

THE
PANDEMIC
AND THE
SUPPLY
CHAIN

Addressing Gaps
in Pharmaceutical
Production and
Distribution



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TABLE OF CONTENTS

i	Summary
1	Policy Problems
	1. Unexpected increases in demand for critical medications
	2. Disruption of production of critical medications
	3. Delayed regulatory oversight of medication production
	4. Interruption of global trade of medicines
	5. Limited understanding of local and demand-driven shortages
	6. Inadequate supply chain planning and management
4	Actions Taken to Date
6	Policy Recommendations
	1. FDA should timely disclose and mitigate demand-driven and local-level shortages
	2. To strengthen pharmaceutical production, Congress should authorize the FDA to create and publish quality metrics for the manufacturing process.
	3. To strengthen the global supply chain, the FDA should establish a database of approved manufacturers of active pharmaceutical ingredients
	4. To expand production capacity, the FDA should expand the current mutual recognition agreement between the United States and Europe.
	5. Congress should further incentivize domestic production of essential pharmaceuticals
	6. The federal government should stand up a comprehensive effort to assess and manage the U.S. pharmaceutical supply chain.
	7. When necessary to mitigate shortages, the Department of Health and Human Services should allow additional manufacturers to produce patented medications
9	Table: FDA Reported Drug Shortages During the COVID-19 Pandemic
11	References

SUMMARY

Provoking both unprecedented shifts in demand and new uncertainties in production and distribution of essential medications, the COVID-19 pandemic has revealed the fragility of the U.S. drug supply in a public health crisis. Documented shortages in recent months have included medications used to treat COVID-19 itself, medications used in intensive care, and medications for related conditions. These shortages point to serious vulnerabilities in the pharmaceutical supply chain that can compromise the response to future crises as well as new waves of the current epidemic that may be yet to come.

Focusing on issues in pharmaceutical production and distribution, this White Paper reviews 6 specific problems, surveys actions taken to date, and recommends 7 additional steps to address them.

POLICY PROBLEMS

PROBLEM 1:

Unexpected increases in demand for critical medications

The COVID-19 pandemic has led to **shortages** of drug products needed to directly mitigate the infection, to support life, or to control related conditions (Table 1). While most non-crisis shortages originate in problems with a drug's production, drug shortages that have been triggered by the COVID-19 epidemic have been mostly driven by increases in demand for certain categories of pharmaceuticals. Such demand increases were unexpected and of great magnitude, exceeding the capacity of manufacturers of maintaining adequate supply levels of these pharmaceuticals.

Drug shortages have been plaguing the US market in the last decade, and low-cost generics have been the drugs **most at risk**.¹ At the onset of the HHS-declared emergency status on January 31, 2020, there were over one hundred drugs in nationwide shortage according to the FDA. Most drugs needed to treat Covid-19 patients - life-supporting drugs such as vasopressors, sedatives, injectable solutions, and others - are generic, low-cost products that were already at risk of shortages or had experienced shortages before the start of the epidemic.

From the perspective of drug shortages, the Covid-19 epidemic has represented an acute stressor on an ongoing problem, prompted by the unexpected increase in demand.

PROBLEM 2:

Disruption of production of critical medications

The high demand driven by the COVID-19 emergency has **exhausted existing**² inventories of drug products and raw materials. Most manufacturing companies produce enough drugs and drug ingredients to meet the needs of their clients based on **predetermined projections**³, including manufacturing quotas for sedatives and hypnotics issued by the Drug Enforcement Agency (DEA). The coronavirus pandemic has expanded demand and lasted **longer**⁴ than anticipated by most drug manufacturers, and therefore drug inventories and manufacturing quotas have been depleted much faster than manufacturers and federal agencies could predict.

The United States imports many finished drug products and raw materials required for drug manufacture from **Europe, India and China**⁵, including active pharmaceutical ingredients (APIs). The shortages associated with the COVID-19 pandemic have affected **both active pharmaceutical ingredients**⁶ and finished pharmaceutical products.

China is a major source of **active pharmaceutical ingredients**⁷ for antibiotics, antihypertensives and antivirals. Due to the **pandemic**⁸, many factories in China had to **close temporarily**⁸, leading to a **halt in production**⁵ of active pharmaceutical ingredients and finished products. Some of these factories have since **reopened**⁸ but they are **understaffed**⁶ due to government instituted lock-downs and **quarantined employees**.⁶ Lock-downs have also led to **shortage of raw materials**⁶ needed for manufacturing APIs because **some suppliers have not resumed work**.⁸ This has disrupted the production of certain drugs dispensed in the Unit.

