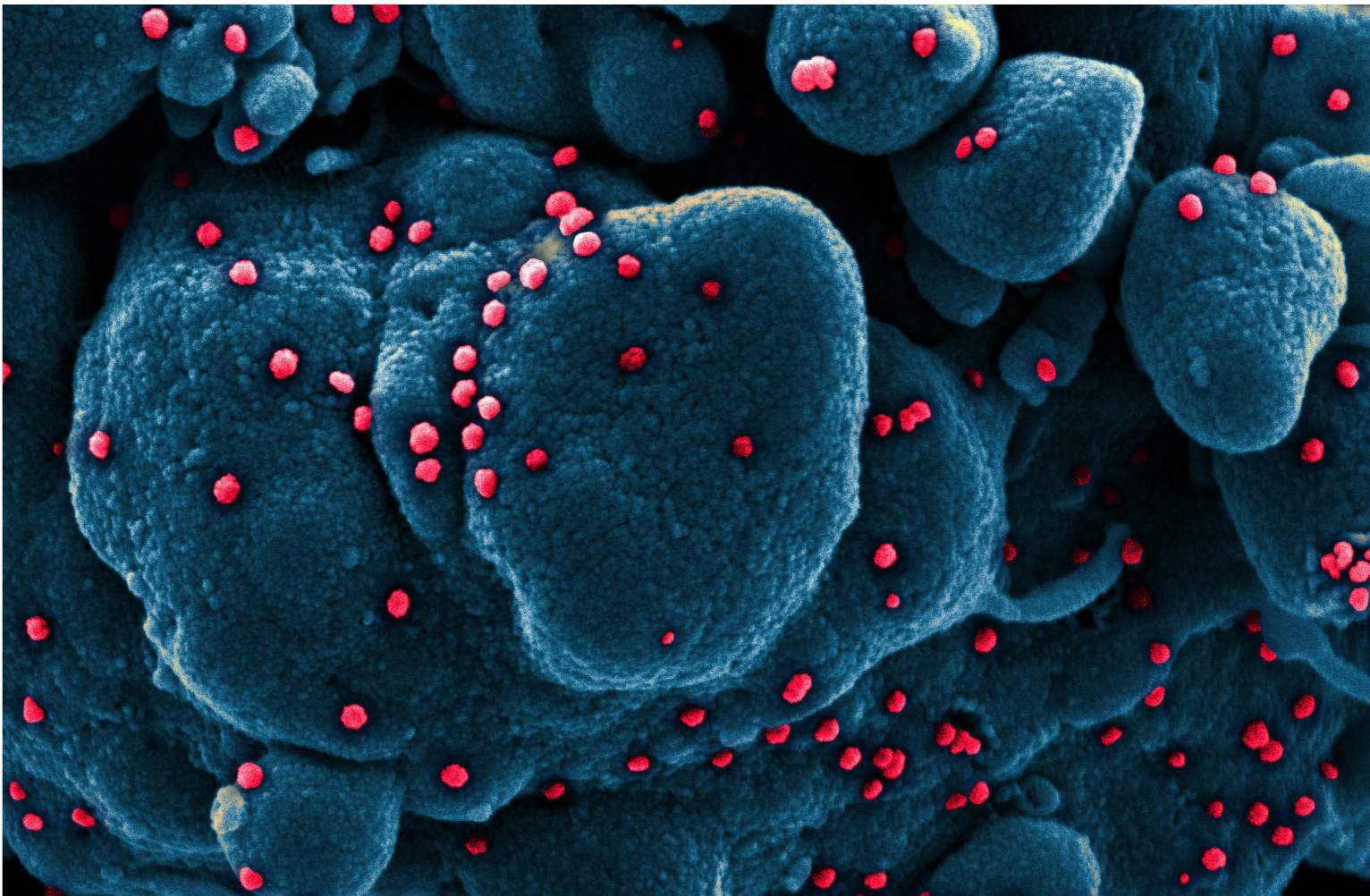# COVID-19:
The CIDRAP Viewpoint

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COVID-19: The CIDRAP Viewpoint

October 21, 2020

Part 6: Ensuring a Resilient US Prescription Drug Supply

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CIDRAP, founded in 2001, is a global leader in addressing public health preparedness and emerging infectious disease response. Part of the Office of the Vice President for Research (OVPR) at the University of Minnesota, CIDRAP works to prevent illness and death from targeted infectious disease threats through research and the translation of scientific information into real-world, practical applications, policies, and solutions. For more information, visit: www.cidrap.umn.edu.

