Statement on

Strategic Assessment of the Resilience of the U.S. Drug Supply with Lessons from the Pandemic & Recommendations for Moving Beyond

at the Senate Hearing on

COVID-19 Part II: Evaluating the Medical Supply Chain and Pandemic Response Gaps

Statement before the

Committee on Homeland Security and Governmental Affairs
United States Senate
Congress of the United States
Wednesday, May 19, 2021, at 2:30 p.m.
Dirksen Senate Office Building, Room SD-342 and
via videoconference.

Statement of

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21-0517A

Thank you Chairman Peters, Ranking Member Portman, and other members of the Senate Committee on Homeland Security and Government Affairs for this opportunity to provide information and insights from a "Strategic Assessment of the Resilience of the U.S. Drug Supply with Lessons from the Pandemic and Recommendations for Moving Beyond."

I am Stephen W. Schondelmeyer, Professor of Pharmaceutical Management & Economics at the University of Minnesota where I serve as Co-Principal Investigator for the Resilient Drug Supply Project in the Center for Infectious Disease Research and Policy (CIDRAP). In addition, I am Director of the *PRIME* Institute which focuses on research and policy issues related to the pharmaceutical market and its impact on society. These remarks are my own views based upon my research and experience in studying the pharmaceutical marketplace for over forty-five years. Thank you for the opportunity to testify at this hearing. Previously, I have had the opportunity to interact with many of the federal entities that shape and influence our nation's healthcare system including the Department of Health and Human Services and many of its divisions such as FDA, CMS, ASPE, ASPR, BARDA and with other federal agencies such as the FTC, GAO, and OMB.

This hearing on the state of drug and medical supply chains, both before and during the COVID-19 pandemic, is very timely. We can examine "How could we have been better prepared to face the challenges that a global pandemic has placed on our healthcare system?" We can evaluate the nation's response to the pandemic as it unfolded and any vulnerabilities that were exposed in the supply chains that we depend upon for the very health and viability of this nation and its people. And, we can look for lessons learned or opportunities to improve the infrastructure of our medical supply chains so that they will be strong, resilient and effective at meeting the public health needs of our society in the face of future pandemics or other serious threats and challenges.

State of the Drug Supply Chain Prior to the Pandemic

First, let me ask a rhetorical question of everyone here. Is there anyone who has never been sick a day in their life? Is there anyone who has never needed or taken a prescription medication in their lifetime? It is hard to imagine someone living in America today who has not needed, taken, or benefited from the valuable medications that we have available today in modern medicine. In other words, there is a universal demand for prescription drugs—virtually everyone needs prescription drugs at some point in their life. The availability of, and access to critical medications is a necessity—not merely a consumer preference or a luxury good. Access to prescription drugs is a foundational component of an effective healthcare system.

Americans have come to count on critical and essential medications for serious and life-threatening diseases such as diabetes, chronic heart disease, asthma, epilepsy, and cancer. We expect that these essential medications will be available at the local hospital or at a nearby community pharmacy when they are needed. However, drug shortages have been, and still 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 at times counterproductive."[1] Drug shortages have been attributed to a variety of factors including unexpected demand surges; manufacturing difficulties; quality problems and recalls; supply and logistic disruptions; low prices for older, well-established generic drugs due to 'over-competition'; market manipulation by various stakeholders; and other factors.[2]

For more than two decades, there has been a substantial number of drug shortages in the U.S. market.[3,4] Both the FDA and the American Society of Health System Pharmacists (ASHP) track and report on drug shortages.[56] ASHP reports that there have been more than 170 drugs in shortage at any point in time since 2014. Many of these drugs in shortage are essential or critical medicines that mean life or death to a specific patient. The drugs in short supply are often older, well-established medications that are generically available at a relatively low cost and many of the shortages have been for sterile injectables.

For some reason, the market has failed to support a sustainable presence and availability of these drugs. While economists would say that "in the long-run these market conditions will resolve themselves", to the patient who needs a life-saving drug in the next few hours or days, very serious consequences—or even death—are virtually certain in the short-run. For example, vincristine—a life-saving drug for certain pediatric cancer patients—was in severe shortage late in 2019.[7,8] For the children who needed

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[1] Schondelmeyer S, Siefert J, Margraf D, et al, COVID-19: The CIDRAP Viewpoint, Part 6: Ensuring a Resilient US Prescription Drug Supply, October 21, 2020, available on the Resilient Drug Supply Project website at: https://www.cidrap.umn.edu/rds or directly at: https://www.cidrap.umn.edu/sites/default/files/public/downloads/cidrap-covid19-viewpoint-part6.pdf

[2] FDA. Drug Shortages: Root Causes and Potential Solutions. Report. Oct 2019.

[3] FDA. Drug Shortages, Oct 2019.

[4] Fox ER, Birt A, James KB, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 2009 Aug 1;66 (15):1399-406; and, ASHP website: https://www.ashp.org/Drug-Shortages/Current-Shortages.

[5] FDA reported drug shortages can be found at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

[6] ASHP reported drug shortages can be found at: https://www.ashp.org/Drug-Shortages/Current-Shortages

[7] Nelson R, 'Complete Disruption' of Supply of Essential Pediatric Chemo, Medscape, Oct 18, 2019; or, https://www.medscape.com/viewarticle/920039

[8] American Childhood Cancer Organization, The Vincristine Drug Shortage: A Medical Crisis for Childhood Cancer Families, November 23, 2019, available at: https://www.acco.org/blog/the-vincristine-drug-shortage-update/

vincristine at that time, they suffered because the drug was not there, at any cost, when they needed it.

The drug shortage situation, even before the pandemic, was in need of a policy re-set. First, *many appear to have accepted that drug shortages are an endemic problem that will always be with us and there is not much that we can, or should, do about them*. They acknowledge that we can track drug shortages and work to resolve them after they have happened. This 'fail and fix' framework does have some value, but it means society will have an ongoing residual of drugs in short supply and patients who cannot get the critical life-saving medications that they need. Instead, *we should adopt a paradigm that assumes that elimination of all drug shortages is possible. This new approach should focus on a 'predict and prevent' paradigm*.

Second, *the current definitions of drug shortages are useful, but they lead to an underestimation of the scope, magnitude and cost of drug shortages.*[9,10] For example, 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."[11] This definition is useful, but incomplete because it characterizes a drug shortage as a market-wide economic problem, but does not recognize the impact of drug shortages on individual patients. 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."[12] This definition is also useful, but it frames drug shortages primarily as a supply and work flow issue. We need to develop a new more comprehensive definition of drug shortages that recognizes drug shortages as a continuum. Certainly when no one in the market has access to a needed drug there is a shortage, but also when even one patient does not have a critical and needed drug that patient has a drug shortage. *A needed drug that one does not have is neither safe nor effective*.

Two changes in the policy framework are urgently needed: (1) drug shortages should be viewed as a critical situation in which the total number of drug shortages can be substantially reduced or even eliminated; and (2) drug shortages should be re-defined to acknowledge that drug shortages exist along a continuum for just one patient who does not have the drug to a point where no patients have the drug. When even one patient who does not have a drug that is needed, it constitutes a drug shortage; and, we need to develop metrics to quantify and estimate the impact of all such drug shortages.

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[9] Institute for Safe Medication Practices. Drug shortages continue to compromise patient care. Jan 11, 2018.

[10] Shaban H, Maurer C, Willborn RJ. Impact of drug shortages on patient safety and pharmacy operation costs. Fed Pract 2018 Jan;35 (1):24-31.

[11] FDA. Drug Shortages, Oct 2019.

[12] Fox ER, et al. ASHP guidelines. Am J Health Syst Pharm 2009 Aug 1;66 (15):1399-406.

Impact of the Pandemic on the Drug Supply Chain

The COVID-19 pandemic has had a monumental impact on the daily life of people around the world. The medical and drug supply chains have not escaped this global impact. The drug supply chain experienced a triple play during the first year of the pandemic: (1) increased demand, (2) disrupted and decreased supply, and (3) exposure of systemic vulnerabilities.

Increased Demand

Covid-19 caused demand surges due to a rise in infected cases that impacted various geographic regions quite differently and at different times. 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 demand for 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 (i.e., cisatracurium), 20-fold (i.e., hydroxychloroquine) or even 40-fold (i.e., tocilizumab). Such explosive growth in critical acute drug use was seen in March and April of 2020 when the number of hospitalizations and critical care COVID-19 patients in New York and New Jersey skyrocketed. In part, the geographic and timing differences of surges helped mitigate some of the impact. If all states would have had the same kind of surge as New York and New Jersey, at the same time, the U.S. would have had more shortages of medical and drug supplies and those shortages would have been much more severe.

As the number of COVID-19 cases grew the healthcare system was stressed by increased hospital admissions, ICU care, ventilator usage, and deaths. Shortages were experienced with various products and services such as personal protective equipment like masks and gowns or with medical devices such as ventilators. Some hospitals adapted to the expected increase in COVID-19 hospitalizations by delaying or cancelling elective surgeries during April and May of 2020. While this adjustment in hospitalizations did help keep hospital and ICU beds open for COVID patients, and it reduced the demand for drugs such as the paralytics and sedatives used by patients receiving ventilation, those patients whose surgeries were delayed did experience the downstream ripple effect of postponed or foregone healthcare. Public health experts need to sort out the role and impact of various actions such as diagnostic testing, mask-wearing, social distancing, isolation and lockdowns, mandates, and other mitigation strategies.

The demand side for drugs saw dramatic U.S. and worldwide increases in certain therapies for COVID-19. Shortages of critical drugs used in treating COVID-19 patients have included propofol, albuterol, midazolam, hydroxychloroquine, cisatracurium, rocuronium, fentanyl, azithromycin, vancomycin, and others. In fact, among 40 critical

COVID-19 drugs identified by the Resilient Drug Supply Project (RDSP) (see Appendix A), 70% of them (28 of 40) were in short supply as recently as the end of January 2021 according to the ASHP drug shortage list.[13] The US FDA, with more stringent criteria for declaring a shortage, showed 40% (16 of 40) of the RDSP critical COVID-19 drugs in shortage at the same time.[14] Both of these drug shortage rates are unacceptable whether in times of a pandemic or not.

Oxygen is another medical supply that experienced increased demand and, in some cases, extreme shortages. Oxygen has a very unique production and distribution system that is different from the traditional drug distribution and supply market. There are many producers and suppliers in regional and local markets, as opposed to a few large producers serving a national market for traditional pharmaceuticals. There are about 36,000 firms registered with the FDA as oxygen manufacturers with businesses located in all 50 states as well as the District of Columbia and the U.S. territories.