Beyond shutdowns, **travel bans**⁹ complicate medication production. These bans have **delayed**

shipping¹⁰ of previously approved raw materials from foreign countries to the United States, which has slowed drug assembly and contributed to drug shortages. One of the drugs that has been affected by these delays is **propofol**¹¹, an anaesthetic used to maintain ventilation of COVID-19 patients.

PROBLEM 3: Delayed regulatory oversight of medication production

The COVID-19 pandemic has slowed FDA oversight of drug production. Travel restrictions have pre-vented FDA officials from **inspecting**⁹ drug manufacturing plants in China. During the COVID-19 epidemic, such restrictions have contributed to delays including in the release of products that are ready for shipping. The pandemic has also prompt-ed the FDA to **postpone**¹² scheduled inspections of all foreign manufacturing plants, with an exception of those facilities that are considered high risk. As a result, there is the increased risk of inferior products entering the United States market.

Regulatory delays particularly affect medications that require special quality assurance procedures. For example, **injectable drugs**¹³ undergo more rigorous **review procedures**¹³ to establish product quality and are especially **susceptible**¹³ to shortages. For example, **Intravenous preparations**⁴ have to undergo weeks of sterility testing before they are approved. The production of sedatives, hypnotics and pain control therapies depends on manufacturing quotas that are established by the DEA. These drugs are crucial to support critically-ill patients such as those with severe COVID-19 infection. An expansion of DEA-issued quotas is required before any increases in manufacturing capacity for such drugs may occur. In the event of a public health emergency, these may be difficult or take too long to obtain.

PROBLEM 4: Interruption of global trade in medicines

The pandemic has revealed the **overdependence**¹⁴ of the United States on other countries for APIs and specific medications. In addition to the disruptions due to delays in foreign inspection, production, and transportation, countries may understandably choose to **prevent the export of**⁹ pharmaceutical products in order to increase the supplies available to treat their own people. India, for example, halted the **export of 26 drugs**¹⁵ and **13 APIs including paracetamol**¹⁶ in the early stages of the epidemic to conserve drug supply for its own citizens.

Reliance on China for active pharmaceutical ingredients has been documented in the **2019 annual report to Congress of the US China Economic and Security Review Commission**.¹⁷ Reliance on several other countries was documented in a recent **FDA shortage report**.¹

PROBLEM 5: Limited understanding of local and demand-driven shortages

The **Food & Drug Administration (FDA)**¹⁸ maintains an online database of current and past drug shortages. However, the FDA focuses on monitoring shortages, using data from manufacturers, of drugs that have nationwide impact and that are driven by disruptions in drug production. The **American Society of Health-System Pharmacists (ASHP)**¹⁹ also maintains an online database of current and past drug shortages. The ASHP database includes signals coming from end-users such as pharmacies and providers; however, it still focuses on shortages of nationwide impact. The Covid-19 epidemic has revealed the difficulty of detecting shortages related to increased demand and shortages of a local nature. For such problems, capturing more detailed information from the end

users of the supply chain—hospitals and group purchasing organizations—at the local and state level is needed.

In late March, a letter sent²⁰ to the Drug Enforcement Administration (DEA) by **several professional organizations**²⁰ informing of shortages experienced by hospitals illustrated this problem. Information from Group Purchasing Organizations have also illustrated the regional profile of shortages. For example, one drug, norepinephrine, has been **associated with increased mortality when in shortage**²¹, and was reported as a shortage early in the pandemic. But, though hospitals reported increased demand and shortage of norepinephrine **well into July**²², this drug was never indicated on the FDA’s shortage list—limiting the steps that could be taken in response.

PROBLEM 6: Inadequate supply chain planning and management

COVID-19 has revealed that the US does not have a system to coordinate and direct sharing of medications across institutions in different regions. Rather, the distribution of limited medical supplies has relied largely on pharmaceutical wholesalers during the current pandemic.