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Part 6: Ensuring a Resilient US Prescription Drug Supply

Preface

Welcome to "COVID-19: The CIDRAP Viewpoint," our series of reports that add key information, address issues that haven't garnered the attention they deserve, and reflect the unique expertise among the CIDRAP team and our expert consultants. In our reports we address timely issues with straight talk and clarity. The steps we recommend are based on our current reality and the best available data. Our goal is to help planners envision some of the situations that might present themselves later this year or next year so that they can take key steps now, while there's still time.

Our first report laid out potential pandemic scenarios, our second report covered crisis communication, our third report described "smart testing," our fourth report was on contact tracing, and our fifth report covered surveillance.

Our hope is that these efforts can help you plan more effectively and understand the many aspects of this pandemic more clearly—and for you and your family, friends, and colleagues to be safer. Thank you.

– Michael T. Osterholm, PhD, MPH, CIDRAP Director

Introduction

An ongoing crisis plagues US healthcare, limits reliable access to critical drugs, and results in serious consequences for patients who need these drugs. Over the past few years, the United States has had more than 250 drug shortages at any point,[1] many for critical medications, including both acute drugs for treating emergency situations and chronic drugs for managing serious long-term conditions. And shortages remain a perennial problem. Even though drug shortages have been recognized and tracked in the United States since 2001, the situation has not significantly improved in more than two decades.[2]

Impact of COVID-19 on the Drug Supply Chain

Emergence of the COVID-19 pandemic in early 2020 has severely stressed the US drug supply chain. COVID-19 has jolted the global pharmaceutical market at all levels and production points. The supply side has been disrupted by production factory closures, shipping delays or shutdowns, and trade limitations or export bans. The demand side has seen dramatically increased need for COVID-19 therapies worldwide.

Shortages have limited critical drugs for treating COVID-19 patients, including propofol, albuterol, midazolam, hydroxychloroquine, cisatracurium, rocuronium, fentanyl, azithromycin, vancomycin, and others. In fact, 72.5% of them (29 of 40) currently have shortage problems, according to the American Society of Health-System Pharmacists (ASHP).[3] The US Food and Drug Administration (FDA), with more stringent criteria for declaring a shortage, currently shows 45% (18 of 40) on its Drug Shortage list. Both these rates (see the Appendix) are unacceptable.[4]

The pandemic has exposed many of the vulnerabilities in the US drug supply chain. COVID-19 tends to strike hard in a discrete geographic area, and when it creates a new hot spot, the hospitals in that area usually see a dramatic spike in admissions and ventilator use. In addition, use of certain critical COVID-19 drugs, such as azithromycin, may more than double overnight, while other drugs may see even steeper jumps of 5-fold (i.e., midazolam), 10-fold (cisatracurium), 20-fold (hydroxychloroquine) or even 40-fold (tocilizumab). Such explosive growth in critical acute drug use was seen in March and April when the number of hospitalizations and critical care COVID-19 patients in New York and New Jersey skyrocketed.

Many COVID-19 events have severely disrupted the global pharmaceutical supply chain. We saw stay-at-home orders and factory lockdowns in China,[5] followed by shipping port slowdowns and shutdowns.[6] Hubei province (and Wuhan city) in China alone had 37 pharmaceutical factories that held Drug Master Files for making active pharmaceutical ingredients (APIs) for US drug products.[7,8] Drugs made in the Hubei region include ibuprofen, hydromorphone, metoprolol, metformin, zidovudine, azithromycin, clindamycin, and levofloxacin.

Meanwhile, many Indian drug makers who rely heavily (about 70%) on China for key starting materials like benzene, as well as APIs, experienced delays in receiving the ingredients to make finished generic drug products for the global market.[9] In early March 2020, the Indian government was so concerned about having enough critical drugs to meet the needs of the Indian market that it restricted the export of 26 APIs and finished drug products to prevent shortages in India.[10] The drugs on India's export ban list accounted for about 10% of India's total pharmaceutical exports and included acetaminophen, metronidazole, erythromycin, clindamycin, and several essential vitamins.[11] India later prohibited the export of hydroxychloroquine because domestic stocks were running low and it wanted to first fulfill its own requirements.[12]

Other countries imposed trade limitations or export bans on pharmaceuticals, including the United Kingdom, which issued a ban on parallel export of 82 drugs, including insulin, amoxicillin, and acetaminophen.[13] China hinted in March that it might impose export controls on shipments of life-saving drugs to the US market, though it did not take that step.[14] This threat is particularly concerning

Pressing Issues

1. US drug shortages pose a perennial problem; though drug shortages have been recognized and tracked in the country since 2001, the situation has not improved since then.

