Report”).

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

¹⁰⁴ *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).

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

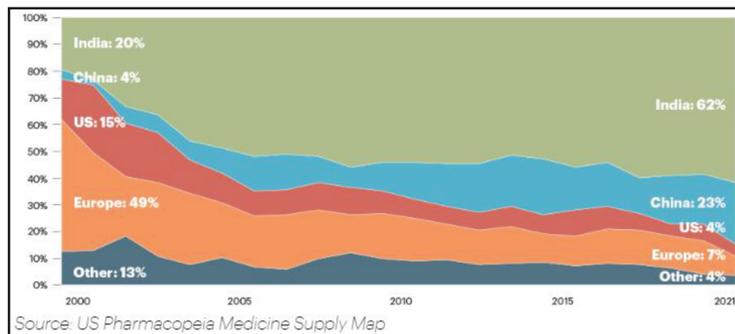
¹⁰⁶ DHS Response; ASPR, ARMI, and NextFAB Report, at 16.



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.¹⁰⁷ See Figure 4. By 2021, 87 percent of generic API manufacturing sites and 63 percent of generic finished dosage manufacturing sites were located overseas.¹⁰⁸ 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.¹⁰⁹ 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.¹¹⁰ 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.¹¹¹

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



¹⁰⁷ FDA Response.

¹⁰⁸ White House 100-Day Supply Chain Review, at 214.

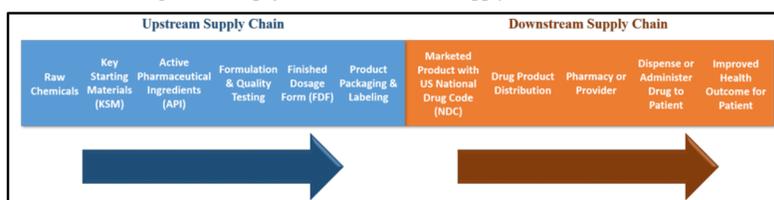
¹⁰⁹ U.S. Pharmacopeia, *Geographic concentration of pharmaceutical manufacturing: USP Medicine Supply Map analysis* (May 18, 2022) (<https://qualitymatters.usp.org/geographic-concentration-pharmaceutical-manufacturing>).

¹¹⁰ *Id.*

¹¹¹ 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.¹¹² 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.”¹¹³ Similarly, pharmaceutical manufacturers contract with a number of suppliers, such as key starting material sources, API manufacturers, finished dosage manufacturers, packagers, labelers, and repackagers.¹¹⁴ The chart shown in Figure 6 below, provides a high-level overview of the pharmaceutical supply chain.

Figure 6. Simplified Pharmaceutical Supply Chain Process¹¹⁵



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.”¹¹⁶ 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.¹¹⁷ 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.”¹¹⁸ 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.”¹¹⁹ USP explained how insight into key

¹¹² 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.

¹¹³ Interview with Dr. Stephen Schondelmeyer.

¹¹⁴ NASEM Supply Chain Report, at 39.

¹¹⁵ 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>).

¹¹⁶ 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”).

¹¹⁷ Interview with Association for Accessible Medicines.

¹¹⁸ Interview with Premier.

¹¹⁹ 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.¹²⁰

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.”¹²¹ 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.”¹²² 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.”¹²³ 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.¹²⁴ Drugs that have a geographically concentrated manufacturing base are more susceptible to shortages.¹²⁵

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.¹²⁶ 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.¹²⁷

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.¹²⁸ 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

¹²⁰ USP Briefing.

¹²¹ DOD IG Report, at 32.

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

¹²³ *Id.*

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

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

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

¹²⁷ Interview with Dr. Stephen Schondelmeyer.

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

there.”¹²⁹ Dr. Erin Fox independently relayed the same concerns to Committee staff and noted, “we do not know which companies are actually making products.”¹³⁰ 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.¹³¹ Below is an example.

FLUDARABINE

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.¹³² The FDA first approved fludarabine in 1991, and generic manufacturers began filing for approval beginning in 2003.¹³³ There are currently 12 FDA approved application holders for fludarabine injection, but only six appear to be actively marketing the product.¹³⁴

What is the concern? Fludarabine is currently in shortage.¹³⁵ According to USP’s Medicine Supply Map, fludarabine currently has a vulnerability score of 95.4 percent.¹³⁶ 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.¹³⁷ 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.¹³⁸

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.¹³⁹

¹²⁹ Interview with Vizient.

¹³⁰ Interview with Dr. Erin Fox.

¹³¹ *Id.*; Interview with Dr. Stephen Schondelmeyer; Interview with Vizient.

¹³² 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).

¹³³ 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).

¹³⁴ 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).

¹³⁵ FDA Drug Shortages Website; ASHP Drug Shortages Website (accessed Mar. 6, 2023).

¹³⁶ 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.

¹³⁷ 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.

¹³⁸ *Drugmaker raises the price of an old chemo medicine tenfold amid persistent shortages*, STAT Pharamlot (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).

¹³⁹ 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 Actavis product. Teva acquired Actavis Generics in 2016.¹⁴⁰ 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.¹⁴¹ Teva told Committee staff that it currently supplies fludarabine for the U.S. market from Sindan Pharma SRL, a facility it owns in Romania.¹⁴² This product is then distributed by Actavis, a company that is owned by Teva.¹⁴³ 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 2022.¹⁴⁴ 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.¹⁴⁵ As a result, Leucadia stopped selling fludarabine prior to April 2022.¹⁴⁶ 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.”¹⁴⁷

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.”¹⁴⁸ According to USP, while there are multiple labelers of fludarabine, they all source from the same three facilities.¹⁴⁹ 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.¹⁵⁰ 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.

¹⁴⁰ 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/>).

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

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

¹⁴³ 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/>).

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

¹⁴⁵ *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>).

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

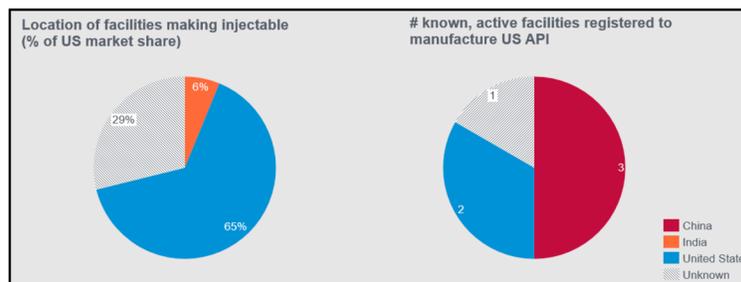
¹⁴⁷ Sagent Pharmaceuticals, Inc. Correspondence to Senate Committee on Homeland Security and Governmental Affairs (Mar. 20, 2023).

¹⁴⁸ Interview with Dr. Erin Fox (Mar. 17, 2023).

¹⁴⁹ USP Briefing and Presentation.