Limitations of this approach include:

- Pharmaceutical wholesalers use **proprietary algorithms**²³ to allocate supplies according to their contracts with hospitals, retail pharmacies, group purchasing organizations, and others. However, such algorithms have been developed to address non-crisis market needs.
- A wholesaler’s ability to redistribute supply across facilities or geographic areas is limited by their lack of objective information on the burden of disease experienced by specific facilities as

well as existing contractual agreements that guarantee certain levels of supply to purchasers across the country.

- Pharmaceutical wholesalers do not report inventory levels to the FDA, HHS, or any federal agency, and it is not possible to ascertain whether scarce resources are being distributed equitably and prioritizing areas and facilities of higher demand.

Existing contracts with a particular group purchasing organization or wholesaler may limit hospitals and pharmacies’ attempts to procure drugs in shortage. For example, hospitals participating in HRSA’s 340B Drug Pricing Program are generally prohibited from obtaining “**covered outpatient drugs through a group purchasing organization or other group purchasing arrangement.**”²⁴ While HRSA has waived this requirement during the pandemic, clinics and hospitals may not have readily available mechanisms to access supplies or transport medications to other facilities.

Inadequate supply chain management can indirectly lead to shortages. Without confidence in a national plan, institutions may opt to stockpile large quantities of certain drugs in the anticipation of a shortage and may be hesitant to divert their supplies to facilities with greater need.

ACTIONS TAKEN TO DATE

Congress

Congress took several actions to address drug shortages in the Coronavirus Aid, Relief, and Economic Security (CARES) Act, passed in March 2020. Among other provisions, this legislation:

- Introduced new reporting requirements on manufacturers about actual and expected medication shortages, including shortages related to active pharmaceutical ingredients. Manufacturers must now report the expected duration of the shortage and the reason for the shortage.
- Required all manufacturers to develop a risk management plan to assess and address shortage risk.
- Required Medicare Part D plans to provide **up to a 90-day (3 month) supply**²⁵ of covered Part D drugs to enrollees who request it.

The White House

The Administration has also taken some steps in recent months to expand domestic production of critical medications. In May, HHS began **providing contracts**²⁶ to US manufacturers for domestic manufacturing of essential medicines. Also in May, the White House issued an **executive order**²⁷ that allows the U.S. International Development Finance Corp to **invest**²⁸ in domestic companies to promote manufacturing of pharmaceutical products that have been depleted by the COVID-19 pandemic. In August, another **executive order**²⁹ required federal drug-procuring agencies (under the guidance of the FDA commissioner) to buy critical medications from American manufacturers and also aimed to accelerate approval of domestically-manufactured products.

The Food and Drug Administration.

Over the last several years, the FDA has taken a series of actions to make drug production more resilient. These efforts include:

- **A drug shortage list.** Through its drug shortage task force, the agency identifies drugs in shortage, **identifies alternative drugs for those drugs that are in shortage**³⁰, and alerts companies that make the alternative drugs to increase production to meet patient demand. These efforts have limitations, including a dependence on nation-wide, manufacturer-provided information and the lack of **reliable and accurate public information**³¹ about expected duration and location of shortages, supply status and location of available alternatives, and institutions and hospitals housing available drugs.
- **Guidance on production.** The FDA has issued **technical and regulatory**³² guidance for drug manufacturers to promote **innovation and improve quality**³² of medical products, an effort aimed at mitigating drug shortages due to poor drug quality. However, the FDA has limited ability to enforce such actions.

Since the onset of the COVID-19 pandemic started, the FDA has issued several guidance documents to help industry navigate rising drug manufacturing challenges.
- **Guidance on regulatory policies.** The FDA has drafted **several guidance documents**³³ to provide information to their staff, industry, and other stakeholders about updated **processing procedures**³⁴ for user fee applications for medical devices, **inspection and approval procedures**³⁵ for drug manufacturing facilities to ensure continued production of approved drugs, and regulatory requirements for the **development and licensing of vaccines to prevent COVID-19**.³⁶

■ **Guidance on production of compounded drugs.**

The FDA issued a [temporary policy guidance](#)³⁷ to temporarily permit outsourcing facilities that are part of the global pharmaceutical supply chain to compound certain drug products for hospitalized COVID-19 patients, provided the corresponding FDA-approved drugs appear on the [FDA drug shortages' list](#)³⁸ and have been reported by hospitals as drugs in shortage.