Disrupted and Decreased Supply

COVID-19 jolted the global pharmaceutical market at all levels and production points. The supply side was disrupted by factory closures, shipping delays or shutdowns, and trade limitations or export bans. As described in an overview[15] (see Appendix B) of the impact of the pandemic on the drug supply market, we saw stay-at-home orders and factory lockdowns in China,[16] followed by shipping port slowdowns and shutdowns.[17] 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.[18,19] 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.[20] 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

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[13] ASHP. Current Drug Shortages: Drug Shortages and Management, https://www.ashp.org/Drug-Shortages/Current-Shortages.
[14] FDA. FDA Drug Shortages, https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.
[15] Schondelmeyer et al, Ensuring a Resilient US Prescription Drug Supply, October 21, 2020.
[16] Yap CW. China's factories struggle to resume operations after coronavirus shutdown. Wall Street Journal. Feb 8, 2020.
[17] Saul J, Baertlein L. China's coronavirus disrupts global container shipping trade. Reuters. Feb 6, 2020.
[18] Schurder G. Hubei vs. COVID-19: an in-depth focus on expected pharmaceutical supply chain disruptions & drug shortages, Supply Chain Channel. Mar 3, 2020.
[19] FDA. FDA Resources for Data Standards: Business Operations.
[20] Chandna H. India to curb export of antibiotics, vitamins as coronavirus crisis hits supplies from China. The Print. Feb 20, 2020.

finished drug products to prevent shortages in India.[21] 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.[22] India later prohibited the export of hydroxychloroquine because domestic stocks were running low and it wanted to first fulfill its own requirements.[23] 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.[24] China hinted in March (2020) that it might impose export controls on shipments of life-saving drugs to the US market, though it did not take that step.[25] This threat is particularly concerning 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.[26]"

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.[27] Italy, however, was hit early and hard by COVID-19 cases,[28,29] and, by early March, it had stopped all commercial activity (including drug factories) except for retail pharmacies and super markets, disrupting this alternate source.[30] 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.[31] 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.[32]

Drug Supply Chain Vulnerabilities Exposed by the Pandemic

The pandemic has exposed many of the vulnerabilities in the US drug supply chain. Among the vulnerabilities of the U.S. drug supply chain are: (1) heavy dependence upon foreign sources for drug production; (2) old factories, equipment and out-dated

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[21] PTI, BloombergQuint. India restricts drug exports as threat of coronavirus rises. Mar 3, 2020.
[22] PTI, BloombergQuint. India restricts drug exports as threat of coronavirus rises. Mar 3, 2020.
[23] Ghangurde A. India bars exports of hydroxychloroquine with some exceptions, Pink Sheet. Mar 25, 2020.
[24] Wallace D. UK blocks 82 from parallel export. Generics Bulletin, Mar 20, 2020.
[25] Chakraborty B. China hints at denying Americans life-saving coronavirus drugs, Fox News, Mar 19, 2020.
[26] Harris G, Palmer AW. China has near-total control of the world's antibiotic supply. Is America at risk as a result? STAT, Apr 28, 2020.
[27] Eurostat. EU production and trade of antibiotics. Nov 18, 2019
[28] Amante A, Balmer C. Coronavirus outbreak grows in northern Italy, 16 cases reported in one day. Reuters. Feb 21, 2020.
[29] Coronavirus. Colpite tutte le regioni. La Protezione civile: ecco i numeri aggiornati (in Italian). Mar 5, 2020.
[30] Sylvers E, Legorano G. Italy hardens nationwide quarantine. Wall Street Journal. Mar 11, 2020.
[31] Henely J, Jones S. Do not let this fire burn: WHO warns Europe over COVID-19. The Guardian. Mar 13, 2020.
[32] Roos R. Experts say COVID-19 will likely lead to US drug shortages. CIDRAP News. Mar 27, 2020.

manufacturing processes; (3) chronic quality problems in certain sectors (i.e., sterile injectables); (4) challenges with inspection and quality control in foreign manufacturing facilities; (5) a shift from in-house manufacturing to a general contractor model of drug production; (6) geographic and economic concentration in certain markets; (7) lack of visibility into the upstream market by policymakers and key stakeholders; (8) a focus on just-in-time inventory control rather than surge management with slack resources for resilience; (9) misaligned regulatory and economic incentives in the pharmaceutical market; and (10) lack of a coordinated policy approach to the pharmaceutical market at the national level.

While emergence of the COVID-19 pandemic in early 2020 severely stressed the US drug supply chain, on balance the drug supply chain showed considerable overall strength and resilience.[33,34] However, many of the vulnerabilities of the drug supply chain need to be improved to avoid future consequences from challenges to the drug supply chain.

The Resilient Drug Supply Project

The University of Minnesota's Center for Infectious Disease Research and Policy (CIDRAP) embarked on a Resilient Drug Supply Project (RDSP) in October 2018.[35] The mission of the RDSP is "to focus on the global supply chain for each prescription drugs used in the U.S. healthcare market in order to reduce or avoid drug shortages due to increased demand or disruptions from any cause and for any reason." The RDSP has 8 broad and ambitious goals (see Appendix C) including: (1) define critical acute drugs; (2) define critical chronic drugs; (3) assess the consequences of drug shortages; (4) map the entire U.S. drug supply chain; (5) develop a model, or models, to predict drug shortages; (6) use predictive modeling and other methods to prevent drug shortages; (7) develop response plans to mitigate challenges to the drug supply and to manage drugs shortages that do occur; and (8) evaluate and understand future trends expected in the pharmaceutical market to develop and facilitate policy directions that will reduce or eliminate drug shortages.

One of the first tasks for the RDSP was development of a list of Critical Acute Drugs. We used an expert panel process to define this term. Critical Acute Drugs were defined as: "Drugs 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

[33] Healthcare Distribution Alliance, Rising to the Challenge: How Distributors Are Supporting a Resilient Pharmaceutical Supply Chain During COVID-19., 2021; available at: https://healthdelivered.org/wp-content/uploads/2021/01/Rising-to-the-Challenge.pdf.

[34] Healthcare Distribution Alliance, The First 90 Days: US Biopharmaceutical Finished Goods Supply Chain Response to COVID-19, 2020.

[35] This RDSP project has been generously funded by a member of the Walton Family Foundation.

disability or death." Absence of a Critical Acute Drug, or lack of availability of an effective substitute, may also cause serious health outcomes or limited ability to provide humane care." A total of 156 drug molecules were designated as Critical Acute Drugs. These 156 drug molecules account for nearly 20,000 actively marketed drug products (at the NDC level[36]) in the U.S. market.

The 156 Critical Acute Drugs were compared against the FDA and ASHP drug shortages list to determine how many of these critical drugs were in shortage. We found that 38.5% of them (60 of 156) were in short supply as recently as the end of January 2021 according to the ASHP drug shortage list.[37] The US FDA, with their more stringent criteria for declaring a shortage, showed 24.4% (38 of 156) of the RDSP critical acute drugs were in shortage at the same time.[38] Both of these drug shortage rates are unacceptable whether in times of a pandemic or not.

The RDSP is using publicly available data from FDA and various commercial sources to map the supply chain for each unique drug product identified in the market. We have started by mapping the NDCs for the 156 critical acute drugs. In particular, we are focusing on the upstream drug supply map because it is the source of many issues that lead to drug shortages, yet it is the most opaque part of the supply chain.

The diagram in Figure 1 below illustrates a simplified version of the drug supply chain. Basically, the dividing point for upstream and downstream is the point at which a drug product has been approved by the FDA for marketing, assigned an NDC number, and is physically in the U.S. and ready for shipment to wholesalers, pharmacies, or other qualified purchasers. While there are some issues in the downstream supply chain that may result in shortages, most drug shortages are the result of things that happen in the upstream supply chain such as quality issues, shipping delays, raw material shortages, geopolitical and economic issues, and other factors.

While most stakeholders know quite a lot about the downstream flow of prescription products, they know very little about the upstream market. If a food-born infection event occurs, the CDC and FDA can track the food supply back to the farm where the food was grown and harvested. Most imported food products bear the country of origin on the consumer label so that the consumer can weigh the risks and value of food products from other markets in the world. For a pharmaceutical product there is usually one company name on the label, but that company is typically only the marketer or distributor and not the actual manufacturer who made and prepared the drug product.

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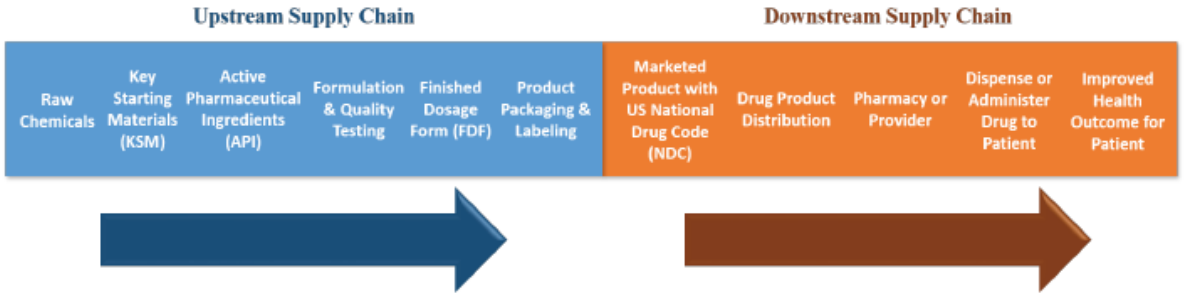
[36] The National Drug Code (NDC) is a unique code given to each drug product similar to the bar code used on items one would purchase at a store. Each unique NDC code specifies a certain drug molecule, dosage form, strength, package size and type and manufacturer or marketer.

[37] ASHP. Current Drug Shortages: Drug Shortages and Management, https://www.ashp.org/Drug-Shortages/Current-Shortages.

[38] FDA. FDA Drug Shortages, https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

Furthermore, the label rarely discloses where the active ingredient was formulated or where the final dosage form of the drug product was prepared. One should ask why don't drug products bear 'country of origin' labeling like food, clothing, appliances, automobiles, and many other consumer goods.

Figure 1



Findings from Mapping the Upstream Drug Supply Chain

Once the RDSP began building the upstream supply map for drug products, we began to look at the patterns based on country of origin for the active pharmaceutical ingredient (API) and the finished dosage form (FDF). Data for our mapping process have come from many sources including the FDA structured product labeling data set and Daily Med profiles, drug product labeling images, FDA NDC listing, FDA approved drugs, the FDA Orange Book and other FDA sources. Although the FDA has a lot of information on specific drug products and much of it is made public through the FDA web site, the information disclosed is not always complete, it is sometimes disjointed and the data across different files often cannot be combined or linked due to inadequate identifiers. Other data sources include shipping data, import-export records, commercial prescription utilization and pricing databases, and pharmaceutical trade and news sources. Selected findings from the RDSP are shown in Appendix D.

First, we examined 30 of the top brand name drugs in the U.S. market. Here is what we found:

- All of the FDA sponsors for these 30 brand name drugs appeared to be U.S. based companies, although many were U.S. subsidiaries of foreign parent companies;
- All, or nearly all, of the marketers and distributors appeared to be U.S. based companies or U.S. subsidiaries of foreign parent companies;
- From the downstream perspective nearly all of the drug products in the U.S. market appeared to be U.S. products;
- When we looked upstream only 20% (6 of 30) NDCs were finished drug products made in the United States; .and, 4 of those 6 were made in Puerto Rico;
- 80% of the finished brand name drug products were made outside of the U.S.;

- Further upstream, only 10% (3 of 30) brand name drug products had API that was made in the U.S. while 90% (27 of 30) were made in foreign countries;
- The foreign countries where the top brand name drugs were made were nearly all in Europe with the exception of one product made in Mexico.