¹⁵⁰ *Id.*

Figure 7. Fludarabine Finished Dosage and API Manufacturers, According to USP¹⁵¹



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.¹⁵²

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.¹⁵³ The COVID-19 pandemic resulted in an unprecedented demand for numerous critical drug products.¹⁵⁴ 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.¹⁵⁵

¹⁵¹ *Id.*

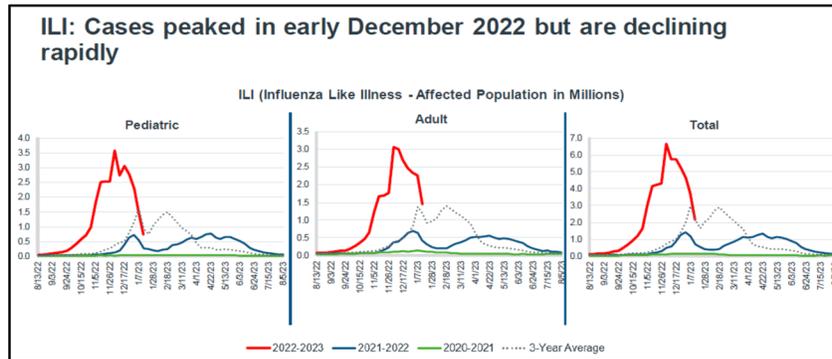
¹⁵² Interview with Vizient.

¹⁵³ American Hospital Association Briefing.

¹⁵⁴ 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”).

¹⁵⁵ *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, 2023¹⁵⁶



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.”¹⁵⁷ 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.¹⁵⁸

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.¹⁵⁹

SODIUM CHLORIDE (IV Saline)

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 1985.¹⁶⁰ IV Saline is also on the FDA’s list of essential medicines.¹⁶¹

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

¹⁵⁷ Premier Drug Shortages Report, at 10.

¹⁵⁸ *Id.*

¹⁵⁹ 21 U.S.C § 356c(a)(2).

¹⁶⁰ 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).

¹⁶¹ 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).¹⁶² According to USP, IV saline currently has a vulnerability score of 95 percent.¹⁶³ 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.¹⁶⁴ AAM told the Majority Committee staff that this past year demand for IV saline “skyrocketed” beyond manufacturers’ predictive modeling based on years prior.¹⁶⁵

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

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.”¹⁷³ 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.”¹⁷⁴ 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,

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

¹⁶³ 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.”

¹⁶⁴ *Id.*

¹⁶⁵ Interview with Association for Accessible Medicines.

¹⁶⁶ *Id.*

¹⁶⁷ *Id.*

¹⁶⁸ *Id.*

¹⁶⁹ 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*.

¹⁷⁰ 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”).

¹⁷¹ USP Briefing and Presentation.

¹⁷² 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).

¹⁷³ American Hospital Association Briefing.

¹⁷⁴ *Id.*

resulting in added costs.¹⁷⁵ 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.¹⁷⁶

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.¹⁷⁷ 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."¹⁷⁸ Post-market approval requirements can also deter suppliers from implementing continual improvements and long approval wait times can discourage suppliers from entering the market.¹⁷⁹ 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.¹⁸⁰ The FDA's Unapproved Drug Initiative has also been cited as contributing to shortages.¹⁸¹

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.¹⁸² 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.¹⁸³ 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.

¹⁷⁵ 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").

¹⁷⁶ American Hospital Association Briefing.

¹⁷⁷ ASPR, ARMI, and NextFAB Report, at 23.

¹⁷⁸ FDA Drug Shortages Report, at 44.

¹⁷⁹ ASPR, ARMI, and NextFAB Report, at 23.

¹⁸⁰ 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.

¹⁸¹ 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).

¹⁸² See DOD IG Report.

¹⁸³ 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. ¹⁸⁴	Japan	Doxycycline, a critical antibiotic ¹⁸⁵
2017	Hurricanes Maria and Irma caused a manufacturing plant closure. ¹⁸⁶	Puerto Rico	IV Saline, a critical supportive care drug ¹⁸⁷
2020	COVID-19 pandemic ¹⁸⁸	China/ Global	Widespread shortages of opioids, sedatives, analgesics, antibiotics, inhalers, and many other critical care hospital drugs. ¹⁸⁹
2021	Ice storm caused a manufacturing plant closure. ¹⁹⁰	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. ¹⁹¹

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.

IV CONTRAST MEDIA

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

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

¹⁸⁵ DOD IG Report, at 2.

¹⁸⁶ *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>).

¹⁸⁷ 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>).

¹⁸⁸ *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>).

¹⁸⁹ 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>).

¹⁹⁰ *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>).

¹⁹¹ *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.¹⁹² While there are other types of IV contrast on the market, these products are not always interchangeable.¹⁹³

What happened? Since April 2022, some manufacturers have made the decision to discontinue certain types of IV contrast.¹⁹⁴ 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.¹⁹⁵ 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].”¹⁹⁶ Some types of IV contrast are currently in shortage.¹⁹⁷

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.¹⁹⁸ 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].”¹⁹⁹ 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.”²⁰⁰ 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.”²⁰¹ 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.”²⁰² GE HealthCare acknowledged “our customers’ frustration throughout the shortage and the impact this had on health care services.”²⁰³

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.²⁰⁴ According to Dr. Andrew Shuman, surgical oncologist and

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

¹⁹³ 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).

¹⁹⁴ 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).

¹⁹⁵ 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=Iodixanol%20Injection&st=r) (accessed Mar. 6, 2023).

¹⁹⁶ GE HealthCare Correspondence to Committee.

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

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

¹⁹⁹ Interview with Premier.

²⁰⁰ *Id.*

²⁰¹ American Hospital Association Briefing.

²⁰² 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>).

²⁰³ GE HealthCare Correspondence to Committee.

²⁰⁴ *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.²⁰⁵ 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.²⁰⁶ GE HealthCare told the Majority Committee staff its plant returned to full capacity in June 2022.²⁰⁷ 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.²⁰⁸ 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.”²⁰⁹

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.²¹⁰ Hospitals generally experience the effects of drug shortages on a daily basis.²¹¹ 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.²¹² 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.”²¹³ 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.²¹⁴

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.”²¹⁵ The selected

²⁰⁵ Interview with Dr. Andrew Shuman.

²⁰⁶ Interview with Dr. Yoram Unguru.

²⁰⁷ GE HealthCare Correspondence to Committee.

²⁰⁸ 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>).

²⁰⁹ GE HealthCare Correspondence to Committee.

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

²¹¹ Interview with Dr. Andrew Shuman and Dr. Yoram Unguru.

²¹² 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”).

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

²¹⁴ 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).

²¹⁵ 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.” ²¹⁶
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. ²¹⁷ The FDA provides dosage and administration guidelines for drug products, but it does not provide guidelines on substituting different drug products. ²¹⁸
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. ²¹⁹ 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. ²²⁰ Further, the study concluded that “mitigation strategies assumed to be effective, such as relying on substitute medications, may be unsafe and require precautions.” ²²¹
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.” ²²²
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. ²²³ 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. ²²⁴

²¹⁶ Interview with Dr. Yoram Unguru.

²¹⁷ American Hospital Association Briefing.