■ **Guidance on reporting manufacturing interruptions.**

FDA issued a [guidance](#)³⁹ under Section 506C of the Federal Food, Drug and Cosmetic Act to ensure that applicants and drug manufacturers report all interruptions and permanent discontinuances in the manufacturing of any drug materials that will eventually disrupt domestic drug production six months in advance. This policy reflects provisions established in the CARES Act passed in March 2020.

Looking ahead, FDA has [endorsed](#)¹ several additional proposals. These include a plan to provide a quality rating for manufacturers that would reflect the risk of a shortage and a proposal to lengthen expiry dates. Other proposals in Congress include a requirement that FDA maintain [shortage lists by region](#)⁴⁰, [permitting importation](#)⁴¹ in the setting of a likely shortage, and [incentivizing new manufacturing technologies](#)⁴² less likely to result in shortages. Finally, some proposals focus on [incentivizing](#)⁴³ domestic manufacturing through tax breaks and forming a [new office within HHS](#)⁴⁴ to support domestic manufacturing of generic drugs.

Multiple bills have been introduced in Congress to incentivize domestic production of pharmaceuticals. [H.R. 6930 - MADE in America Act of 2020](#)⁴³ establishes tax incentives to increase domestic pharmaceutical and medical device production. [H.R.6708 - Securing America's Medicine Cabinet Act of 2020](#)⁴² seeks to expedite the approval

of drug applications that involve domestic new drug manufacturing technologies that are likely to prevent and resolve a drug shortage and/or help maintain an adequate supply of critical medications for national emergencies. This bill would also designate eligible academic research institutions as National Centers of Excellence for Advanced Pharmaceutical manufacturing to promote research and development of active pharmaceutical ingredients in the U.S. [S.3162 - Affordable Drug Manufacturing Act of 2018](#)⁴⁴ would create an Office of Drug Manufacturing within HHS that would either manufacture generic medications itself or contract with others when it determined that (1) a drug is not readily available from existing suppliers, (2) HHS manufacture would facilitate market entry of other generics, or (3) such actions are necessary for the Office to carry out its duties.

POLICY RECOMMENDATIONS

RECOMMENDATION 1:

FDA should timely disclose and mitigate demand-driven and local-level shortages

In the event of a public health emergency declared by the Department of Health and Human Services, the FDA should expand its drug shortage surveillance system to capture information on difficulties procuring drugs provided by drug purchasers such as hospitals, pharmacies, group purchasing organizations, and wholesalers.

Adding a drug to the shortage list would allow the FDA to more quickly deploy the strategies to increase manufacturing that it typically reserves to drugs that it has incorporated in the shortage list. Such strategies include expedited review of manufacturing changes, assistance in establishing new lines of production, extended expiration dating, or redirection of products from outside of U.S. markets.

RECOMMENDATION 2:

To strengthen pharmaceutical production, Congress should authorize FDA to create and publish quality metrics for the manufacturing process.

The FDA has proposed the use of publicly available **quality metrics**⁴⁵ to address drugs shortages that stem from poor manufacturing practices. To further this agenda, the FDA issued a **guidance**⁴⁶ in 2016 on how quality metrics could be used for evaluation of facilities. The agency also asked for funding for development of quality metrics to improve oversight in next generation sequencing (diagnostics) in their **FY 2020 financial budget**.⁴⁷

At present, FDA is currently implementing a **voluntary industry reporting system**⁴⁶ of selected quality metrics. However, the voluntary basis of this system constitutes a weakness. Industry

stakeholders have **questioned**⁴⁸ the legal authority of the agency to require domestic and foreign manufacturers to report the information needed to calculate quality metrics.

To resolve this issue, Congress should authorize the FDA to develop, publish, and implement metrics that accurately reflect the quality of drugs produced at manufacturing facilities.

The FDA will then be able to provide information about the risk of shortages coming from manufacturing to stakeholders such as drug companies, wholesalers and hospitals who purchase drug products. Purchasers will have the option to choose from manufacturers that have more resilient production capabilities, and competitor manufacturers may choose to enter the market if all available products have poor quality ratings. A quality metrics system will create incentives for manufacturing facilities to self-correct, and lead to improved product quality thus mitigating drug shortages.

RECOMMENDATION 3:

To strengthen the global supply chain, the FDA should establish a database of approved manufacturers of active pharmaceutical ingredients

When a drug manufacturer relies on another company to produce an API, the FDA must approve the API source. This is a lengthy and costly process often involving FDA inspections of the API manufacturer's facilities. In a public health emergency where generic drugs are in shortage, drug manufacturers must often find alternative sources of APIs quickly.