Next, we examined 30 of the top generic drugs in the U.S. market. This time we found:

- All of the FDA sponsors for these 30 generic drugs appeared to be U.S. based companies, although many were U.S. subsidiaries of foreign parent companies;
- All, or nearly all, of the generic marketers and distributors appeared to be U.S. based companies or U.S. subsidiaries of foreign parent companies;
- From the downstream perspective nearly all of the generic drug products in the U.S. market appeared to be U.S. products;
- When we looked upstream 80% (24 of 30) generic NDCs had finished drug products with foreign or unknown sources;
- Further upstream, 90% (27 of 30) generic drug products had API that was from foreign or unknown sources, while only 10% (3 of 30) were made in the U.S.;
- The foreign countries where the top generic drugs were made were nearly all in from India with 4 from Canada.

We examined one of the Critical Acute Drugs (Atracurium injection) and found that:

- Atracurium comes from 5 different sources with each source producing 2 NDCs.
- The downstream marketers and distributors all appear to be U.S. based companies or U.S. subsidiaries of foreign companies.
- These appear to be U.S. made drug products based on the downstream information.
- 2 of the NDCs were packed and labeled in India and the other 8 NDCs were from a source of unknown origin.
- The finished dosage form for 4 of the 10 NDCs were made in China and another 4 of the 10 NDCs were made in India, while 2 NDCs were from a source of unknown origin.
- The source of the active pharmaceutical ingredient was not disclosed for any of the 10 NDCs.

Critical Acute Drug (CA 005): Atracurium Besylate

Resilient Drug Supply Project, CIDRAP, University of Minnesota

	Critical Drug #	CA005	CA005	CA005	CA005	CA005	CA005	CA005	CA005	CA005	CA005
	NDC #	00409-1105	00409-1109	25021-0659	25021-0672	55150-0216	55150-0217	71288-0701	71288-0702	67457-0698	67457-0699
	Product	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium	Atra-curium
	Drug Firm	Hospira, Inc.	Hospira, Inc.	Sagent Pharmaceuticals	Sagent Pharmaceuticals	AuroMedics PharmaLLC	AuroMedics PharmaLLC	Meitheal Pharmaceuticals Inc.	Meitheal Pharmaceuticals Inc.	Mylan Institutional	Mylan Institutional
Up Stream Supply Chain	Key Starting Materials	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	API Manufacture	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Finished Drug Manufacture	India	India	China	China	India	India	China	China	NR	NR
	Pack & Label Pack & Label	India	India	NR	NR	NR	NR	NR	NR	NR	NR
Down Stream Supply Chain	FDA Sponsor (BLA | NDA | ANDA)	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
		ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA
	Manufactured for:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Marketed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Distributed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Whlse & GPO Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Pharmacy Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Patient	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA

USA
USA-Puerto Rico
No. America (Mexico & Canada)
Europe
Asia
India
Not Reported

Overall, we found that the top prescribed, and used, U.S. drug products, both brand and generic, are heavily dependent upon foreign sources for both the finished dosage form and the active pharmaceutical ingredients.

While production of pharmaceuticals in foreign countries is not necessarily a bad thing, there are several forces that raise questions about the level of dependence on foreign sources for the U.S. drug supply. Historically, the FDA has not been able to inspect foreign based plants with either the frequency or the candor that has been used when inspecting U.S. plants. There may be more concerns with quality in foreign-based plants that do not have the same level of regulatory oversight. Second, when drug products are coming from other countries there are more opportunities for logistical and shipping delays, as well as product damage in transit. Third, our dependence on other countries can provide those countries with opportunities for political and economic leverage on the United States. Depending upon the philosophy, ethics, and politics of other countries who grow to be in a dominant position for certain drug categories, the United States could find itself held hostage economically or politically over essential drugs.

This data showing that we are heavily dependent upon foreign sources for our domestic prescription drug supply. The re-shoring of some pharmaceutical production may be beneficial economically and logistically. However, we must also remember that diverse geographic locations for supply may be more resilient if specific events affect a certain

geographic region such as Hurricane Maria that devastated Puerto Rico in 2017 and disrupted the flow of large volume parenterals in the United States.

Recommendations for Moving the Drug Supply Chain Beyond the Pandemic

The United States should have a process and infrastructure for analyzing, predicting, managing, and preventing shortages of critical medications. Currently, the U.S. does not have a coordinated effort to establish market-wide policy for the pharmaceutical market even though pharmaceuticals account for about 4% of the entire economy. While the FDA does have authority for regulating the safety and effectiveness of drug therapy, it does not have authority to assess or act on economic or market-based factors. The FDA does engage in substantial effort related to managing drug shortages. However, other government agencies often do not have access to the FDA data for operational or policy analysis. This fact became clear early in the pandemic as multiple federal and state agencies were scrambling to find information on the drug supply, how to anticipate what was ahead, and how to manage it to best mitigate drug shortages. To be fair, there was, and is, no silver bullet that could have quickly and easily protected the U.S. drug supply chain once the pandemic emerged. However, the ability to share drug-related data across federal agencies such as FDA, HHS, DHS, FEMA, BARDA, ASPE, ASPR, VA, TRICARE, and others could have been made more clear and could have been clearly authorized by Congress.

An in-depth map of the U.S. drug supply is needed and should be maintained on an ongoing basis to facilitate planning for, and management of, market distorting events such as pandemics, weather events, man-made disasters, political and hostile threats and other situations that may arise.

Congress should authorize and fund a national entity to: (1) build and maintain the U.S. drug supply map; (2) make the drug supply chain more transparent and the quality of drug products more visible; and (3) coordinate development of relevant national policy to reduce and eliminate drug shortages and to strengthen and improve the resilience of the U.S. drug supply as it faces future threats of all kinds. This national effort could be either a new entity or a re-tasking of an existing entity. The United States Pharmacopeial Convention is an independent, scientific and non-profit entity with a 200 year history of collaborating with government and the private market to improve the quality of drug therapy and outcomes. This history provides USP with a unique and intriguing position that could coordinate a public-private effort to address elimination and reduction of drug shortages. If a new entity was to be created, Congress may establish a new NIH National Institute for Pharmaceutical Resilience or it could create a quasi-governmental body such as the Prescription Drug Policy Review Commission in a manner similar and parallel to the Medicare Payment Advisory Commission (MedPAC). If an existing agency is to be tasked with this new focus, the possible candidates would

include the National Institutes of Health (NIH), the Food & Drug Administration (FDA), or the National Library of Medicine.

Establish an ongoing research program on resilience of the US drug supply chain to include, but not be limited to: (1) development of a sentinel system that can predict and prevent supply chain disruptions; (2) reduce or eliminate drug shortages; and (3) coordinate a national response to drug shortages if they do happen.

In summary, drug shortages were here before the pandemic and they will still be here as we move beyond the pandemic. The efforts to track and mitigate drug shortages over the past decade have had a marginal impact, but drug shortages have not been substantially reduced in recent years, and drug product quality concerns are precipitating more widespread drug recalls (e.g., valsartan, ranitidine, and metformin). Continuing the status quo may threaten 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, other federal entities, and industry stakeholders, the U.S. pharmaceutical market can significantly reduce or eliminate drug shortages. Only then can we ensure a resilient supply of needed medications for the American population.

Appendix A

Resilient Drug Supply Project:
Critical Acute Drug List & Critical COVID-19 Drug List
Drug Shortages Reported by ASHP & FDA
Shortages as of
5-9-2021

Resilient Drug Supply Project:
Critical Acute Drug List & Critical COVID-19 Drug List
Drug Shortages Reported by ASHP & FDA

					Shortages as of 5/9/2021	
			UMN RDSP	UMN RDSP	ASHP	FDA
Drug #	Critical Acute Drugs Generic Name	Drug Category	List of 156 Critical Acute Drugs	List of 40 Critical COVID-19 Drugs	Drug Shortage List	Drug Shortage List
1	Cisatracurium	Paralytic	X	X	Yes	Yes
2	Rocuronium	Paralytic	X	X	Yes	
3	Vecuronium	Paralytic	X	X	Yes	Yes
4	Succinylcholine	Paralytic	X	X		
5	Atracurium	Paralytic	X			
6	Propofol	Sedation	X	X	Yes	Yes
7	Midazolam	Sedation	X	X	Yes	Yes
8	Lorazepam	Sedation	X	X	Yes	Yes
9	Dexmedetomidine	Sedation/Anesthesia	X	X	Yes	Yes
10	Phenobarbital	Sedation	X			
11	Ketamine	Sedation/Anesthesia	X	X	Yes	Yes
12	Diazepam	Sedation	X			
13	Lidocaine	Local Anesthetic	X		Yes	Yes
14	Bupivacaine	Local Anesthetic	X		Yes	Yes
15	Fentanyl	Pain	X	X	Yes	Yes
16	Hydromorphone	Pain	X	X	Yes	Yes
17	Morphine	Pain	X	X	Yes	Yes
18	Oxycodone	Pain	X	X		
19	Acetaminophen	Pain & Fever	X			
20	Ketorolac	Pain	X		Yes	Yes
21	Anakinra	Pain	X			
22	Oxygen	Medical Gas	X	X		
23	Nitric Oxide	Medical Gas	X			
24	Sevoflurane	Medical Gas	X			
25	Albuterol	Bronchodilator	X	X	Yes	
26	Ipratropium (Inhaler)	Bronchodilator	X			
27	Azithromycin	Anti-infective	X	X	Yes	Yes
28	Piperacillin-Tazobactam	Anti-infective	X	X		
29	Cefepime	Anti-infective	X	X	Yes	
30	Ceftriaxone	Anti-infective	X			
31	Vancomycin	Anti-infective	X	X	Yes	
32	Doxycycline	Anti-infective	X			
33	Meropenem	Anti-infective	X	X		
34	Cefazolin	Anti-infective	X	X	Yes	Yes
35	Levofloxacin	Anti-infective	X			
36	Linezolid	Anti-infective	X			
37	Ampicillin-Sulbactam	Anti-infective	X		Yes	
38	Sulfamethoxazole-Trimethoprim	Anti-infective	X			
39	Ceftazidime	Anti-infective	X	X	Yes	
40	Ciprofloxacin	Anti-infective	X			
41	Clindamycin	Anti-infective	X		Yes	
42	Gentamicin	Anti-infective	X		Yes	
43	Imipenem	Anti-infective	X			
44	Metronidazole	Anti-infective	X			
45	Ampicillin	Anti-infective	X			
46	Nafcillin	Anti-infective	X			
47	Oxacillin	Anti-infective	X			
48	Penicillin G	Anti-infective	X			
49	Tobramycin	Anti-infective	X			
50	Amphotericin B	Anti-infective	X			
51	Posaconazole	Antifungal	X			