²¹⁸ Park Dissertation, Boston University, at 85.

²¹⁹ Hospital Survey Responses.

²²⁰ Park Dissertation, Boston University, at 4.

²²¹ *Id.*

²²² Interview with Dr. Yoram Unguru.

²²³ American Hospital Association Briefing.

²²⁴ 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. ²²⁵
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. ²²⁶ 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. ²²⁷

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.²²⁸ 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.”²²⁹ The Administration’s 100-day supply report found, there is no “mechanism to ensure appropriate allocation of essential drugs during acute shortages.”²³⁰

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.²³¹ 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.²³² 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].”²³³ 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.²³⁴ While the FDA developed an Essential Medicines list in 2020, the agency is currently unable to assess the percentage of life-

²²⁵ Interview with Dr. Andrew Shuman and Dr. Yoram Unguru.

²²⁶ *Id.*; American Hospital Association Briefing.

²²⁷ Hospital Survey Responses.

²²⁸ Interview with Dr. Yoram Unguru.

²²⁹ Interview with Dr. Andrew Shuman.

²³⁰ White House 100-Day Supply Chain Review, at 219.

²³¹ Interview with Dr. Stephen Schondelmeyer.

²³² 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).

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

²³⁴ 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.²³⁵

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.²³⁶ 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.²³⁷ 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.²³⁸ 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.²³⁹ 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.²⁴⁰

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.”²⁴¹ 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.”²⁴²

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 2021.²⁴³ However, both new and active drug shortages are back on the rise with 160 new

²³⁵ FDA Response.

²³⁶ 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*.

²³⁷ FDASIA of 2012, Sec. 1001.

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

²³⁹ CARES Act of 2020, Sec. 3112.

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

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

²⁴² 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/>).

²⁴³ 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 2022.²⁴⁴ 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.²⁴⁵ 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.²⁴⁶ 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.²⁴⁷ 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).²⁴⁸ AAM expressed concern that the FDA—even with the information it currently has—does not have the ability to evaluate and predict shortages.²⁴⁹

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

²⁴⁴ 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).

²⁴⁵ 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>).

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

²⁴⁷ Interview with Premier.

²⁴⁸ *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).

²⁴⁹ 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.²⁵⁰ 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.”²⁵¹ 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.²⁵² 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.”²⁵³

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.²⁵⁴ 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.²⁵⁵

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).²⁵⁶ 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

²⁵⁰ 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.

²⁵¹ *Id.*

²⁵² *Id.*

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

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

²⁵⁵ FDA Briefing.

²⁵⁶ *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.²⁵⁷ 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.”²⁵⁸ The FDA is constrained by statutory requirements and agreements with companies on what information they are able to share with federal partners.²⁵⁹ 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.²⁶⁰ 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.”²⁶¹ 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.”²⁶² Insufficient information sharing among industry partners also “limits the ability to predict and prevent shortages, making it more difficult to track product allocations.”²⁶³

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.²⁶⁴ According to the Biden Administration’s 100 Day Supply Report, the U.S. does not have domestic production capacity for many generic antibiotics.²⁶⁵ 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.”²⁶⁶ 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.²⁶⁷ Investment in continuous

²⁵⁷ Section 510(j)(3) of the Federal Food, Drug, and Cosmetic Act as added by the CARES Act, Section 3112(c).

²⁵⁸ ASPR, ARMI, and NextFAB Report, at 20.

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

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

²⁶¹ ASPR Supply Chain and Industrial Analysis Report, at 3.

²⁶² DOD Response.

²⁶³ ASPR, ARMI, and NextFAB Report, at 20.

²⁶⁴ HSGAC Minority Staff Report, *A Price Too High*, at 5.

²⁶⁵ White House 100-Day Supply Chain Review, at 231.

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

²⁶⁷ 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.²⁶⁸ According to GAO, continuous manufacturing can produce “finished drug products in days as opposed to traditional batch manufacturing that can take months.”²⁶⁹

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.²⁷⁰ 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.²⁷¹ 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).²⁷² In March 2023, ASPR established the “Industrial Base Management and Supply Chain Office . . . to ensure that critical supplies are manufactured in the United States.”²⁷³ 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.”²⁷⁴ 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

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”).

²⁶⁸ White House 100-Day Supply Chain Review, at 212.

²⁶⁹ 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”).

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

²⁷¹ 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).

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

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

²⁷⁴ ASPR, ARMI, and NextFAB Report, at 18.

goals.”²⁷⁵ 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.²⁷⁶ 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.”²⁷⁷

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.

²⁷⁵ 2023 GAO Report on Drug Manufacturing, at 1.

²⁷⁶ *Id.* at 26.

²⁷⁷ 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).



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Association for Clinical Oncology

Statement prepared for:

U.S. Senate Committee on Homeland Security and Government Affairs

**Drug Shortage Health and National Security Risks: Underlying Causes and
Needed Reforms**

March 22, 2023

The Association for Clinical Oncology (ASCO) is pleased to submit this statement for the record of the hearing entitled, "Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms." ASCO is grateful that the U.S. Senate Committee on Homeland Security and Government Affairs has provided the medical community the opportunity to share our concerns regarding drug shortages and the risk they pose to our national security. We strongly believe that Congress and policymakers within U.S. federal agencies need to intervene to secure the pharmaceutical pipeline to mitigate drug shortages and protect the U.S. from vulnerabilities that risk our national security.

ASCO is the national organization representing nearly 45,000 physicians and other professionals who care for people with cancer. ASCO members are dedicated to conducting research that leads to improved patient outcomes, and we are also committed to ensuring that evidence-based practices for the prevention, diagnosis and treatment of cancer are available to all Americans, including Medicare beneficiaries.

For years, the medical community has experienced shortages of critical drugs that are used to treat a variety of conditions. These shortages are caused by a multitude of factors, including quality issues, manufacturer business decisions, disruptions to raw ingredient and excipient supplies, natural disasters, and other emergencies that take place in countries that house critical drug manufacturing facilities. In recent years, the U.S. has experienced shortages in broadly used essential products such as saline, morphine, and fentanyl, in addition to products critical to smaller patient populations.

In 2010 and 2011, our affiliate organization, the American Society of Clinical Oncology (the Society) began hearing concerns regarding drug shortages from its members. The oncology community rapidly identified drug shortages as a

serious issue directly impacting patient care; as early as 2013 we were highlighting the effect of these shortages at our Annual Meeting.^{1,2,3} Since that time, we have engaged with lawmakers, federal agencies, and stakeholder organizations to raise awareness and pass legislation providing the Food and Drug Administration (FDA) with necessary tools to help mitigate drug shortages.⁴ In partnership with other major national organizations, we have held summits, released reports and recommendations, and advocated for policy changes aiming to get to the root of the problem.^{5,6,7} Along with collaborating organizations, we were amongst the first groups to identify drug shortages as a matter of national security.⁸

In response to Executive Order 14017,⁹ ASCO and other organizations highlighted in a letter to the U.S. Department of Health and Human Services (HHS) Secretary that the COVID-19 public health emergency further underscored the vulnerability of our nation's healthcare supply chain. During the pandemic, health care providers struggled to obtain medications and supplies essential to patient care, including the sedatives necessary to mechanically ventilate patients, personal protective equipment (PPE) such as gloves and masks, and ancillary devices and supplies, such as syringes and swabs. The pandemic stressed our supply chains, highlighting their fragilities and deficiencies, throwing the need for immediate corrective action into sharp relief.