2. Drug shortages can be a matter of life and death, and some shortages mean that a life-saving drug is not available to US patients at any price.

3. Lack of visibility into the upstream drug supply chain severely hampers the ability of the market and of policymakers to monitor and address drug quality issues and facilitates market conditions that lead to drug shortages.

4. A number of serious threats to the US drug supply chain could precipitate a major shortage, intentionally or through natural causes, and such disruptions could lead to major healthcare consequences and costs.

5. The upstream US drug supply chain depends heavily on foreign sources for prescription drug products at all stages. The Food and Drug Administration (FDA) said in 2019 that officials do not know whether Chinese facilities are actually producing active pharmaceutical ingredients (APIs), how much they are producing, or where their APIs are distributed worldwide, and the agency lacks information to assess the effect on US manufacturing should China withdraw from supplying the US market.

6. Americans do not know where a given drug product was made or where it has been.

7. Information on US drug supply chain vulnerabilities is not transparent enough to support timely management of drug shortages and makes prediction of shortages nearly impossible.

8. While the FDA may have some of this information on a drug-by-drug basis, the drug sponsors and marketers consider the identity of the factory—or even the country—where a given drug is made to be proprietary.

because of China's dominance in the antibiotic market. China makes "nearly all" supplies of penicillin G and about 80% of the world's supply of many antibiotics.[15]

Many European Union (EU) countries and the United States looked to Italy as an alternate source of antibiotics when their supplies from China and India were disrupted. Italy was the EU's largest producer of antibiotics in 2018, accounting for 34% of the total EU consumption.[16] Italy, however, was hit early and hard by COVID-19 cases,[17,18] and, by early March, it had stopped all commercial activity (including drug factories) except for retail pharmacies and super markets, disrupting this alternate source.[19] By mid-March, most major European countries, including Spain, France, Germany, Switzerland, England, the Netherlands, Norway, Denmark, and Ireland, were severely affected by the pandemic.[20] Keep in mind that, in 2018, 19 of the top 20 brand name drug products in the United States were made overseas, mostly in Europe.[21]

US Drug Shortages Persist

Certainly, drug shortages existed long before the pandemic and will likely persist long afterward. 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 its supply."[22] The FDA's definition reflects an economic framework based on supply and demand. This perspective is useful but inadequate, since it focuses primarily on fixing the problems after the market has failed, and results in patients not having access to the right drug when they need it. The American Society for Health-System Pharmacists (ASHP) defines a drug shortage 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."[23] This definition uses both a supply chain/labor point of view and a clinical outcome framework. Despite their limitations, each of these perspectives is important to understanding the impact of drug shortages, but they have not been sufficient to significantly reduce them.

Drug shortages arise for many reasons, such as raw materials shortages, manufacturing capacity, production quality concerns, recalls, and business decisions to discontinue a drug product. Root causes are often not immediately apparent. US officials track drug shortages "after the fact" based on a manufacturer or a hospital reporting lack of drug product in the market. While this process is helpful to providers caring for patients and the retrospective tracking of shortages is important to understanding how to mitigate their potential impact, it has not been sufficient to significantly reduce the number of drug shortages.

Drug shortages are not just an inconvenience; they can be a matter of life and death. Last year, for example, vincristine—a pediatric cancer drug—was in severe short supply. One oncologist explained that vincristine is the "single most widely used chemotherapeutic (agent) in childhood cancer."[24] This was not an affordability problem, since the average sales price of a vial of vincristine is less than $10. Instead, the drug simply was not available at any price. One of only two US manufacturers of vincristine exited the market, and the second experienced production delays and quality problems.[25] The vincristine shortage exposed a failure in the drug quality assurance system and in the robustness of the pharmaceutical market and supply chain.

Heparin, a widely used anticoagulant, is another example. Contamination of the key starting material for making heparin occurred at multiple suppliers in China back in 2007. This undetected adulteration of heparin led to dozens of Americans suffering severe consequences, including death.[26] Concentrated production in China set the stage for substitution of cheaper ingredients, which led to poor quality product reaching the market. Recalls and serious patient harm resulted from poor visibility into, and oversight of, product quality in the upstream supply chain for this drug product.