One option is to approve a new source for an API. However, a long review process may delay the feasibility of this alternative. An alternative would be to find another existing manufacturer. But no

database currently exists to identify approved API sources for potential generic drug manufacturers. An FDA database would accelerate the process of finding alternative suppliers that meet agency requirements.

**RECOMMENDATION 4:
To expand production capacity, FDA should expand the current mutual recognition agreement between the United States and Europe.**

The **mutual recognition agreement** between the United States and Europe, which was finalized in 2017, allows the FDA and European regulators to recognize each other's **surveillance inspections** of manufacturing facilities. However, the agreement only covers manufacturing facilities in the United States and Europe. With the concurrence of the Office of the United States Trade Representative, the agreement should be revised to cover inspections of Asian manufacturing facilities conducted by either the FDA or European regulators, and to cover inspections of manufacturing plants that produce active pharmaceutical ingredients as well as pre-approval inspections of finished products.

This expansion is very important given the high reliance on European and Asian countries to produce drugs and active pharmaceutical ingredients for the US market. This cooperation would increase the efficiency of FDA's oversight of manufacturing facilities because it would help the FDA allocate resources towards inspecting facilities that have not been inspected and approved by European regulators, including in Asia.

In addition, mutual recognition agreements could be sought with other countries with advanced pharmaceutical markets such as Japan and Australia. The result would be having a greater number of facilities able to supply medications for

the U.S. market for a cheaper cost to the federal agency as well as a faster turnaround time for review and approval of manufacturing changes both in regular times and in the event of a public health crisis.

**RECOMMENDATION 5:
Congress should further incentivize domestic production of essential pharmaceuticals**

Beyond actions to date taken by the administration, Congress can establish a legislative framework to describe, define, and sustain all activities to increase domestic production of critical medications over time. Such a framework can focus investments and efforts where they will produce the greatest benefit, while maintaining a robust global market in pharmaceuticals. A proposal should:

- Specify the characteristics of eligible drugs, applicable circumstances, and eligible institutions for contracts for domestic manufacturers. Considerations might include the potential for shortage in an emergency.
- Empowering the FDA to require that manufacturers demonstrate that they have and maintain a certain level of stockpile of APIs when approving a new drug.
- Empowering the FDA to expedite approvals of new drugs or manufacturing changes of existing drugs when the manufacturing process strengthens domestic manufacturing of key medications.
- Empowering the FDA to track and publicly disclose the countries involved in the manufacturing of each drug commercialized in the United States, including its active ingredients and excipients.

RECOMMENDATION 6:**The federal government should stand up a comprehensive effort to assess and manage the U.S. pharmaceutical supply chain.**

Supply chain management in an emergency includes the assessment of available supplies, the ability to purchase additional supplies into and distribute from a government stockpile, and the ability to allocate supplies across the market in an emergency. These capabilities can be built to address serious drug shortages of all kinds and mobilized broadly during emergencies. Existing emergency authority exists in the Defense Production Act and other laws, and Congress could broaden this authority for use for other critical shortages.

During an emergency, a comprehensive supply chain effort would involve collecting information about available stocks from the manufacturer to the end user, contracting for additional supplies (utilizing the Defense Procurement Act where necessary) for a national supply, and establishing a distribution system based on levels of need. Such systems should be built in non-crisis times, such that they can be quickly and efficiently deployed in the event of a public health emergency.

FDA should have the authority to declare a critical drug shortage. With this declaration, an agency empowered to manage the supply chain should be able to compel information about stocks of key medicines, and, where necessary for public health, redirect supplies to where most needed. The agency's authority should include creating a pathway for sharing of supplies between end users, which should supersede contractual restrictions and other hindrances.

The use of a system for specific critical drug shortages outside of an emergency will support a state of readiness for a major national emergency.

RECOMMENDATION 7:**When necessary to mitigate shortages, the Department of Health and Human Services should allow additional manufacturers to produce patented medications**

Two statutes permit the government to make copies of patented medications in shortage. The federal government should adopt a policy to use these laws as needed in a crisis, if companies cannot themselves produce sufficient quantities to meet the demand.

28 USC § 1498. This statute allows the federal government to permit additional manufacturers to produce patented drugs without approval from the patent holder as long as the patent holder is given fair compensation.