Oncology Drug Shortages

Within the oncology pharmaceutical supply chain, patients and providers continue to face shortages of potentially life-saving treatments. A recent survey of U.S. oncology pharmacists found that oncology drug shortages occurred frequently in 2020 and led to delays in chemotherapy and changes in treatment or omission, complicated clinical research, and increased risk of medication errors and adverse outcomes.¹⁰ The study also reported that the most difficult oncology drugs to obtain at the time were vincristine, vinblastine, intravenous immunoglobulin, leucovorin, and Bacillus Calmette-Guerin. Currently, the cytotoxic chemotherapy drug fludarabine remains on the FDA drug shortage list and has been on the list throughout the COVID-19 pandemic. Many large volume cancer centers across the U.S. have completely run out of the drug, which is a critical component of induction prior to CAR T-cell therapy. The centers have been forced to choose between offering an inferior replacement induction chemotherapy, or potentially ineffective CAR T-cell therapy. Because the CAR T-cell treatment is a genetically modified cellular product from the immune system of the patient who receives the treatment, this treatment can often not be repeated due to cost, logistics, and cancer related factors. Thus, the lack of this critical chemotherapy drug could result in patients, who would otherwise be cured

¹ https://journals.lww.com/oncology-times/fulltext/2013/07100/new_surveys_document__cancer_drug_shortages.5.aspx

² <https://www.ajmc.com/view/-drug-shortages-persist-in-months-after-surveys-make-headlines-at-asco>

³ https://www.youtube.com/watch?v=eX_lBrFLUx0

⁴ <https://www.ashp.org/advocacy-and-issues/key-issues/drug-shortages/meds-act>

⁵ <https://www.ashp.org/drug-shortages/shortage-resources/roundtable-report?loginreturnUrl=SSOCheckOnly>

⁶ <https://www.ashp.org/news/2018/09/19/summit-on-drug-shortages-to-examine-impact-on-national-security-and-health-care-infrastructure>

⁷ <https://www.ashp.org/-/media/assets/advocacy-issues/docs/Recommendations-Drug-Shortages-as-Matter-of-Natl-security.ashx>

⁸ <https://www.ashp.org/news/2018/09/19/summit-on-drug-shortages-to-examine-impact-on-national-security-and-health-care-infrastructure>

⁹ <https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf>

¹⁰ <https://ascopubs.org/doi/full/10.1200/OP.21.00883>

if fludarabine was available, having poorer outcomes from their cancer. A current list of oncology drug shortages can be found on FDA's website.¹¹

We appreciate Congress' efforts thus far to secure the drug supply chain, especially with the inclusion of key policy provisions from the Mitigating Emergency Drug Shortages (MEDS) Act in the enacted Coronavirus Aid, Relief, and Economic Security (CARES) Act. However, more action is necessary.

Recommendations to Mitigate Drug Shortages

ASCO and other stakeholders have long collaborated on efforts to improve our nation's drug supply chain and mitigate shortages. As such, we worked together to put forth the following recommendations¹² to improve the resilience of the nation's health care infrastructure. These recommendations are meant to provide a range of potential policy and marketplace changes to guide policymakers in their efforts to address these challenges.

Regulatory

1. Develop a comprehensive list of critical drugs. Use the World Health Organization Model Lists of Essential Medicines and other existing resources as a starting point to define what a shortage is and develop a list of critical drugs needed for 1) emergency response and 2) saving and preserving life. Using historical data and manufacturing input, address why these drugs have been on the shortage list. The critical list can be used to:
 - a. Stabilize the availability of critical drugs by working with manufacturers and the FDA to create redundant product in multiple locations in anticipation of natural disasters and other supply chain threats.
 - b. Assess the quality of pharmaceutical manufacturers measured against the importance of drugs on the critical list.
 - c. Work with the private sector for greater transparency surrounding the source of raw materials and manufacturing locations so providers can more easily assess pharmaceutical product quality. The FDA has proposed a star rating system for pharmaceutical manufacturers, which could increase transparency.
2. Create a multi-stakeholder advisory panel with the FDA to address key issues, such as the possibility of creating a stockpile of critical drugs, the logistics of warehousing such excess pharmaceutical inventory and where the excess inventory should be stored.
3. Enhance communication with the entire drug supply chain, including healthcare providers during, or in advance of, a public health emergency or other event that may create a drug shortage. FDA should provide the healthcare community with information simultaneously on the type of products that may be impacted and the expected duration of the impact. To prevent hoarding of inventory that could result from such communication, manufacturers could put product on allocation to ensure that remaining supply is distributed equitably.
4. Streamline regulations to incentivize increased manufacturing production.
 - a. Compounding regulations: 503(b) outsourcers need incentives to make drugs in short supply; it is costly to ramp up for only a short duration.

¹¹ <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>

¹² <https://www.ashp.org/-/media/assets/advocacy-issues/docs/Recommendations-Drug-Shortages-as-Matter-of-Natl-security.ashx>

- b. Global regulatory environment: there are multiple agencies internationally, all with competing requirements for manufacturers.
 - c. Aligns with FDA's initiative to harmonize international technical standards for approval of generic drugs.
5. Engage the Centers for Medicare and Medicaid Services (CMS) to discuss the practice of citing hospitals that use medications after the guaranteed stability period in product labeling. This may, for example, address a powder after it is solubilized, which can contribute to unnecessary medical waste.
 - a. There are situations where evidence exists in the literature that stability goes well beyond the period of time listed in product labeling. However, CMS and the Joint Commission will cite a hospital even though the organization has evaluated this evidence and revised the date based on that. This warrants further discussion with CMS to see what might be needed to avoid or address drug shortage situations.
 6. Encourage FDA to consider how reducing the number of unapproved (pre-1938 Federal Food, Drug, and Cosmetic Act) drugs on the market might impact shortages.
 - a. FDA has been assisting companies with finding opportunities to legally market older "grandfathered" products that are currently marketed without the required FDA approval. While the FDA approval process ensures that marketed drugs meet current FDA standards for safety, efficacy, quality, and labeling, there have been concerns that these efforts to bring widely used but unapproved drugs into compliance with current FDA requirements have resulted in drug shortages. For context, it may cost drug manufacturers more to invest in obtaining formal drug approval. As such, some may drop out of the market rather than make the investment, thus leading to potential drug shortages.