Resilient Drug Supply Project
University of Minnesota

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

PRIME Institute
University of Minnesota

Drug #	Critical Acute Drugs Generic Name	Drug Category	UMN RDSP List of 156 Critical Acute Drugs	UMN RDSP List of 40 Critical COVID-19 Drugs	ASHP Drug Shortage List	FDA Drug Shortage List
52	Ganciclovir (IV)	Antiviral	X			
53	Highly Active Anti-Retroviral Therapies**	Antiviral	X			
54	Hydroxychloroquine	Antiviral (Lupus, RA)	X	X	Yes	
55	Chlorhexidine	Antiseptic	X	X		
56	Betadine	Antiseptic	X			
57	Ethanol	Antiseptic	X			
58	Norepinephrine	Vasopressor	X	X	Yes	
59	Epinephrine	Vasopressor	X	X	Yes	Yes
60	Vasopressin	Vasopressor	X	X		
61	Phenylephrine	Vasopressor	X			
62	Amiodarone	Cardiovascular	X	X	Yes	
63	Hydralazine	Cardiovascular	X		Yes	Yes
64	Nicardipine	Cardiovascular	X			
65	Labetalol	Cardiovascular	X		Yes	
66	Metoprolol	Cardiovascular	X		Yes	
67	Esmolol	Cardiovascular	X			
68	Verapamil	Cardiovascular	X		Yes	
69	Diltiazem	Cardiovascular	X		Yes	Yes
70	Atropine	Cardiovascular	X		Yes	Yes
71	Adenosine	Cardiovascular	X			
72	Epoprostenol	Pulmonary Vasodilator	X			
73	Bosentan	Pulmonary Vasodilator	X			
74	Milrinone	Pulmonary Vasodilator	X			
75	Dexamethasone	Corticosteroids	X		Yes	Yes
76	Methylprednisolone	Corticosteroids	X			
77	Hydrocortisone	Corticosteroids	X		Yes	Yes
78	Betamethasone	Corticosteroids	X		Yes	
79	Prednisone	Corticosteroids	X		Yes	
80	Furosemide	Diuretic	X		Yes	Yes
81	Potassium chloride (IV)	Electrolyte Replacement	X			
82	Magnesium (IV)	Electrolyte Replacement	X		Yes	
83	Calcium chloride	Electrolyte Replacement	X	X		
84	Calcium gluconate	Electrolyte Replacement	X		Yes	Yes
85	Calcium carbonate	Electrolyte Replacement	X			
86	Sevelamer carbonate	Electrolyte Replacement	X			
87	Sodium bicarbonate	Electrolyte Replacement	X		Yes	Yes
88	Phosphorous	Electrolyte Replacement	X			
89	Zinc	Electrolyte Replacement	X			Yes
90	Sodium chloride (0.9%, 3%, 5%)	Electrolyte & Fluids	X		Yes	Yes
91	Lactated Ringers	Electrolyte & Fluids	X			
92	Dextrose (50%)	Electrolyte & Fluids	X			
93	Anticoagulant Citrate Dextrose Solution A	Electrolyte & Fluids	X			
94	Hemodialysis, Intermittent (IHD) Solution	Electrolyte & Fluids	X			
95	Peritoneal Dialysis (PD) Solution	Electrolyte & Fluids	X			
96	Renal Replacement Therapy, Continuous (CRRT)	Electrolyte & Fluids	X			Yes
97	Organ Preservation Solution	Electrolyte & Fluids	X			
98	Enoxaparin	Anticoagulant	X	X	Yes	
99	Heparin	Anticoagulant	X	X	Yes	Yes
100	Argatroban	Anticoagulant	X	X	Yes	
101	Tissue Plasminogen Activator (TPA)	Anticoagulant	X			
102	Warfarin	Anticoagulant	X			
103	Prothrombin complex conc. (Kcentra)	Warfarin Reversal	X			
104	Vitamin K (phytonadione)	Warfarin Reversal	X			
105	Insulin, Short acting- Regular (aspart)	Insulin & Endocrine	X			
106	Insulin, Long acting (Lantus, NPH)	Insulin & Endocrine	X			

			UMN RDSP	UMN RDSP	ASHP	FDA
Drug #	Critical Acute Drugs Generic Name	Drug Category	List of 156 Critical Acute Drugs	List of 40 Critical COVID-19 Drugs	Drug Shortage List	Drug Shortage List
107	Desmopressin Acetate (DDAVP)	Insulin & Endocrine	X		Yes	Yes
108	Glucagon	Insulin & Endocrine	X			
109	Valproate sodium	Anti-epileptic	X		Yes	Yes
110	Carbamazepine	Anti-epileptic	X			
111	Fosphenytoin	Anti-epileptic	X			
112	Levetiracetam	Anti-epileptic	X		Yes	
113	Phenytoin	Anti-epileptic	X		Yes	
114	Antivenom, Snake (CroFab)	Antidote	X			
115	Antivenom, Spider	Antidote	X			
116	Dantrolene	Antidote	X			
117	Diphenhydramine	Antidote	X			
118	Epinephrine (EpiPen, auto-injector)	Antidote	X		Yes	Yes
119	Levocarnitine	Antidote	X			
120	Lipid emulsion (IV)	Antidote	X			
121	Methylene Blue	Antidote	X			
122	N-acetylcysteine	Antidote	X		Yes	
123	Naloxone	Antidote	X			
124	Neostigmine	Antidote	X			
125	Protamine	Antidote	X		Yes	Yes
126	Rabies Vaccine IG	Antidote	X			
127	Sugammadex	Antidote	X			
128	Tetanus toxoid	Antidote	X			
129	Vitamin B12 (hydroxocobalamin)	Antidote	X		Yes	Yes
130	Immune globulin (IV)	Immunodeficiency	X		Yes	
131	Epoetin	Blood Modifier	X			
132	Granulocyte-Colony Stimulating Factor (GSCF)	Blood Modifier	X			
133	Granulocyte-Macrophage Colony- Stimulating Factor	Blood Modifier	X			
134	NPEG-Granulocyte-Colony Stimulating Factor (NPEG-GSCF)	Blood Modifier	X			
135	Blood Factor IX	Hemophilia	X			
136	Blood Factor VII	Hemophilia	X			
137	Blood Factor VIII	Hemophilia	X			
138	Anti-inhibitor coagulant complex (FEIBA)	Hemophilia	X			
139	Tranexamic Acid	Hemophilia	X			
140	Mycophenolate Mofetil (MMF)	Immunosuppressant	X		Yes	
141	Tacrolimus	Immunosuppressant	X		Yes	Yes
142	Cyclophosphamide (CHOP regimen)	Lymphoma / Leukemia	X			
143	Doxorubicin (CHOP regimen)	Lymphoma / Leukemia	X		Yes	
144	Mechlorethamine (MOPP regimen)	Lymphoma / Leukemia	X			
145	Procarbazine (MOPP regimen)	Lymphoma / Leukemia	X			
146	Vincristine (CHOP, MOPP regimen)	Lymphoma / Leukemia	X			
147	Ondansetron (oral & inj)	Anti-emetics	X		Yes	Yes
148	Prochlorperazine	Anti-emetics	X		Yes	
149	Metoclopramide	Anti-emetics	X			
150	Methylergonovine	Pregnancy-related Medication	X			
151	Oxytocin	Pregnancy-related Medication	X			Yes
152	Surfactants	Pregnancy-related Medication	X			
153	Terbutaline	Pregnancy-related Medication	X			
154	Fluoxetine	Anti-psychotic	X			
155	Haloperidol	Anti-psychotic	X		Yes	
156	Olanzapine	Anti-psychotic	X			

Drug #	Critical Acute Drugs Generic Name	Drug Category	UMN RDSP List of 156 Critical Acute Drugs	UMN RDSP List of 40 Critical COVID-19 Drugs	ASHP Drug Shortage List	FDA Drug Shortage List
Additional Critical Drugs for Treatment of COVID-19 Patients						
C1	Remdesivir*	Other Critical COVID-19 Drugs		X	Yes	Yes
C2	Lopinavir-Ritonavir	Other Critical COVID-19 Drugs		X		
C3	Oseltamivir	Other Critical COVID-19 Drugs		X		
C4	Chloroquine	Other Critical COVID-19 Drugs		X	Yes	
C5	Droperidol	Other Critical COVID-19 Drugs		X	Yes	
C6	Etomidate	Other Critical COVID-19 Drugs		X		
C7	Fluconazole	Other Critical COVID-19 Drugs		X		
C8	Vitamin C	Other Critical COVID-19 Drugs		X		
		# of Drugs on Critical List	156	40		
		# of Drugs in Shortage (ASHP)	60	27	63	
		% of Drugs in Shortage (ASHP)	**38.5%**	**67.5%**		
		# of Drugs in Shortage (FDA)	36	15		37
		% of Drugs in Shortage (FDA)	**23.1%**	**37.5%**		

Resilient Drug Supply Project (RDSP)

The Resilient Drug Supply Project is a research program of the University of Minnesota's CIDRAP and the PRIME Institute.
The RDSP has been funded by a generous gift from the Walton Family Foundation

UMN RDSP List of 156 Critical Acute Drugs

Critical Acute Drugs are drugs 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. Absence of a Critical Acute Drug, or lack of availability of an effective substitute, may cause serious health outcomes or limited ability to provide humane care."
Source of Critical Acute Drug List: Created by an expert panel convened by the Univ, of Minnesota's RDSP on December 11 & 12, 2018.
Participating experts came from government, academia, and the private sector and represented the fields of pharmacy, medicine, nursing, public health, others in clinical health care, pharmaceutical supply chains, emergency preparedness and response, emergency medical services, and drug distribution.

UMN RDSP List of 40 Critical COVID-19 Drugs

Critical COVID-19 Drugs: drugs used in the active treatment of COVID-19 positive patients or their COVID-19 related symptoms.
Source of Critical COVID-19 Drug List: Created by the Univ. of Minnesota's Resilient Drug Supply Project staff in January of 2020.

"X" means that a drug is on the list named at the top of the column.
"Yes" means that a drug is on the active shortage list named at the top of the column (either ASHP or FDA).
* Remdesivir (Gilead) has been approved by the FDA for treatment of COVID-19 requiring hospitalization in adults and pediatric patients age 12 and older.
** Highly Active Anti-Retroviral Therapies (HAART) and particularly agents used for post-exposure prophylaxis (PEP) are included on the critical acute drug list.
( ) Information in parentheses after a drug name indicates a specific dosage form, strength or product name that is of interest on the Critical List.

ASHP Drug Shortage List: Drug shortages reported by the American Society of Health Systems can be found at:
https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages&loginreturnUrl=SSOCheckOnly

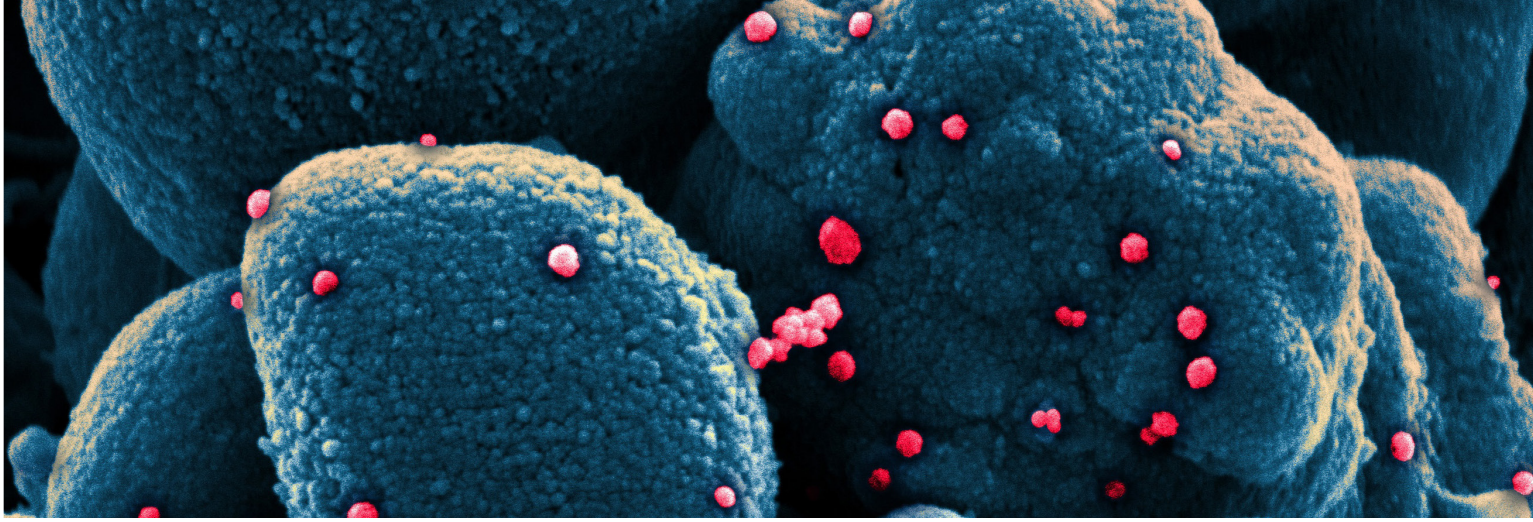
FDA Drug Shortage List: Drug shortages reported by the U.S. Food & Drug Administration can be found at:
https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