The Bayh-Dole Act. This statute provides the U.S. government "march-in" rights that allow a federal agency, in special circumstances, to require the patent owner to grant a "nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants." The Bayh-Dole Act can be invoked if the patent holder was considered to be failing at taking "effective steps to achieve practical application of the subject invention."

TABLE FDA Reported Drug Shortages during the COVID-19 pandemic. (Jan 31-present)

Name	Therapeutic Category	Day Posted	COVID Relation
Pindolol Tablets	Cardiovascular	2020-02-21	Relation Unknown
AVYCAZÂ® (ceftazidime and avibactam) for Injection, 2 grams/0.5 grams	Anti-Infective	2020-02-26	ICU care
Amoxapine Tablets	Psychiatry	2020-03-09	Relation Unknown
Rifapentine Tablets	Anti-Infective	2020-03-25	Relation Unknown
Nizatidine Capsules	Gastroenterology	2020-03-27	Relation Unknown
Chloroquine Phosphate Tablets	Anti-Infective	2020-03-31	COVID Treatment
Hydroxychloroquine Sulfate Tablets	Anti-Infective; Other; Rheumatology	2020-03-31	COVID Treatment
Hydrocortisone Tablets, USP	Endocrinology/Metabolism	2020-04-02	Indirect
Midazolam Injection, USP	Anesthesia; Neurology	2020-04-02	ICU Care
Furosemide Injection, USP	Cardiovascular	2020-04-07	ICU Care
Cisatracurium Besylate Injection	Anesthesia	2020-04-08	ICU Care
Dexmedetomidine Injection	Anesthesia	2020-04-10	ICU Care
Etomidate Injection	Anesthesia	2020-04-10	ICU Care
Propofol Injectable Emulsion	Anesthesia	2020-04-10	ICU Care
Azithromycin Tablets	Anti-Infective	2020-04-14	COVID Treatment
Continuous Renal Replacement Therapy (CRRT) Solutions	Renal	2020-04-22	ICU Care
Sulfasalazine Tablets	Gastroenterology	2020-04-24	Relation Unknown
Hydroxypropyl (Lacrisert) Cellulose Ophthalmic Insert	Ophthalmology	2020-05-01	Indirect
Famotidine Tablets	Gastroenterology	2020-05-04	ICU Care
Famotidine Injection	Gastroenterology	2020-05-05	ICU Care
Lithium Oral Solution	Psychiatry	2020-05-06	Relation Unknown
Vecuronium Bromide for Injection	Anesthesia	2020-05-06	ICU Care
Dimercaprol (Bal in Oil) Injection USP	Hematology; Other	2020-05-11	Relation Unknown
Amifostine Injection	Oncology	2020-05-21	Relation Unknown
Sertraline Hydrochloride Oral Solution, USP	Psychiatry	2020-05-26	Indirect
Sertraline Hydrochloride Tablets	Pediatric; Psychiatry	2020-05-29	Indirect

continued

Name	Therapeutic Category	Day Posted	COVID Relation
Timolol Maleate Ophthalmic Gel Forming Solution	Ophthalmology	2020-05-29	Indirect
Timolol Maleate Ophthalmic Solution	Ophthalmology	2020-05-29	Relation Unknown
Doxycycline Hyclate Injection	Anti-Infective	2020-07-10	ICU Care
Leuprolide Acetate Injection	Endocrinology/Metabolism; Oncology	2020-07-24	Relation Unknown
Chlorothiazide (Diuril) Oral Suspension	Cardiovascular; Pediatric	2020-08-12	Relation Unknown
Tobramycin Lyophilized Powder for Injection	Anti-Infective; Pediatric	2020-08-24	ICU Care
Hydralazine Hydrochloride Injection, USP	Cardiovascular	2020-09-08	ICU Care

Notes: **COVID treatment** represents a drug that can be used in the direct treatment of COVID-19 infection; **Indirect** represents a drug whose shortage has been described as triggered or related to the COVID-19 pandemic, though not due to the direct treatment of COVID-19 infection; **ICU Care** represents a drug commonly used in treatment of critically ill patients, such as patients with severe COVID-19 illness; and **Relation Unknown** represents drugs that were listed by the FDA on the shortage list during the COVID-19 pandemic, but which lack clear evidence attributing this shortage to the pandemic itself.

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