Legislative

1. Enact legislation that requires a notification requirement for medical product devices and equipment needed to administer medications, similar to the legislation enacted in 2012 that requires drug manufacturers to notify the FDA "of any changes in production that is reasonably likely to lead to reduction in supply" of a covered drug in the U.S.
 - a. E.g. fluid containers to dilute medications for infusion.
2. Enact legislation requiring a risk assessment of foreign source active pharmaceutical ingredients (APIs).
 - a. Relying predominantly on other countries for the necessary ingredients to manufacture crucial drugs puts the U.S. at risk. This was especially evident during the COVID-19 pandemic. With U.S.-China relations strained, the Chinese government used its posture as a main source of U.S. APIs to gain the upper hand on foreign relations issues tied to the pandemic.
3. Require federal government authorities with jurisdiction over national security to conduct an analysis of domestic drug and medical device manufacturing capability and capacity for critical products to assess whether a threat to national security exists.
4. Require a U.S. Government Accountability Office study to examine all aspects of the drug supply chain to see if there are any new issues exacerbating drug shortages.

Legislative and Regulatory

1. Develop incentives for drug manufacturers to have contingency or redundant production plans for their pharmaceutical products on the critical drug list. The back-up plan should include

- prioritizing the most medically necessary products, qualifying third party suppliers across their network, and increasing production and inventory for API and finished goods.
2. Investigate developing a system of paying suppliers to hold inventory, perhaps similar to the system employed by the U.S. Department of Defense (DoD) Defense Logistics Agency. Consider partnering with the DoD to create contractual leverage with drug manufacturers for civilian hospitals.
 3. Incentivize manufacturers and work with the FDA to repackaging pharmaceuticals according to the amount of medication commonly used to reduce waste.
 - a. E.g. only a 30 mL vial of a drug is available when most common volume needed is 5 mL.
 4. Create an Office of Clinical Affairs within the Drug Enforcement Agency (DEA), so DEA personnel will be available to address the clinical side of medication shortages of controlled substances, rather than just the diversion enforcement aspect.

Market/Non-Legislative or Regulatory

1. Standardize medical concentration, containers, and sizes to stabilize pharmaceutical supply and reduce the probability of patient harm due to constantly needing to change concentrations and associated technology. Standardizing products reduces the risk of adverse drug events when shortage products are substituted. Standardizing the concentration of compounded products within organizations also helps provide a critical mass for industry to consider making previously unavailable products available.
2. Identify tools that address supply access, such as Pfizer's web access tool, which provides information about happenings at Pfizer's facilities, latest product updates and a Q&A forum.
3. Ensure hospital staff, healthcare providers and pharmacies have the capacity to manage drug shortages.
 - a. Ensure early notification of predictable medication shortages and medication substitutes so staff can build necessary information into communication efforts.
 - b. Work with medical and specialty organizations to ensure necessary information is built into educational efforts, such as national guidelines and continuing education.
4. Examine how changes in United States Pharmacopeia (USP) standards for drugs with a solid historical safety record can affect supply, and whether these changes are necessary.
 - a. Consult with USP representatives about pharmaceutical regulations that may lack an evidence base.
5. Request that electronic health record (EHR) vendors amend their systems to ease the burden of making drug product changes when a shortage occurs. An example would be some sort of tool that makes changes to various integrated technology databases at the same time (like EHR and smart pump drug libraries, or automated dispensing cabinets and pharmacy inventory systems).

Thank you for the opportunity to provide ASCO's comments, concerns, and solutions to address drug shortages. We would welcome the opportunity to engage with Congress in a meaningful dialogue about these issues. Please contact Megan Tweed at Megan.Tweed@asco.org with any questions.



Submitted Public Comment of Steve Wosahla
Chief Executive Officer – Children's Cancer Cause

Senate Homeland Security and Government Affairs Committee
**Hearing on Drug Shortage Health and National Security Risks: Underlying Causes
and Needed Reforms**

March 28, 2023

Mr. Chairman, Ranking Member, and other Members of the Committee,

Thank you for holding this important hearing on our nation's drug shortages and the impact on national security. I am the Chief Executive Officer of Children's Cancer Cause.

The Children's Cancer Cause is a leading national advocacy organization working to achieve access to less toxic and more effective pediatric cancer therapies; to expand resources for research and specialized care; and to address the unique needs and challenges of childhood cancer survivors and their families. Children's Cancer Cause leads efforts to ensure that these needs and perspectives of children with cancer are integrated into the highest level deliberations on health care and policy.

Each year in the U.S. approximately 16,000 children are diagnosed with cancer. Today, thanks to major treatment advances and participation in clinical trials, the 5-year survival rate is 85% for children and 86% for teens. Between 1970 and 2020, the number of deaths from cancer in children and teens decreased by more than 50% due to advances in treatment. Unfortunately, cancer remains the most common cause of death by disease for children in America.

The excellent statistics are dependent on an adequate and stable supply of life-saving drugs. We must continue to support the uninterrupted treatment of children with cancer who need these drugs to eradicate their disease. To this effect, we must guarantee adequate supplies of drugs for children in the United States.

Our community knows firsthand the impact of drug shortages which are too common in pediatric oncology. In a survey done by Children's Cancer Cause in 2017, a survivor shared that her treatment regimen was altered due to a shortage, and she was given alternative drugs. They only worked for a short time, and she suffered a relapse within months.

A mother of a child with cancer shared: "The chemo drug was no longer available and my daughter had a life-threatening allergy to the only available alternative. We had no choice but to start the alternate drug in the ICU at a low rate in hopes of breaking through the sensitivities and reactions." One family told us that a shortage delayed the



start of their child's clinical trial by a full three months with untold consequences to his effective cancer treatment. Some families reported having to travel significant distances—further from home and support networks—to find a treatment center with the available chemotherapy drug.

Children are uniquely vulnerable to drug shortages and data suggests they have an impact on survival for patients with cancer. In the last five years, 75% of the 20 most essential pediatric cancer drugs have been in shortage, according to the advocacy group Angels For Change. Not only are pediatric oncology drugs more likely to go into shortage than adult essential therapies, but those shortages last about one-third longer than adult shortages.

During the hearing, an oncologist, Dr. Shuman from the University of Michigan Medical School, testified of a critical shortage of etoposide, a drug that is often used to treat children. He reported having to weigh the burden as a clinician to decide which patients, young and old, with lung, brain and testicular cancer, should receive the limited number of available doses. He described the systemic issue adding: "Our pharmacists should not be desperately trying to squeeze out a few last drops when a life may be on the line."

In 2019, there was a national shortage of vincristine—the single most widely used chemotherapy agent in treating childhood cancers. As the New York Times reported the vincristine shortage was just the latest of dozens of drug shortages in recent years, The persistent problem of shortages prompted the Food and Drug Administration (FDA) to review the shortage of sterile injectables.

A 2019 FDA report (updated in February 2020) found that in the ten-year period from 2009-2019, nine of the eleven drugs used to treat acute lymphoblastic leukemia were in and out of shortage. The report went on: "Despite recent evidence that adding nelarabine to children's treatment regimens improves survival rates and is thus becoming the new standard of care, nelarabine has been in shortage recently, causing much anguish and grief for patients, parents, and clinicians."