Appendix B

Viewpoint, Part 6: Ensuring a Resilient US Prescription Drug Supply,
October 21, 2020,
Schondelmeyer S, Siefert J, Margraf D, et al,

available on the
Resilient Drug Supply Project website at:
https://www.cidrap.umn.edu/rds

or directly at:
https://www.cidrap.umn.edu/sites/default/files/public/downloads/cidrap-covid19-viewpoint-part6.pdf



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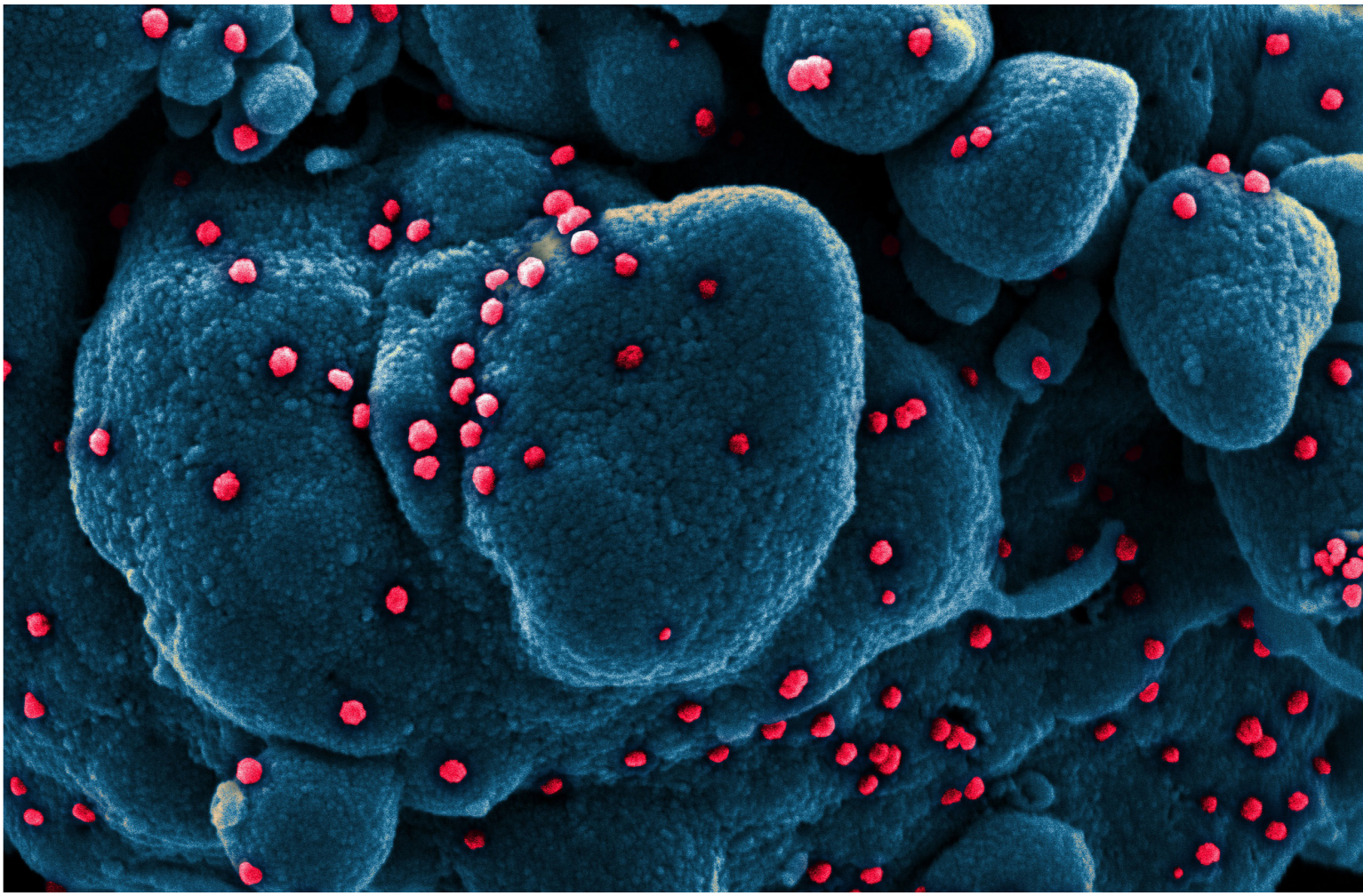

CIDRAP

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.

The PRIME Institute, founded in 1991 at the UMN, is an independent and global research, education, and consulting organization whose mission includes the study of economic and policy issues on pharmaceuticals.

The Walton Family Foundation is, at its core, a family-led foundation. It supports the work of the RDSP. To learn more, visit: www.waltonfamilyfoundation.org.

COVID-19 Viewpoint reports are made possible with support from the University of Minnesota OVPR and the Bentson Foundation.

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.

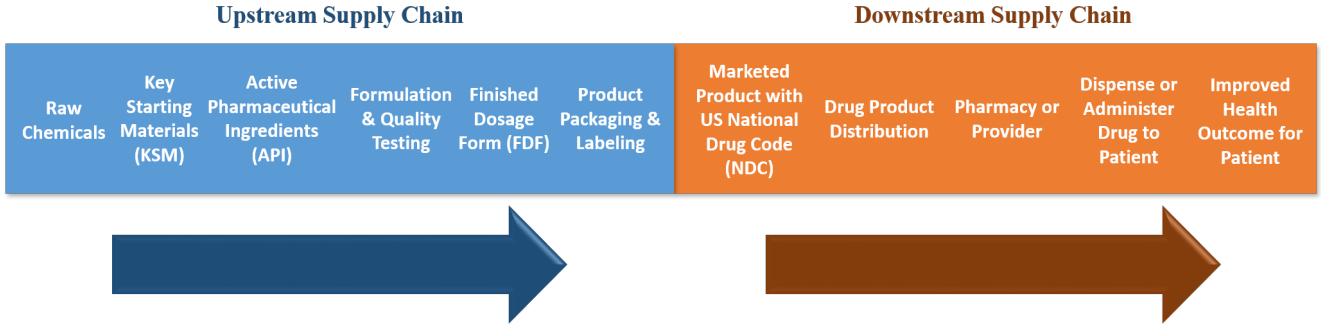
One way generic injectable manufacturers have managed to survive is to limit re-investment in modern production methods and in new production facilities, which also raises the risk of a drug shortage. At the same time, high economic and regulatory barriers to entry have limited new producers and competitors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

"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.

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."

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.

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.

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: (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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Appendix C

Resilient Drug Security & Supply Chain
Project Objectives

Resilient Drug Security & Supply Chain

Project Objectives

The Resilient Drug Security & Supply Chain project is being conducted to address the issues of drug shortages in the U.S. There are 8 major objectives of the project that will be addressed from October 1, 2018 to March 30, 2021.

Objective 1: **Critical Acute Drugs**
Identify a set of Critical Acute Drugs and the impact of drug shortages and supply chain disruptions and incorporate the efforts of the collaborative networks, findings, and action items identified in Year One.

Objective 2: **Essential Chronic Drugs**
Identify a set of Essential Chronic Drugs (i.e., drugs that would lead to patients perishing in a short period [days to months] if these drugs were not widely available in the U.S.) and the impact of drug shortages and supply chain disruptions for these Essential Chronic Drugs building on the work done being done on Critical Acute Drugs.

Objective 3: **Consequences of Drug Shortages**
Assess the relative importance of the Critical Acute Drugs and the Essential Chronic Drugs by a variety of factors such as: (a) number of people using them, (b) the severity of consequences due to absence of the drug, (c) the potential morbidity and mortality in the U.S. if a catastrophic event (i.e., health, social, economic, political, or other) happens, (d) the availability of reasonable therapeutic alternatives, and (e) other relevant and important factors.

Objective 4: **Mapping Drug Supply Chain**
Analyze and map the supply chain for each drug (i.e., Critical Access and Essential Chronic) from API to consumer using databases from FDA, commercial, shipping, and other sources and determine the dependence of each specific drug by country of origin. This task will build upon the databases examined in Year 1 (e.g., Panjiva, MediSpan, FDA) and will add other databases that provide new and unique information on the supply chain (e.g., IQVia, IBM Health MarketScan, New Zealand Medicines, RxResources, and others).

Objective 5: **Predicting Drug Shortages**
Use modeling techniques to identify the factors that may signal and precede supply chain disruption and drug shortages for Critical Acute Drugs and for Essential Chronic Drugs in the U.S. Determine if the models are similar across types of drugs (i.e., critical acute drugs vs essential chronic drugs) or type of trigger event precipitating a shortage or supply change issue.

Objective 6: **Prevention of Drug Shortages**
Identify methods and processes to prevent various types of events that could lead to widespread absence of Critical Acute Drugs or Essential Chronic Drugs. This task will include use of consultants from the stakeholder groups (i.e., FDA, DOD, NSA, brand and generic manufacturers, wholesalers, retail chains, hospitals and health systems, physicians, nurses, pharmacists, and consumers).

Objective 7: **Response to Drug Shortages**
Develop a response plan and approach for managing a supply chain disruption or a drug shortage for either a Critical Acute Drug or an Essential Chronic Drug including management of the existing and remaining or limited supply, distribution methods, use of repositories, allocation rules for medication use, and other appropriate responses.

Objective 8: **Market Change & Future Policy to Minimize Drug Shortages**
Describe the changing landscape of pharmaceutical manufacturing and the drug supply industry as a whole including steps to modernize drug production and the safety and security of the drug supply chain such as track and trace regulations, shipping regulations, and country of origin labeling. Policy initiatives derived from research and real world data on drug supply chains will be proposed and include policies to incentivize increased drug manufacturing (both API and finished dosage form) based in the U.S. in order to increase the security of the U.S. drug supply.