Both vincristine and heparin are injectable drugs used mostly in hospitals. Injectable drugs as a category have accounted for 50% to 70% of all drug shortages over the past two decades,[1] which is substantially larger than

Recommendations

1. The United States should have a national process and infrastructure for analyzing, predicting, managing, and preventing shortages of critical medications.

2. An in-depth map of the US drug supply chain is needed to identify where each drug product in the US market was made, including where the starting materials, active pharmaceutical ingredients, and finished drug product were produced.

3. Congress should authorize and fund a national entity to build the map noted above, publish information on each drug's supply chain, acquire and analyze prescription drug expenditure data, estimate the consequences of failing to address drug shortages, and coordinate the development of related national policy.

4. This national entity could be an existing agency such as the Food and Drug Administration (FDA), National Institutes of Health (NIH), National Library of Medicine, or US Pharmacopeia Convention. Alternatively, a new federal entity may be established, such as the National Institute for Pharmaceutical Resilience (housed within NIH) or a Prescription Drug Policy Review Commission.

5. Prescription drug profiles for each drug product (at the National Drug Code level) should be made publicly available on a consumer-friendly website, with information as noted in the text (see page 10).

6. An ongoing research program on the resilience of the US drug supply chain should be conducted and include, but not be limited to, the development of a sentinel system that can detect signals that may precede a supply chain disruption or drug shortage.

7. The country should develop and regularly update lists of essential or critical drugs to be used for ensuring a high-quality and resilient drug supply for the military, triage during natural disasters, and the general public's need for critical drugs for both acute and chronic conditions.

8. Congress should authorize a federal agency (such as the FDA or Department of Health and Human Services) to prepare a response plan for managing and mitigating drug shortages and other supply chain disruptions.

9. Congress should authorize and fund a federal agency to monitor the changing landscape of pharmaceutical manufacturing and the supply chain for prescription drugs (see page 9 for key functions).

the share that injectables represent in the overall market. Only a few drug manufacturers produce and market generic injectable drugs. On the one hand, large hospital group purchasing organizations (GPOs) force the generic injectable drug companies to compete on price in exchange for large-volume purchases from hospital systems. Over time, however, as prices continue to decline, fewer manufacturers can afford to make these generic injectables and remain profitable in the market. These price reductions tend to lead to a single generic in the market and a single point of failure in the drug supply chain.

One way generic injectable manufacturers have managed to survive is to limit re-investment in modern production methods and in new production facilities, which also raises the risk of a drug shortage. At the same time, high economic and regulatory barriers to entry have limited new producers and competitors in this market.

There is no quick fix for either the quality issues or the economic market conditions that contribute to ongoing US drug shortages. Nevertheless, one obvious place to start is a detailed examination and understanding of the drug supply chain. There is an urgent need for new, more effective policy with robust transparency to solve the persistent drug shortage issues plaguing the US healthcare system for the active military as well as for the general population.

Role of the Drug Supply Chain

Many steps in the drug supply chain are required to prepare a prescription drug product before it can be safely and effectively used by a patient. A simplified supply chain is shown in Figure 1. This supply chain includes not only points for production, refinement, processing, and packaging of a drug product, but each of the steps shown in the supply chain represent points at which the drug product, or its ingredients, may be transferred or shipped from one factory to another and sometimes from one country to another. The vast majority of the upstream supply chain for US drugs heavily depends on production and shipments in foreign countries, while the downstream supply chain from marketer to patient occurs almost entirely within the United States.