We acknowledge that the drug shortage issue is complicated and involves multiple factors, such as aging manufacturing facilities overseas and a consolidation of supplier. More than Europe, most experts believe the US is not impacted by shortages and payment policies are the root of many of the shortages. While shortage problems will not be solved by a single solution, we must ensure that families in the future are not faced with devastating shortages of drugs to treat their children's cancer

The above examples frame the history and issues our community has faced and will continue to encounter in the future. They serve as notice that we must act now and put steps in place to mitigate drug shortages.



We wish to re-iterate and emphasize the earlier recommendations made by the Children's Oncology Group during the 2019 drug shortage. As proposed in 2019, solutions that could be enacted in a reasonable time frame for today's children include but are not limited to: (1) establishment and maintenance of a national stockpile of key cancer drugs used for the treatment of children with cancer, and (2) US government purchasing contracts that provide a guaranteed buyer and may help stabilize a fragile market.

There undoubtedly are other ideas to consider, and we are committed to working with lawmakers and the childhood cancer community in galvanizing these efforts. We hope to work with you and the Committee on solutions to this difficult problem. Thank you for your efforts to bring attention to the drug shortages issue.



April 6, 2023

The Honorable Gary Peters
Chair
Committee on Homeland
Security and Governmental Affairs
United States Senate
Washington, DC 20510

The Honorable Rand Paul, M.D.
Ranking Member
Committee on Homeland
Security and Governmental Affairs
United States Senate
Washington, DC 20510

Re: Statement for the Record on the March 22, 2023, Homeland Security and Governmental Affairs Senate Committee Hearing on Drug and Product Shortages

Dear Chair Peters and Ranking Member Paul,

On behalf of the Healthcare Supply Chain Association (HSCA), which represents the nation's leading healthcare group purchasing organizations (GPOs), we appreciate the opportunity to provide a statement for the record regarding the work of GPOs to prevent and mitigate drug and product shortages. HSCA applauds your leadership and bipartisan efforts to address shortages across the healthcare supply chain.

Healthcare GPOs are the sourcing and purchasing partners to virtually all of America's 7,000+ hospitals, as well as the vast majority of the 68,000+ long-term care facilities, surgery centers, clinics, and other healthcare providers. GPOs lower costs for patients, providers, payers, Medicare and Medicaid, and taxpayers. A 2018 [analysis](#) found that GPOs save the U.S. healthcare system \$34.1 billion annually, up to \$456.6 billion over ten years, and up to \$116.3 billion in Medicare savings and \$90.2 billion in Medicaid savings over the same period.

GPOs allow small and rural healthcare providers – who often lack the purchasing power to access competitive pricing for essential supplies – to take advantage of the same efficiencies and discounts as larger providers. The value and services that GPOs provide allow healthcare providers and physicians to focus on their core mission: providing first-class patient care.

Healthcare GPOs played a critical role in supporting COVID-19 response efforts at the height of the pandemic, working closely with all stakeholders in the healthcare system as well as Federal, state, and local health and emergency management agencies to safeguard patient care. Many GPOs took steps to strengthen the resiliency of the healthcare supply chain, establishing programs to promote domestic manufacturing by rapidly adding new manufacturers and suppliers to contracts to increase supply. GPOs also advocated for policies to reduce shortages during the COVID-19 public health crisis, such as expediting approval processes for products with unhealthy markets, requirements for manufacturer contingency plans in the event of an emergency, and requirements for suppliers to give advanced notice before discontinuing production.

Multiple GPOs launched programs to invest in domestic and geographically diverse manufacturers to ensure a robust and resilient supply chain, entering into strategic partnership agreements with several

domestic manufacturers. Since establishing these agreements, these companies expanded production capacity and increased GPO member hospital access to sought-after PPE and other necessary equipment. GPOs also identified lists of essential medications whose absences threatened the ability of hospitals to provide immediate and high-quality patient care, and provided this information to various stakeholders, including government authorities, working to prioritize supply at a vulnerable time.

Product shortages in the healthcare industry place significant strains on hospitals, health systems, healthcare providers and suppliers, and patients. The U.S. Food and Drug Administration (FDA) has explained that primary causes of shortages in the healthcare sector are due to manufacturing problems, quality control issues, a lack of raw materials, and barriers to getting new suppliers when supply is disrupted.

To mitigate drug and product shortages across the healthcare industry, GPOs routinely track data on shortages and raw materials on a global scale to determine possible supply disruptions and provide suppliers with notices to plan for production capacity. GPOs also identify and bring to market additional manufacturers of at-risk products, ensuring that there are auxiliary suppliers of essential medications and products. Participating in a GPO contract is completely voluntary, which allows providers to purchase outside of contracts to meet patient needs if necessary.

GPOs are the most transparent industry in healthcare and champion transparency across the healthcare supply chain. All HSCA GPOs subscribe to a transparency and ethics initiative, with GPOs and the member advisory boards carefully evaluating suppliers based on several factors including their reliability, product quality, supplier reputation, transparency in product manufacturing and sourcing, and their capacity and distribution capabilities.

To maintain a healthy supply chain, GPOs work diligently to ensure that a robust, competitive market for drugs and healthcare products exists. GPOs collaborate with suppliers to manage price fluctuations that occur with drugs and healthcare products. GPOs also work to expand the number of suppliers of essential products and life-saving medications and continue to provide stability and savings across the healthcare continuum.

Based on their unique line of sight across the entire healthcare delivery system, HSCA and its member GPOs recommend greater transparency and data-sharing between the public and private sectors to allow stakeholders to take a more proactive approach in mitigating drug and product shortages across the healthcare continuum.

GPOs have provided input on and supported Federal proposals to mitigate both drug and product shortages, including the strategic development of new supply sources. HSCA convened a Drug Shortage Working Group consisting of healthcare provider organizations to provide policy recommendations to help prevent and address drug shortages, ensure stable supply of critical medications, and support the resiliency of the healthcare supply chain. The working group directly engaged with senior FDA officials to share information and determine possible solutions. HSCA is a member of the [End Drug Shortages Alliance](#), a forum for key stakeholders to take strategic aim at drug shortages that disrupt patient care, and a founding member of the [Duke-Margolis Drug Supply Chain Resilience and Advanced Manufacturing Consortium](#), a consortium designed to identify effective policy solutions that promote a resilient drug supply chain and reduce the frequency and severity of drug shortages.

We appreciate the opportunity to provide the Committee with our statement and we look forward to continuing to serve as a resource to your offices, other Members of Congress, and all stakeholders to continue improving the healthcare continuum. Please do not hesitate to contact me directly if HSCA can be a resource on this issue moving forward. I can be reached at (202) 629-5833 and tebert@supplychainassociation.org.

Sincerely,



Todd Ebert, R. Ph.
President & CEO
Healthcare Supply Chain Association (HSCA)

**Post-Hearing Questions for the Record
Submitted to Vimala Raghavendran
From Senator Roger Marshall, M.D.**

**“Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms”
March 21, 2023**

1. Over the past decade, and especially since 2019, we have seen very troubling statistics on the lack of availability of novel antibiotics and antifungals for patients. At the same time, many of the small biotech companies in this space have gone bankrupt due to problems with reimbursement reform for new antibiotics. What measures could Congress and relevant agencies take to ensure hospitals have a robust supply of commercially available novel, next generation antibiotics?