Appendix D

Improving Resilience & Reducing Shortages in the Drug Supply Chain: Roles of the USP, CIDRAP & Others

Presented to:
USP Council of the Convention
May 12, 2021

Stephen W. Schondelmeyer, PharmD, MPubAdm, PhD, FAPhA
Co-Principal Investigator, Resilient Drug Supply Project
CMC Endowed Chair in Pharmaceutical Management & Economics
Professor & Director, PRIME Institute
Dept. of Pharmaceutical Care & Health Systems
College of Pharmacy, University of Minnesota

Improving Resilience & Reducing Shortages in the Drug Supply Chain:

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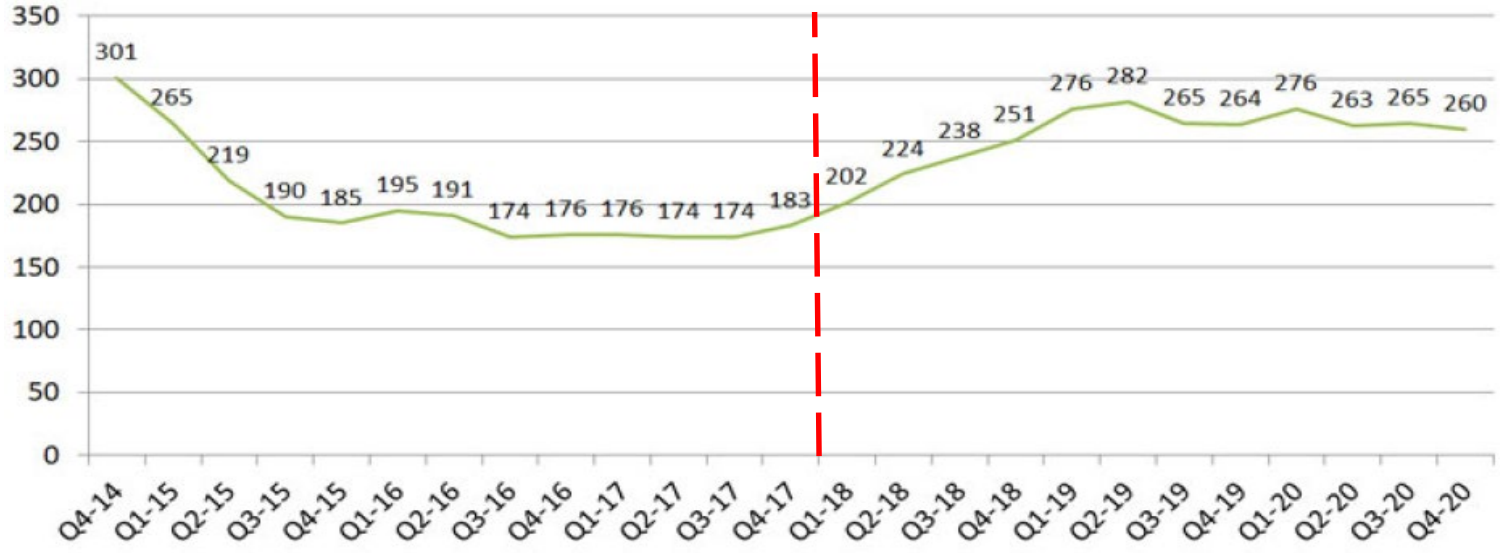
CIDRAP
Center for Infectious Disease Research and Policy

PRIME Institute
University of Minnesota

History of Drug Shortages in the U.S.

- **Drug Shortages Have Been Tracked in U.S. for More Than 25 Years**
  - > 200 Drugs in Shortage (per ASHP) Each Quarter from Q1-2018 to Q4-2020
  - Drug Shortages Have a Median ***Duration*** **> 1 Year**
  - Despite Tracking, Drug Shortages Have Not Significantly Decreased



[1] **FDA.** Drug Shortages: Root Causes and Potential Solutions. Report. Oct 2019

[2] Fox ER, Birt A, James KB, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 2009 Aug 1;66(15):1399-406; and, ASHP website: https://www.ashp.org/Drug-Shortages/Current-Shortages.

Definition of Drug Shortages in the U.S.

- **Definition of Drug Shortage:**
  - **FDA**:
    "A period of time when the demand or projected demand for the drug within the U.S. exceeds its supply."[1]
  - **ASHP**:
    "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."[2]

[1] **FDA.** Drug Shortages: Root Causes and Potential Solutions. Report. Oct 2019
[2] Fox ER, Birt A, James KB, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 2009 Aug 1;66(15):1399-406; and, ASHP website: https://www.ashp.org/Drug-Shortages/Current-Shortages.

Status of Drug Shortages in the U.S.

- **FDA Drug Shortages** [1]

- **ASHP Drug Shortages** [2]

1 FDA. file:///D|/!MyDocs%20D/!!!Drug%20Shortages%20&%20Foreign%20Dependancy/Communications/CIDRAP%20Viewpoint/!Viewpoint%20Oct%202020/Website
2 ASHP. https://www.ashp.org/Drug-Shortages/Current-Shortages

Definition of Resilient Drug Supply in the U.S.

- **Definition of Resilient Drug Supply:**

  - **Resilient Drug Supply**:

    "A pharmaceutical market and drug supply chain that can recognize and respond to extraordinary increases in demand or disruptions in supply, or both, and still provide drugs that meet the needs of the American population."

  - **U.S. Drug Supply**:

    "The U.S. drug supply focuses on providing optimal drug therapy to patients in the U.S. at the time that they need the drug, although the preparation, manufacturing, and finishing of those drugs is dependent upon an upstream supply chain that is truly global in scope and reach."

[1] **FDA.** Drug Shortages: Root Causes and Potential Solutions. Report. Oct 2019

[2] Fox ER, Birt A, James KB, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 2009 Aug 1;66(15):1399-406; and, ASHP website: https://www.ashp.org/Drug-Shortages/Current-Shortages.

USP's Medicines Supply Map

- **USP's Medicine Supply Map Mission**

  Mission: USP's Medicine Supply Map enhances transparency of the upstream pharmaceutical supply chain to help identify vulnerabilities and deliver insights that can guide risk mitigation strategies and investment in supply chain resilience.

- **Drug Supply Resilience Model**
  - *Goal*: identify, characterize and quantify risk and resilience in upstream supply chain
  - > 200 million data points & 20+ data sources (USP, FDA, CMS, EMA & private sources)
  - Visibility to identify vulnerabilities and lower quality risks
  - Leverage insights from ~22,000 locations where USP standards are used
  - Learn from USP's presence in global manufacturing hubs (India, China, Europe & U.S.)
  - Drug Supply Resilience Model is only one application of the Medicine Supply Map
- **Developed Pilot Project & List of Critical Drugs**
  - Pilot project developed jointly with *Angels for Change* & *Vizient, Inc.*
  - Identified Critical Pediatric Drugs (17 drugs)
  - Applied the Drug Supply Resilience Model to identify factors leading to shortages
- **Shortages of Critical Pediatric Drugs Are More Likely When There Is:**
  - More competition & prices are too low
  - Increased quality citations by FDA
  - Geographic concentration of production facilities

CIDRAP's Resilient Drug Supply Project* (RDSP)

- **Project Initiated in Fall 2018**

  Mission: The RDSP focuses on the global supply chain for each prescription drug used in the U.S. healthcare market in order to reduce or avoid disruptions from any cause and for any reason.

- **Develop Lists of Critical Drugs**
  - Critical Acute Drugs (156 drugs identified Dec. 2018)
  - Critical COVID-19 Drugs (40 drugs identified Jan. 2020)
  - Critical Chronic Drugs (~300-750 drugs (Brand, Generic & Specialty) products expected June 2021)
- **Map Supply Chain (pre-API to patient) for Each Drug in the U.S.**
  - Establish a drug supply, shortage, and tracking framework
  - Assess & characterize the root cause for each drug shortage (beyond FDA categories)
  - Conduct risk assessment along entire supply chain for drugs (up-stream & down-stream)
- **Predict & Prevent Drug Shortages**
  - Investigate effects of infrastructure failures (e.g., trade, transportation, power, geopolitics, economic)
  - Determine pre-cursors of shortages & methods to monitor & modify them
  - **Build a real-time, ongoing platform to assess & predict critical supply failures**

** Funded by a generous grant from the Walton Family Foundation*

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

Defining Critical Acute Drugs

Critical Acute Drugs:

"Drugs 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."

Absence of a **Critical Acute Drug**, or lack of availability of an effective substitute, may cause serious health outcomes or limited ability to provide humane care."

- **156** drug molecules
- **24.4%** (38/156) in shortage according to FDA (1-25-21)
- **38.5%** (60/156) in shortage according to ASHP (1-25-21)

Defining Critical COVID-19 Drugs

Critical COVID-19 Drugs:

"Drugs used in the active treatment of COVID-19 positive patients or their COVID-19 related symptoms.”*

* This list was created by the Univ. of Minnesota's Resilient Drug Supply Project team in January of 2020.

Absence of a **Critical COVID-19 Drug**, or lack of availability of an effective substitute, may cause serious health outcomes or limited ability to provide humane care."

- **40** drug molecules
- **40.0%** (16/40) in shortage according to FDA (1-25-21)
- **70.0%** (28/40) in shortage according to ASHP (1-25-21)

Resilient Drug Supply Project:
Critical Acute Drug List & Critical COVID-19 Drug List
Drug Shortages Reported by ASHP & FDA

			UMN RDSP	UMN RDSP	Shortages as of 1/25/2021 ASHP	FDA
Drug #	Critical Acute Drugs Generic Name	Drug Category	List of 156 Critical Acute Drugs	List of 40 Critical COVID-19 Drugs	Drug Shortage List	Drug Shortage List
1	Cisatracurium	Paralytic	X	X	Yes	Yes
2	Rocuronium	Paralytic	X	X	Yes	
3	Vecuronium	Paralytic	X	X	Yes	Yes
4	Succinylcholine	Paralytic	X	X		
5	Atracurium	Paralytic	X			
6	Propofol	Sedation	X	X	Yes	Yes
7	Midazolam	Sedation	X	X	Yes	Yes
8	Lorazepam	Sedation	X	X	Yes	Yes
9	Dexmedetomidine	Sedation/Anesthesia	X	X	Yes	Yes
10	Phenobarbital	Sedation	X			
11	Ketamine	Sedation/Anesthesia	X	X	Yes	Yes
12	Diazepam	Sedation	X			
13	Lidocaine	Local Anesthetic	X		Yes	Yes
14	Bupivacaine	Local Anesthetic	X		Yes	Yes
15	Fentanyl	Pain	X	X	Yes	Yes
16	Hydromorphone	Pain	X	X	Yes	Yes
17	Morphine	Pain	X	X	Yes	Yes
18	Oxycodone	Pain	X	X		
19	Acetaminophen	Pain & Fever	X			
20	Ketorolac	Pain	X		Yes	Yes
21	Anakinra	Pain	X			
22	Oxygen	Medical Gas	X	X		
23	Nitric Oxide	Medical Gas	X			
24	Sevoflurane	Medical Gas	X			
25	Albuterol	Bronchodilator	X	X	Yes	
26	Ipratropium (Inhaler)	Bronchodilator	X			
27	Azithromycin	Anti-infective	X	X	Yes	
28	Piperacillin-Tazobactam	Anti-infective	X	X		
29	Cefepime	Anti-infective	X	X	Yes	Yes
30	Ceftriaxone	Anti-infective	X			
31	Vancomycin	Anti-infective	X	X	Yes	
32	Doxycycline	Anti-infective	X			
33	Meropenem	Anti-infective	X	X		
34	Cefazolin	Anti-infective	X	X	Yes	Yes
35	Levofloxacin	Anti-infective	X			
36	Linezolid	Anti-infective	X			
37	Ampicillin-Sulbactam	Anti-infective	X		Yes	
38	Sulfadiazine-Trimethoprim	Anti-infective	X			
39	Ceftazidime	Anti-infective	X	X	Yes	
40	Ciprofloxacin	Anti-infective	X			
41	Clindamycin	Anti-infective	X		Yes	
42	Gentamicin	Anti-infective	X			
43	Imipenem	Anti-infective	X			
44	Metronidazole	Anti-infective	X			Yes
45	Ampicillin	Anti-infective	X			
46	Nafcillin	Anti-infective	X			
47	Oxacillin	Anti-infective	X			
48	Penicillin G	Anti-infective	X			
49	Tobramycin	Anti-infective	X		Yes	Yes
50	Amphotericin B	Anti-infective	X		Yes	
51	Posaconazole	Antifungal	X		Yes	