Figure 1
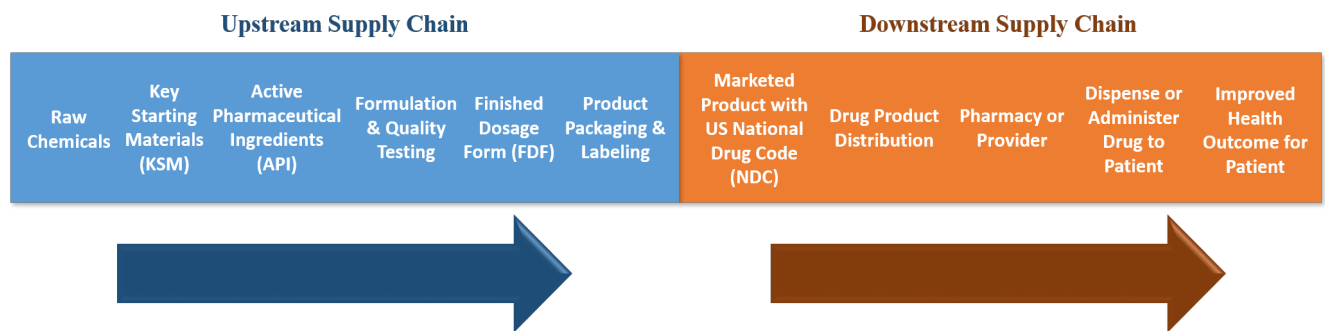
The pharmaceutical market has a complex, opaque structure. It is truly global, with various operations in the pharmaceutical supply chain from raw chemicals to finished dosage forms (FDF) (e.g., tablets and capsules) occurring in different countries. The more touch-points there are in a given drug's supply chain, the more potential points there are for supply chain disruption. Naturally, when there is only a single source of supply for a critical raw material or API, a single untoward event can disrupt the entire US or global supply of that product. The upstream supply chain for many drugs may face a serious threat of disruption, not just at one point but at multiple points. The supply chain works much like dominoes triggering a chain reaction.

Whether an upstream supply chain disruption occurs at a single point or multiple points, the effects are nonetheless felt downstream. Adjustments have to be made in the downstream distribution chain and ultimately in the healthcare delivery system.[27] Supply chain disruptions cause increased costs to drug marketers, wholesalers, health systems, pharmacists, and physicians. These disruptions create an open-ended healthcare cost liability for both public payers such as Medicare and Medicaid and private payers such as employer-based insurance and self-pay plans. Patients may suffer or even die if a needed drug is unavailable.[28] Overall, US health systems spend more than $500 million a year on estimated costs related to drug shortages, with approximately $200 million in direct costs and up to $360 million on indirect costs.[22,28,29]

Threats to the US Drug Supply

The US drug supply chain has been greatly stressed in recent years, even before the COVID-19 pandemic. We have seen, on average, more than 160 new drug shortages per year over the past decade.[30] Shortages often originate from issues in the upstream supply chain, such as materials availability, production capacity, or

product quality issues. In 2019, the country saw 186 new drug shortages, 82% of which were classified as due to "unknown" reasons largely because of the intentional opacity and secrecy of the upstream supply chain.[1]

Several major triggers may lead to a drug shortage, including: (1) increased demand (or medical need) for a drug, (2) unavailability of raw materials, (3) lack of production capacity, (4) poor quality processes and products, (5) disruption of shipping and transport, and (6) business decisions related to corporate priorities and profit. Some shortages have a single trigger, while others may have multiple triggers.

Shortages of critical need drugs may occur when a "trigger event" stimulates a crisis or disaster of some type at one or more places along the global supply chain. Trigger events that lead to drug shortages may be either a single point-in-time event (e.g., a hurricane) or an ongoing situation (e.g., COVID-19). These trigger events may occur because of conditions in the business, economic, climatic, political, regulatory, and technological environments.

The supply chain for a critical drug can be disrupted in many ways and have a serious impact on the US pharmaceutical market. The following scenarios are plausible, and in fact most have already occurred somewhere in the world. Potential threat scenarios include:

1. Climate change and natural disasters such as hurricanes, tornadoes, tsunamis, floods, infectious disease outbreaks and pandemics

2. Human behavior in response to actual or rumored drug shortages, including responses such as panic, hoarding, or changes in trust of therapies or vaccines

3. Human-made disasters such as fires, explosions, or nuclear disasters

4. Unintentional contamination while synthesizing and manufacturing a drug product (e.g., valsartan in 2018, ranitidine in 2019, and metformin in 2020 with nitrosamine contaminants)

5. Intentional contamination (or terrorism) of critical acute or chronic drugs during the synthesis, production, or distribution process

6. Business decisions and industry consolidation among drug firms

7. Bankruptcy or other economic behavior of a major pharmaceutical firm

8. Political or diplomatic crisis such as India's ban on export of certain drugs this year

9. Military action or war with one or more major countries, such as China, North Korea, or Iran

The continued risk of drug shortages is not surprising, given the current structure and dynamics of the US pharmaceutical market. In 2019, two thirds of the US drug supply (by $ value) is imported, while about 72% of the manufacturers of APIs that are used to make pharmaceuticals are located outside of the country.[31] Also, about 55% (based on $ value) of biologics and specialty drugs are imported.[32] India is the major source of finished generics for the US market.[33] India depends on China for 70% or more of its API. And, for certain drug products, China accounts for nearly 100% of the API used for drugs such as penicillin G, levodopa, and acetaminophen and more than two thirds of the API for other major drugs including anti-diabetics, anti-hypertensives, anti-retrovirals, and other antibiotics.[34] Given the heavy reliance of the US drug supply on foreign sources, any of the above scenarios is plausible today, and many have to at least a certain extent already occurred.