Recent trends, such as unpredictable market dynamics and the inability to recover high investment costs, have discouraged the research into, and development of, new antibiotics and other novel antimicrobial products.¹ A stagnant pipeline for the development of new antimicrobial medicines threatens public health given the global spread of AMR, which occurs when changes in microbes such as bacteria, viruses, and parasites cause the drugs used to treat infections caused by those microbes to become less effective. In the United States, more than 2.8 million antibiotic-resistant infections occur each year, resulting in more than 35,000 deaths.² The World Health Organization declared antimicrobial resistance (AMR) one of the top 10 global public health threats facing humanity and a recent study estimated that 1.27 million people died worldwide in 2019 due to AMR.³ Without an immediate, collaborative global response, AMR could lead to 10 million deaths a year by 2050.⁴ Sustaining a resilient supply of antimicrobials that continues to remain effective against disease is a global health imperative. Strategies to combat AMR will require global partnerships and alliances and must include the conservation of existing antimicrobial medicines along with the concurrent innovation of novel products.

Unfortunately, efforts to address AMR have been diverted over the last several years due to the global SARS-CoV-2 public health emergency, during which misuse of antibiotics increased; in many circumstances, patients received antibiotics for COVID-19 although they are entirely ineffective in treating it. For instance, a meta-analysis found that 71.9 percent of patients hospitalized with COVID-19 before mid-April 2020 received antibiotics, even though only 6.9 percent of these hospital admissions were associated with bacterial infections. A similar study by Pew Charitable Trusts suggests that in 96 percent of admissions for patients diagnosed with

¹ USP. 2020. Addressing Antimicrobial Resistance. Available at: <https://www.usp.org/sites/default/files/usp/document/about-public-policy/policy-position-paper-amr-2020.pdf>

² Centers for Disease Control and Prevention. Biggest Threats and Data: 2019 AR Threats Report. 2019 [cited 2020 August 17]; Available from: <https://www.cdc.gov/drugresistance/biggest-threats.html>.

³ Murray, C.J.L., et al., *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis*. The Lancet, 2022. **399**(10325): p. 629-655.

⁴ World Health Organization. *New report calls for urgent action to avert antimicrobial resistance crisis*. 2019 [cited 2020 August 17]; Available from: <https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis>.

COVID-19, an antibiotic was given prior to confirmation of a bacterial infection.⁵

In addition, increasingly common shortages of antimicrobials and the lack of antimicrobials to meet all patients' needs are serious issues and contribute to the emergence and exacerbation of AMR. According to a recent analysis⁶ from USP's Medicine Supply Map,⁷ antibiotics are 42 percent more likely to be in shortage compared to all other drugs. Medication shortages can lead to substandard and falsified versions entering the supply chain, and increased risk of AMR development. Additionally, the USP analysis shows a geographic concentration in the registration of antimicrobials API manufacturing sites exists; India and China combined hold 58 percent of antibacterial API registrations and 83 percent of antiviral APIs. As Congress considers potential legislation related to supporting a robust and diverse supply of antibiotics, such as exploring incentives for the manufacture and utilization of new antibiotic products to meet this growing threat, it is important to consider the dynamics driving this public health challenge. The main drivers of supply chain disruptions are geographic concentration, manufacturing complexity, market competition, price, and quality.

We encourage Congress and relevant agencies to consider other approaches to address AMR. USP supports a multifaceted approach to addressing AMR,⁸ including:

- Prioritizing building resiliency for the supply of antimicrobials, including investment in manufacturing innovation.
- Building capabilities among global stakeholders to reduce the proliferation of poor-quality anti-microbials. Ongoing research via the USP Quality Institute⁹ and other efforts provide evidence that resistance emerges when pathogens are exposed to substandard antimicrobial medications and that resistance may spread across product classes. So, while it is imperative to incentivize new antimicrobials, it is equally essential to focus on conserving the effectiveness of existing medicines. Otherwise, the U.S. and the world will face a continuing cycle of pathogen resistance to each new antimicrobial product.¹⁰
- Improving antimicrobial stewardship by addressing over- and inappropriate prescribing.
- Improving patient adherence to treatment regimens.

⁵ Pew Charitable Trusts. 2021. Could Efforts to Fight the Coronavirus Lead to Overuse of Antibiotics? Available at: <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/could-efforts-to-fight-the-coronavirus-lead-to-overuse-of-antibiotics>

⁶ <https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines>

⁷ <https://www.usp.org/supply-chain/medicine-supply-map>

⁸ USP. 2020. Addressing Antimicrobial Resistance. Available at: <https://www.usp.org/sites/default/files/usp/document/about/public-policy/policy-position-paper-amr-2020.pdf>.

⁹ USP Quality Institute, at <https://www.usp.org/our-impact/quality-institute>.

¹⁰ A World Health Assembly resolution adopted in 2015 introduced a [Global action plan on antimicrobial resistance](#) that outlined five objectives, including an increased focus on preventing, detecting, and responding to poor quality antimicrobials as a key tool to conserving the effectiveness of antimicrobial medicines. This resolution was sponsored and supported by the U.S. government.

- Implementing steps to fund or incentivize more research and development into the next generation of products, including investments in public-private partnerships. Over 80 percent of research in this area is conducted by small biotech companies due to the unstable marketplace for antibiotics; CARB- X and the AMR Action Fund are examples of successful public-private investments to incentivize novel antibiotic development.^{11,12}
2. In addition to the threat that infectious diseases pose to the general population, our troops also face an increased risk of chemical or biological agents that prompt the onset of secondary, multi-drug resistant (MDR) infections. What steps is the Department of Defense taking to procure novel antibiotics as a part of its ongoing supply chain security strategy to combat these threats?

We agree that the threat of MDR poses a significant public health challenge to US troops around the world; the Department of Defense is better positioned to speak to the actions the Department is taking in this area. However, USP recognizes that the threat of MDR poses a significant challenge to the US and worldwide, and many of the steps we support to increase the supply, and variability of the antimicrobial supply overall would likely help facilitate a reliable supply of novel antibiotics for deployment by the Department of Defense to combat the threat of MDR. USP supports both better supply chain intelligence and policies to incentive the development of new antibiotics.

¹¹ CARB-X. *CARB-X: Combatting Antibiotic-Resistant Bacteria*. 2022 [cited 2022 August 24]; Available from: <https://carb-x.org/>.

¹² AMR Action Fund. *AMR Action Fund: Bridging the Gap Between Science and Patients*. 2022 [cited 2022 August 24]; Available from: <https://www.amractionfund.com/>.

To: Senator Roger Marshall, M.D.