WEEKLY UPDATE of CRITICAL DRUG SHORTAGES:

* Critical Acute Drugs (156)

* Critical COVID-19 Drugs (40)

Shortages according to:

* ASHP Definitions

* FDA Definitions

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Note: This is a partial list. The complete and updated list is available at the RDSP web site: https://www.cidrap.umn.edu/rds

Defining Critical Chronic Drugs

Critical Chronic Drugs:

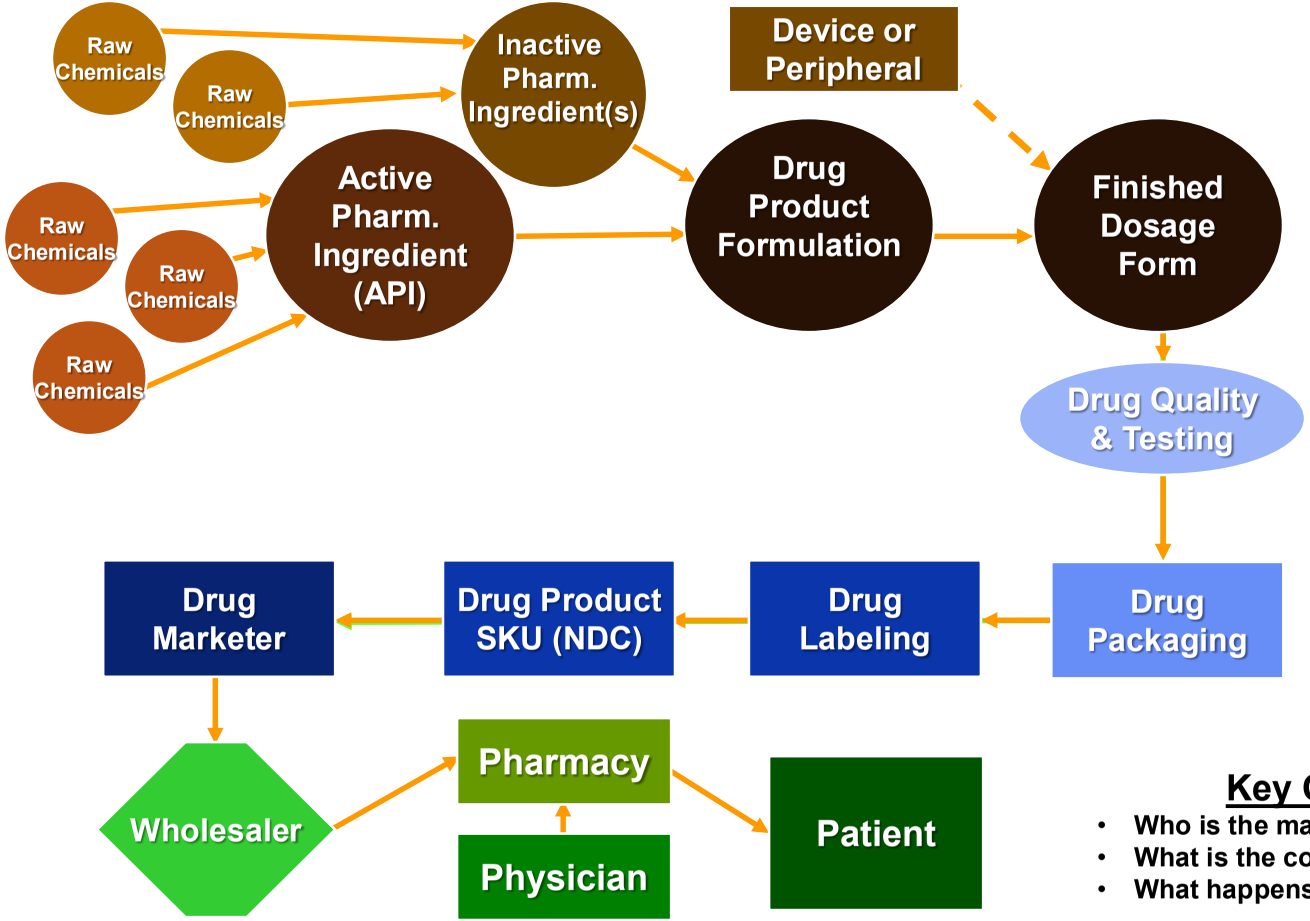
"Drugs that when medically needed in chronic care must be available and used within a few days or weeks of the need, and on a regular basis, or the patient will suffer serious outcomes which may include debilitating disease progression and worsening health status resulting in emergency care, hospitalization or death."

Absence of a **Critical Chronic Drug**, or lack of availability of an effective substitute, may cause serious health outcomes or shortened life span due to death.

The vast majority of medical conditions are chronic diseases such as diabetes, high blood pressure, asthma, epilepsy, thyroid problems, or cancer. For example, insulin is a Critical Chronic Drug for most Type I diabetic patients.

- **~500** drug molecules expected in list under development
- **? %** (? /500) in shortage according to FDA
- **? %** (? /500) in shortage according to ASHP

Drug Supply Chain: Pre-API to Patient



Key Questions:

- Who is the manufacturer?
- What is the country of origin?
- What happens if API is not available?

Contextual Factors Related to Shortages

1. **Natural Disasters, Weather & Climate Change** (e.g., hurricanes, tornadoes, tsunamis, floods)
2. **Health Disasters** (e.g., sanitation, infectious disease outbreaks, pandemics)
3. **Human Behavioral Responses** (e.g., stockpiling, hoarding, panic, or trust in science or vaccines)
4. **Human-made Disasters** (e.g., fires, explosions, nuclear disasters)
5. **Unintentional Contamination** while synthesizing & manufacturing a drug product
   (e.g., valsartan (2018), ranitidine (2019), metformin (2020) with nitrosamine contaminants; heparin with melamine)
6. **Intentional Contamination** (or terrorism) of drugs during synthesis, production, or distribution process
   (e.g., Tylenol poisoning, anthrax in the mail)
7. **Business Decisions & Industry Consolidation**
   (e.g., antitrust-Mylan API monopolization of lorazepam, vincristine discontinued by Pfizer)
8. **Economic & Ethical Behavior** of drug firms (e.g., bankruptcy of Purdue Pharma (opioids) & others)
9. **Political & Trade Relations** (e.g., India's ban on certain drug exports, UK-EU vaccine trade battle, China)
10. **Military Action or War** (e.g., hostilities exist with certain countries such as North Korea, Iran, Russia & China)

Data Sources for Drug Supply Information

Drug Products & Properties
- FDA NDC List & Medispan (NDC matrix with >750,000 active & inactive NDCs)
- FDA Approved Drugs & Biologics lists (> 15,000 current & former drug molecules)
- FDA List of Critical APIs & Other Critical Drug Lists (Acute, Chronic, COVID, drug shortages, pediatric, etc)
- Drug properties (e.g., molecular weight, stereoisomers, # of rings, years on market, ther. class, ref. std.)

Drug Production & Supply Sources
- FDA Drug Registration & Listing System (~10,000 Drug facilities listed with FDA)
- FDA Drug Master File (DMF) list (~35,000 active & inactive DMFs for API)
- FDA NDC Structured Data Elements (NDSE) & Structured Product Labeling (SPL)
- NLM Daily Med website with Drug Product & Labeling lookup
- Other FDA data sets

Drug Regulation & Quality
- FDA Drug Inspections (→ 483s, Official Action Indicated (OAI) citations, recalls, import actions)
- FDA Recalls & Seizures (Drugs with recalls or seizures)
- Regulatory Status (Patents, Exclusivities, orphan designations, generics & biosimilars)

Market Demand & Economics
- Changes in Disease Incidence & Prevalence (e.g., # of other indications, new indications, seasonal)
- Sales of Drug Products (IQVIA data on price, revenue, # of Rxs, daily doses over time; U.S. & Global)
- Trade & Shipment data (imports & exports by country; shipments by land, sea, & air)

Political & Business Environment
- Geographic & Economic concentration (API & FDF concentration, mergers & acquisitions, bankruptcies)
- Supply Chain Limitations (Foreign production, import-export climate, other)
- Trade climate (Sanctions, tariffs, incentives, political disputes)

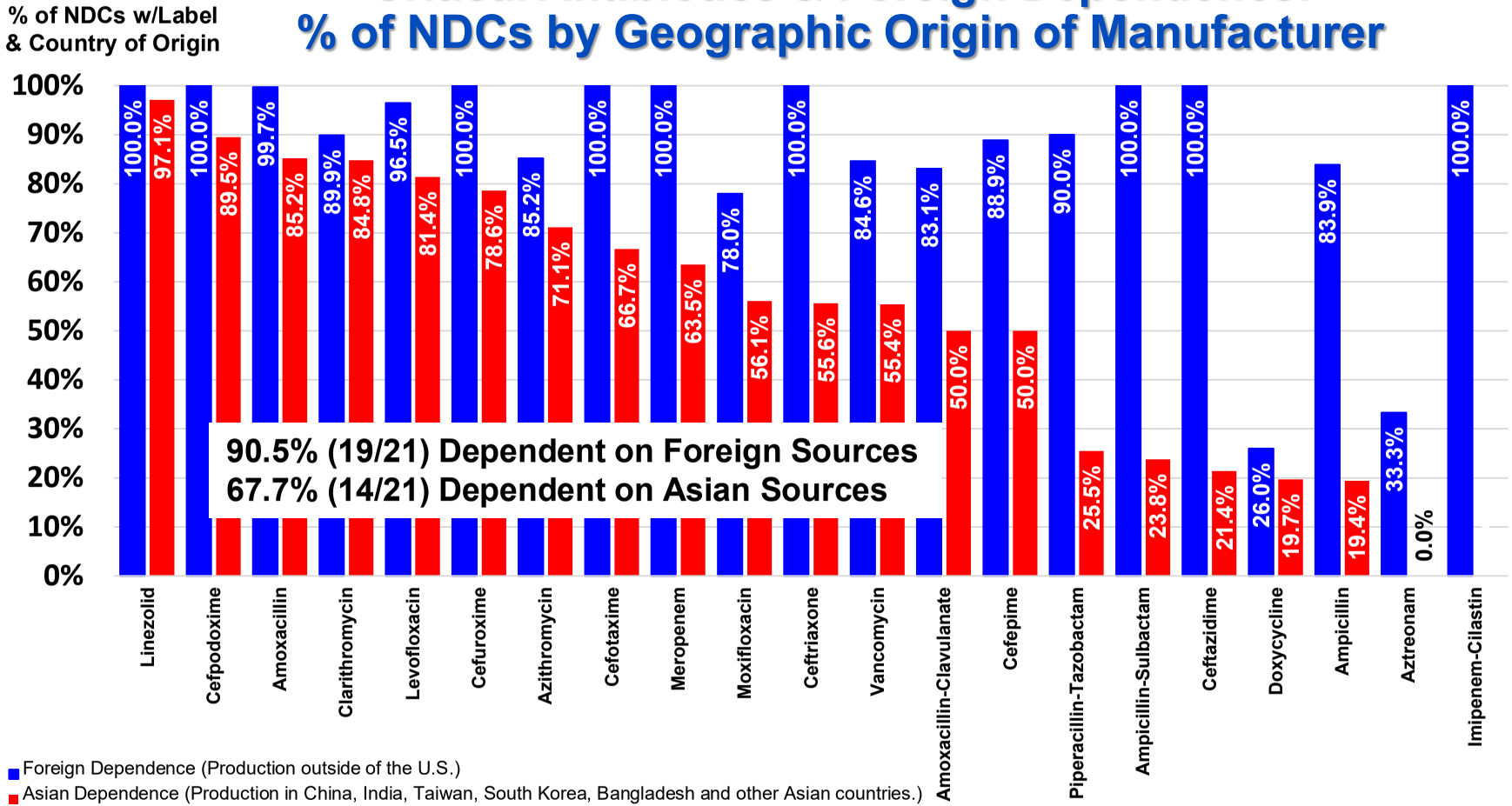
Other Information & Data
- Reference standard acquisition (USP), media mention of drug use, other