If a threat scenario causes long-term consequences for the US drug supply, the fix is usually time-consuming. Most drugs have only a 1- to 6-month supply of product filling the entire supply chain. These limited levels of

inventory in the system are due, in part, to just-in-time production and pressures to minimize inventory-on-hand. In general, no alternative sources of drug supply exist to meet the needs of the entire US market since Americans consume about half of the world's drugs.[35] The efforts to get alternative production up and running to expand the supply of critical medications may take 3 months to 3 years or more.

If supply chain disruptions eliminate drugs for critical chronic conditions (e.g., diabetes, epilepsy, asthma), many patients without these "critical chronic" medications (such as insulin, phenytoin, or albuterol) would be hospitalized or die. Such disruptions could be even more widespread and more devastating than shortages for critical acute life-saving drugs.

Need for Increased Supply Chain Transparency

A first step that would improve the US drug shortage problem would be a dramatic increase in transparency at every step of the supply chain. The current lack of transparency makes the timely management and resolution of drug shortages challenging and renders their prediction nearly impossible. Remarkably, a key FDA official reported to Congress in 2019 that FDA doesn't "know whether Chinese facilities are actually producing APIs, how much they are producing, or where the APIs they are producing are being distributed worldwide, including in the United States."[35] The FDA testimony went on to say, "Similarly, we do not have information that would enable us to assess the resilience of the U.S. manufacturing base, should it be tested by China's withdrawal from supplying the U.S. market."

> "If supply chain disruptions eliminate drugs for critical chronic conditions (e.g., diabetes, epilepsy, asthma), many patients without these "critical chronic" medications (such as insulin, phenytoin or albuterol) would be hospitalized or die.

While the FDA may have some of this supply chain information on a drug-by-drug basis, the drug sponsors and marketers argue that the identity of the factory, or even the country in which a given drug is made is "proprietary" and confidential. Often the US players in the downstream supply chain do not have meaningful visibility upstream past the US marketing sponsor. This limits the ability of policymakers and major purchasers to recognize vulnerabilities and to develop contingency and redundancy plans.

US consumers can find the "Country of Origin" on many products, such as foods, veterinary drugs, clothing, and electronics. "Country of Origin" is defined in US Customs and Border Protection regulations as "the country of manufacture, production, or growth of any article of foreign origin entering the United States."[36] This country-of-origin regulation, however, is not routinely followed for prescription drug products and is not enforced by US Customs inspectors.

The US Pharmacopeia Convention (USP) recently conducted a study of the labels for US prescription drug products,[37] based on drug labels available from the joint FDA and National Library of Medicine database known as DailyMed. USP analyzed the labels of 40,178 prescription drug products and found that only 3% reported the API manufacturer, 30% reported the finished product manufacturer, 45% reported only the labeler or packer, and 25% reported no information on the upstream supply chain. In other words, more than two thirds of prescription drug labels contain no information about who actually made the drug product and where it was made. As noted by the USP, "Manufacturers are required and do report suppliers to US FDA [but not to the public or on the labeling], also sharing supply chain information publicly could help providers proactively safeguard patient health. For example, when a safety issue is identified with an API manufacturer, providers will have on-hand information about impacted brands."[38]

In contrast to the US situation, information on the supply chain for prescription drug products in New Zealand is publicly disclosed and transparent. New Zealand collects and makes public the name and location of the API and the FDF manufacturers, in addition to the drug product sponsor and marketer in the country. The public transparency of this information does not appear to have commercially harmed the manufacturers or marketers of drug products in New Zealand. Many of the same corporate entities marketing drugs in New Zealand are marketing the same, or similar, drugs in the United States.

Data on the New Zealand Medsafe public access website[39] can be analyzed to quickly determine the sites of manufacture (API and FDF) of all critical drugs to determine which ones have the highest dependence upon a certain geographic location such as Wuhan, China, or Puerto Rico or any other location. Within hours of the news of a plant closure in China, New Zealand could know which drug products will be affected and can look for other producers of the same drug to supplement the country's drug supply.