From: Erin R. Fox, PharmD, MHA, Associate Chief Pharmacy Officer – Shared Services,
University of Utah Health

Subject: Responses to Post-Hearing Questions for the Record “Drug Shortage Health and
National Security Risks: Underlying Causes and Needed Reforms”

Date: May 10, 2023

1. Since the COVID-19 pandemic, we have seen shortages for generic essential medicines as well as commonplace drugs, such as amoxicillin. What measures could Congress and the Administration take to ensure that the nation has a surge capacity of commonplace “first-line therapies” available in the event of a pandemic influenza or other public health emergency?

Response: The CARES Act requires drug manufacturers to “develop, maintain, and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable for each establishment in which the drug or active pharmaceutical ingredient (API) is manufactured.” FDA issued [nonbinding guidance](#) stating a risk management plan should “identify the normal capacity and surge capacity of the manufacturing facility to manufacture a drug or its components that are vulnerable to shortage.” Congress provided no penalties for companies that are not complying and the overall level of compliance is not transparent. Congress could ask FDA to report on compliance with this guidance to determine if these actions should be mandatory.

2. The entire nation was caught flat footed when COVID-19 hit. That was particularly evident with the SNS program within ASPR. Now that we are on the other side of the pandemic, do you believe you have all the tools necessary should another pandemic hit?

Response: This will depend on the type of pandemic. For example, early in the COVID-19 pandemic, health-systems were preparing to have large numbers of patients on ventilators and health-systems were scrambling to obtain sufficient medications to allow for those ventilated patients. However, as we learned more about taking care of patients infected with SARS-CoV-2, large amounts of medications used for ventilated patients were no longer needed.

It’s difficult to know exactly which medications might be needed for a pandemic. However, a resilient medication supply chain should be able to flex to ramp up needed supplies quickly. We need to learn more about which products are most vulnerable. As far as tools, we need a better analytics infrastructure to understand which products rely on sole sources of API or other critical precursors. We also need to understand which

products are only made in a single facility, or a single part of the globe. Once we identify the products most at risk for shortage, we can leverage scarce resources to preferentially shore up those products.

In addition to pandemics, these data would also be helpful during disasters. When Hurricane Maria struck Puerto Rico, health-systems scrambled to try to understand which products could be affected. There was [no list publicly available](#), because FDA could not reveal the information that manufacturers wanted kept secret.

The CARES Act directed the National Academies of Sciences, Engineering, and Medicine to study the security of the US medical product supply chain. I served on this committee and our team offers multiple solutions to improve resiliency in our [report](#). The key to implementing many of these improved resiliency tactics is additional transparency. Here are a few suggestions that may improve resiliency:

- FDA should develop a rating system for the quality and reliability of drug and device suppliers. For drugs, this would be an extension of the current AB rating system with the additions that (1) revision of the rating can occur as a result of random product checks by FDA, rather than only by investigations triggered by user complaints, and (2) the rating will include a reliability dimension that reflects the manufacturers continuity of supply.
 - Congress should update 21 C.F.R. §202.1 to require the name and place of business of the manufacturer on the label. FDA should use the Office of Pharmaceutical Quality's Risk-Based Site Selection Model (<https://www.fda.gov/media/116004/download>) to publicize the overall reliability of specific manufacturing sites. Only with additional transparency can purchasers make quality-based purchasing decisions by matching a product's manufacturer with their overall risk rating.
 - FDA should include sole manufacturers or sole API suppliers as risk factors in CDER's Risk-Based Site Selection Model. FDA should not exclude sites manufacturing inactive ingredients (excipients) in MAPP 5014.1. (<https://www.fda.gov/media/116004/download>).
 - FDA should also work with private partners to expand drug quality sampling and testing programs changing the responsible party for ensuring the quality of products from pharmaceutical manufacturers, to public / private independent testing sites to ensure the quality of products using their risk-based model.
3. Specifically, do you believe there should be a continuous cycle rotation of pharmaceuticals that are part of the SNS?

Response: I think a more resilient, continuous cycle rotation of SNS pharmaceuticals may help, however the amount available is typically small and may only provide up to a week of supplies. How the SNS is accessed and the amounts stored would need to change for the SNS to be helpful. We need a resilient medication supply chain that can ramp up production of needed supplies to meet unmet demand. Certainly, a well-stocked and rotated SNS could help bridge that gap, but we also need a well-functioning

high quality medical supply chain. In March 2020, most of the medications required for maintaining patients on ventilators were already in short supply due to quality and manufacturing problems even before the pandemic started.

4. Do you believe additional products, such as generic shortage products, be included in the SNS and/or as part of a new stockpile of essential medicines to help prevent and mitigate shortages?

Response: I think it's challenging to know what will or will not be needed for any given emergency outside of known antidotes. There are a variety of critical or essential medicines lists and none are perfect. A new rotated stockpile outside of the SNS could help bridge gaps for those products most at risk for shortages. The SNS is not practical due to limitations in [how supplies can be accessed](#). I also believe it would be challenging to stockpile everything on an essential list – it probably makes the most sense to target stockpiles of those medications that are at highest risk of shortage vs. just those on an essential list. I also think targeted strategies to improve the quality of medication production would improve the overall shortage situation the most. We need to identify which medications are most at risk of shortage and also require companies to comply with the risk management planning described in the CARES Act. Hospitals and utilities are required to have business continuity plans, why not drug manufacturers?

5. Do you believe a more robust program is needed to better protect the public?

Response: Yes. The current system is not working. My co-authors and I recently outlined [response strategies](#) to improve resilience. Patients and hospitals routinely cannot access the most basic and essential medications. Further, for all the talk about manufacturing more products in the US, we are seeing US companies close. For example, in February, Akorn pharmaceuticals (based in Illinois) [closed permanently](#) with chapter 7 bankruptcy leaving 400 without jobs. Additionally, as part of the bankruptcy agreement, most Akorn products are now recalled. The pharmacy department at our health system is going to have to spend approximately 250 hours to process this recall in the setting of staff shortages and this recall is going to worsen many current and ongoing shortages.

We need a system that will value quality manufacturing and consistent supplies over the lowest price. Currently, FDA sees differences in the quality of manufacturing facilities, but these differences are not communicated to purchasers who only have price as the single differentiating factor. FDA and others have advocated for years that a ratings system for pharmaceuticals is essential to improve quality. Until quality is transparent, purchasers can't favor drug companies that are prioritizing quality and good supplies. FDA has an internal ratings system that is not transparent. Private companies are unable to build comprehensive ratings systems due to the overall lack of transparency around where drugs are made and by which companies.

6. Do you believe partnerships with industry can improve both response times for products and volume of products?

Response: Yes. Government and purchaser partnership with industry are needed. The government has no manufacturing facilities, and the FDA can't force any company to continue manufacturing any drug, no matter how critical or life-saving. Industry has to make changes, yet the current market forces that value products on price alone can't create change. The federal government plays an important role in prioritizing industry efforts and providing the data, incentives, and mandates to steer the industry to make these investments. Congress plays a role in funding these steps. Hospitals can ask industry for more information about their products and when possible, preferentially purchase from companies focused on quality and good supplies.