If the United States adopted a similar transparency policy, both the FDA and public policy analysts could monitor the US upstream pharmaceutical supply chain to identify potential trigger points that could lead to supply chain vulnerability and to predict drug products that may face shortages in the United States. Potential points of vulnerability for drug products could be monitored and assessed for multiple factors. Drug purchasers could assess risk through a transparent database that identifies a drug product's supply chain in a manner similar to New Zealand's Medsafe. The drug product profile could also include information such as recall and seizure history of the drug product, FDA warning letters to the manufacturer, import holds, Form 483 citations of the manufacturing facility, and other quality control and regulatory actions.

Need for Resilient Drug Supply Database and Analysis

The lack of information on upstream drug product supplies has resulted in serious health consequences for US patients and added substantial healthcare costs. Drug shortages can appear with little warning to healthcare providers (e.g., azithromycin, vincristine) and may require prescribers to look for alternatives, if any. At times, all or most of the suppliers of a given drug product (e.g., ranitidine) may face recalls at about the same time, leaving little or no drug product on the market due to inadequate production, inventories, or quality control measures. Business decisions can also deprive patients of critical drugs (e.g., vincristine).

The decades-long persistence of critical drug shortages demonstrates that a more systematic, comprehensive approach to ensuring a continuous, resilient supply of critical drugs is needed.

The country should have a national process and a common ongoing infrastructure for describing, analyzing, predicting, managing, and preventing shortages of critical medications to better inform policymakers and the public.

Building an in-depth map of the US drug supply chain will help identify where each drug product (at the National Drug Code [NDC] level) in the US market was made, including where the starting materials, APIs, and finished drug product were produced. The map should also track how the drug product is shipped from manufacturer to labeler (or marketer) to wholesaler and to the pharmacy or provider and consumer. This supply map should incorporate data from the FDA, suppliers and manufacturers, wholesalers, commercial sources, shipping records, and other sources. The map will be used to determine the networking and interdependence of suppliers at all levels in the supply chain and to report and assess its vulnerabilities.

Congress should authorize and fund a specific national entity to: (1) build an in-depth map of the US drug supply chain; (2) publish appropriate information on each drug's supply chain; (3) acquire and analyze data on the volume and expenditures for prescription drug products in the US market, including Medicaid, Medicare, other

government programs, managed care and commercial insurance, and cash pay markets; (4) estimate drugs with the most serious consequences of failure to mitigate or eliminate drug shortages; and (5) coordinate development of national policy related to the pharmaceutical market and ensuring a high-quality, resilient drug supply. This federal entity should design, develop, maintain, enhance, analyze, and publish information on the supply chain for all drug products (at the NDC level) in the US market. Market data should be combined with information on the supply chain patterns and related risk factors to prioritize drug products for which a shortage will have the greatest impact.

This national entity may be the FDA or another national agency such as the National Institutes of Health, the National Library of Medicine, or USP. Or a new agency could be established, such as a National Institute for Pharmaceutical Resilience (housed within NIH), or a Prescription Drug Policy Review Commission similar to the Medicare Payment Advisory Commission (MedPAC) could be created.

Prescription drug profiles for each drug product (at the NDC level) should be publicly available on a consumer-friendly website. The transparent information for each drug product should include:

> " An ongoing research program on the resilience of the US drug supply chain should include, but not be limited to, development of a sentinel system that can detect signals that may precede a supply chain disruption or drug shortage.

(1) each major step in the supply chain, (2) manufacturer recall and FDA seizure history, (3) FDA warning letters, (4) facility inspections and Form 483 reports, (5) import holds, (6) marketing and advertising letters and warnings, (7) other regulatory actions, (8) public and private assessments of product quality using validated measures, (9) quality assurance reports, and (10) other relevant information.

An ongoing research program on the resilience of the US drug supply chain should include, but not be limited to, development of a sentinel system that can detect signals that may precede a supply chain disruption or drug shortage. This sentinel analysis system may use big data modeling and statistical techniques to look for potential and probable trigger events that are highly likely to lead to a drug supply shortage. Additional analysis should be performed to determine if the precipitating trigger events and predictive models for drug shortages are similar for all types of drugs or if different models and signals are needed for different types of drug products (e.g., critical acute drugs vs critical chronic drugs, injectable drugs vs oral solid dosage forms vs inhalers, or various therapeutic categories).

The United States should develop and regularly update lists of essential drugs to be used for ensuring a high-quality, resilient drug supply for (1) the active military, (2) triage during a natural disaster for a large population and for simultaneous disasters, (3) the critical acute drug needs of the general public, and (4) the critical chronic drug needs of the American public.

Critical Acute Drugs are those that, "when medically needed in acute care must be available and used within hours or days of the need or the patient will suffer serious outcomes which may include disability or death." Also, the "absence of a Critical Acute Drug, or even the lack of availability of an effective substitute, may also lead to serious health outcomes or limited ability to provide humane care." A list of 156 critical acute drug molecules has been identified by the University of Minnesota's Resilient Drug Supply Project (RDSP).[40]

Critical Chronic Drugs are those that, "when medically needed must be available and used within a few days or weeks or the patient's health will deteriorate, worsen substantially, or lead to serious outcomes such as

hospitalization or death." The vast majority of medical conditions are chronic diseases such as diabetes, high blood pressure, asthma, epilepsy, thyroid problems, and cancer. If a critical chronic medication is not available because of a drug shortage, some patients, such as type 1 diabetics without insulin, may experience serious problems.

The RDSP is developing a list of about 500 critical chronic drug molecules that should be among the first drugs to include on supply maps. The RDSP lists of critical acute and critical chronic drugs should be maintained and updated through collaboration with various stakeholders including the FDA, Department of Defense, National Security Agency, drug firms, wholesalers, retail pharmacies, hospitals, and others.

Congress should authorize and fund a federal entity (such as the FDA, Health Resources & Services Administration, Federal Emergency Management Agency, or Biomedical Advanced Research and Development Authority) to prepare a readiness and response plan for managing and mitigating drug shortages and other supply chain disruptions that arise in the US market. This plan should involve a nationally coordinated effort to tally remaining and limited supplies; establish rules, procedures, and priorities for allocating limited supplies; define the role of drug repositories; identify alternative supplies or alternative drug products; and establish other appropriate methods and responses for managing a drug shortage in order to provide critical drug therapy to patients in need.

Congress should authorize and fund a specific national entity to monitor the changing landscape of pharmaceutical manufacturing and the supply chain for prescription drugs, including steps to: (1) modernize drug production and quality; (2) monitor the safety, security and resilience of the drug supply chain; (3) track and trace the drug supply; (4) oversee trade policies and shipping security and safety; (5) require and enforce country-of-origin labeling for prescription drug products; and (6) implement supply chain transparency. This monitoring effort should lead to policy proposals to improve and ensure drug product quality and to incentivize increased drug manufacturing (both API and FDF) based in the United States in order to increase the quality, security, and resilience of the US drug supply.

Overall, the United States should have a national process and a common ongoing infrastructure for describing, analyzing, predicting, managing, and preventing shortages of critical medications to better inform policymakers and the public. This national effort should include certain public data elements on critical acute and critical chronic drugs that will be made transparent and will be provided through a public communication interface such as a website. The drug supply map and related databases will also include a confidential and comprehensive archival database for critical drugs with certain strategic information limited and accessible only to secure governmental and authorized industry stakeholders. This national effort will involve collaboration of multiple public stakeholders with select others to deploy strategic analytics and security tools to predict, prevent, and respond to future critical drug supply disruption, shortages, and related consequences.

Having Drugs Available When We Need Them

In summary, prescription drugs are foundational to an effective healthcare system in the United States. Virtually everyone needs prescription drugs at some point, and they tremendously benefit both personal and public health. Americans count on drugs—particularly essential drugs for diseases, such as diabetes, chronic heart disease, and cancer—being available at the local hospital or at their community pharmacy. However, shortages are a serious and recurring problem resulting from a web of factors rooted in an opaque drug production and drug supply chain, underfunded and underperforming government agencies, and a drug purchasing and distribution system with product allocation practices that are often secretive, unknown, and counterproductive.

Drug shortages have only worsened in recent years, and drug product quality concerns are precipitating more widespread drug recalls. Continuing the status quo threatens our confidence in the quality of prescription drugs and their availability. Obviously, we need to shift from a "fail and fix" framework to a "predict and prevent" paradigm. Implementing the recommendations in this report will provide a new national entity focused on better understanding the complex reasons for drug shortages and will establish a systematic approach for analyzing, predicting, preventing, and mitigating drug shortages. With the support of policymakers and cooperation of the FDA and industry stakeholders, the US pharmaceutical market can significantly reduce drug shortages. Only then can we ensure a resilient supply of needed medications.

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