U.S. Drug Supply's Foreign Dependence Based on Shipping Data for Critical Access Drugs: 2019

China	Asia	Any Foreign
Critical Access Drugs with >50% from China:	**Critical Access Drugs with >50% from Asia:**	**Critical Access Drugs with >50% Foreign Source:**
Hydrocortisone	Hydralazine	Azithromycin
Doxycycline	Meropenem	Lorazepam
Acetaminophen	Dexamethasone	Midazolam
Potassium	Betamethasone	Propofol
Phenytoin	Methylprednisolone	Prednisone
Fosphenytoin	Furosemide	Warfarin
Epinephrine	Torsemide	Fentanyl
Sodium Phosphate	Enoxaparin	Diphenhydramine
Succinylcholine	Heparin	Ampicillin
	Mycophenolate	Gentamicin
		Penicillin
		Insulin
% of Drugs With Shortage in 2020	77.8%	80.0%	75.0%

Source: Data is Average Annual % of Shipments to the US for Critical Drugs by Country of Origin from Panjiva (Shipments) Data for 2019.

Critical Antibiotics & Foreign Dependence: % of NDCs by Geographic Origin of Manufacturer



Source: Antibiotics identified in Metlay J, et al, Diagnosis and Treatment of Adults with Community-acquired Pneumonia, Am J Respir Crit Care Med Vol 200, Iss 7, pp e45–e67, Oct 1, 2019. The Geographic origin of drug products at the NDC level were identified by extracting data from the FDA Drug Label Files as of February 2, 2020 and found at https://dailymed.nlm.nih.gov/dailymed/spl-resources-all-drug-labels.cfm.

Drug Supply Map: Top 30 Generic Drugs

	Rank	G001	G002	G003	G004	G005	G006	G007	G008	G009	G010	G011	G012	G013	G014	G015	G016	G017	G018	G019	G020	G021	G022	G023	G024	G025	G026	G027	G028	G029	G030
	NDC#	68382-0132-01	00378-2351-93	59651-0052-30	60505-2580-08	68382-0711-19	60505-2579-08	55111-0789-27	70377-0007-12	55111-0466-05	68382-0096-01	62037-0831-10	66993-0664-30	66993-0165-02	31722-0713-90	68382-0412-05	00406-0125-01	65862-0357-05	60505-2578-08	60505-3849-01	70377-0008-12	00093-5343-56	62037-0832-01	29300-0220-19	00781-2234-10	00378-8770-35	68180-0339-09	00093-7202-98	00527-1343-10	00527-1342-10	65162-0102-50
	Product	tamsulosin HCl	esomeprazole magnesiu	ezetimibe	atorvastatin calcium	mesalamine	atorvastatin calcium	sevelamer carbonat	rosuvastatin calcium	metoprolol succinate	hydroxychloroquine sulfate	metoprolol succinate	duloxetine HCl	colchicine	pantoprazole sodium	omeprazole	hydrocodone-acetamin	clopidogrel bisulfate	atorvastatin calcium	celecoxib	rosuvastatin calcium	sildenafil citrate	metoprolol succinate	monteluk ast sodium	omeprazole	estradiol	metformin HCl	pravastatin sodium	levothyroxine sodium	levothyroxine sodium	gabapentin
	Drug Firm	Zydus Pharmaceuticals (Usa)	Mylan	Aurobindo Pharma	Apotex	Zydus Pharmaceuticals (Usa)	Apotex	Dr.Reddy's Laboratories	Biocon Pharma	Dr.Reddy's Laboratories	Zydus Pharmaceuticals (Usa)	Actavis Pharma	Prasco Laboratories	Prasco Laboratories	Camber Pharmaceuticals	Zydus Pharmaceuticals (Usa)	Mallinckrodt Pharm	Aurobindo Pharma	Apotex	Apotex	Biocon Pharma	Teva Pharmaceuticals USA	Actavis Pharma	Unichem Pharmaceuticals	Sandoz	Mylan	Lupin Pharmaceuticals	Teva Pharmaceuticals USA	Lannett	Lannett	Amneal Pharmaceuticals
Up Stream Supply Chain / Finished Drug Manufacture	Key Starting Materials	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	API Manufacture	NR	NR	NR	NR	NR	NR	NR	India	NR	NR	NR	NR	NR	NR	NR	USA	NR	NR	NR	India	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Finished Drug Manufacture	India	India	India	Canada	India	Canada	India	India	India	India	USA	India	NR	India	India	USA	India	Canada	Canada	India	Croatia	USA	India	Slovenia	USA	India	Caech Republic	Puerto Rico	Puerto Rico	India
	Pack & Label	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Down Stream Supply Chain	FDA Sponsor (BLA | NDA | ANDA)	USA	USA	USA	USA	USA	USA	USA	USA	India	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
		ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	NDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	ANDA	NDA	NDA	ANDA
	Manufactured for:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Marketed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Distributed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Whlse & GPO Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Pharmacy Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Patient	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA

- USA
- USA-Puerto Rico
- No. America (Mexico & Canada)
- Europe
- Asia
- India
- Not Reported

* **90% (27/30) of API Manufacture are Unknown Sources**
* **80% (24/30) of Finished Drug Manufacture are Foreign Sources**
* **50% (15/30) of Packing & Labeling are Unknown Sources**

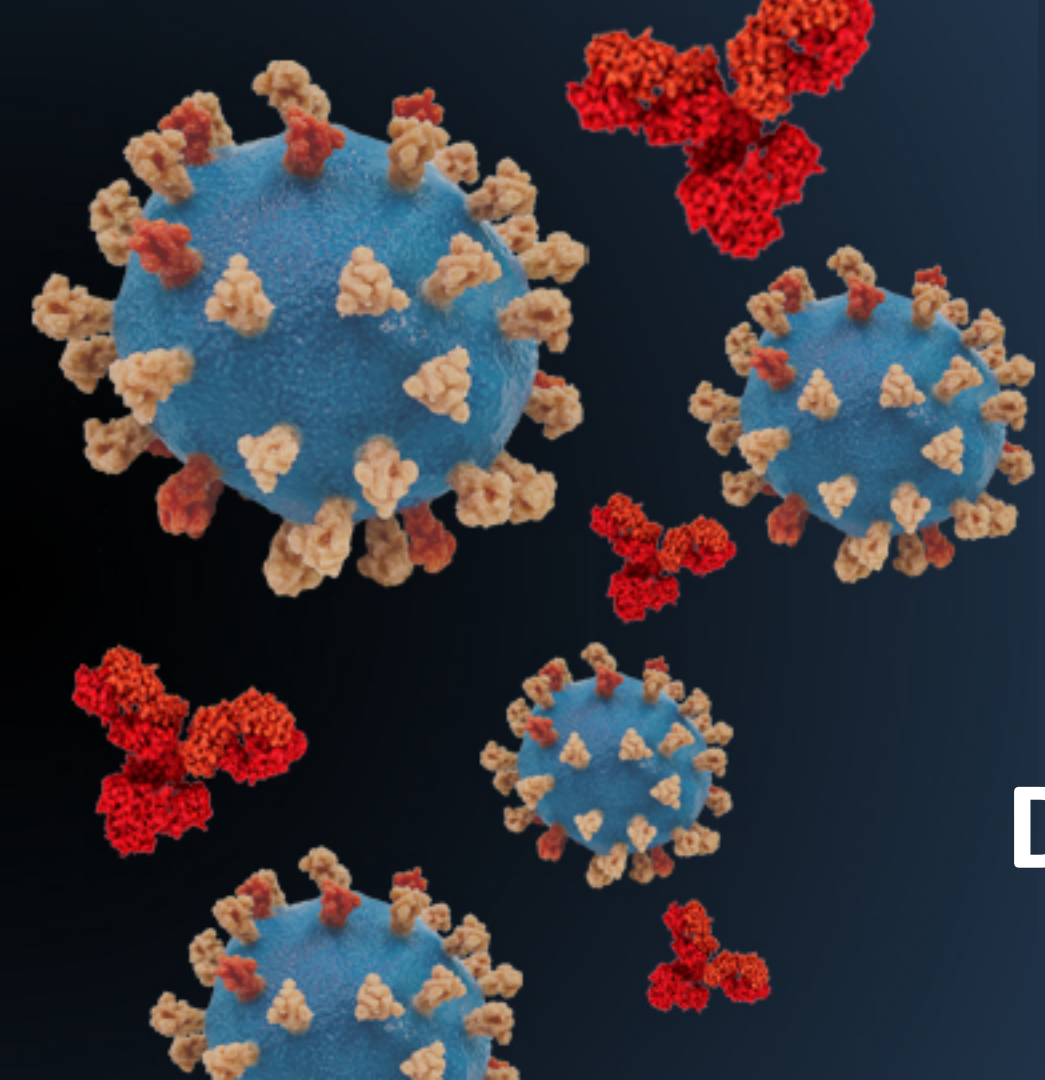
Drug Supply Map: Top 30 Brand Drugs

	Rank	B001	B002	B003	B004	B005	B006	B007	B008	B009	B010	B011	B012	B013	B014	B015	B016	B017	B018	B019	B020	B021	B022	B023	B024	B025	B026	B027	B028	B029	B030
	NDC #	00003-0894-21	00169-4060-13	00088-2219-05	50458-0579-30	00173-0696-00	00006-0277-31	00002-8799-59	00597-0075-41	00002-1434-80	00186-0370-20	00169-6438-10	00023-9163-60	00003-0893-21	00088-2220-33	00002-7510-01	00173-0697-00	59310-0579-22	00024-5869-03	00002-1433-80	00469-2602-30	00169-6339-10	00173-0859-10	00597-0153-30	50458-0578-30	00597-0140-30	00006-0112-31	00597-0152-30	00173-0882-10	00173-0696-00	00169-7501-10
	Product	Eliquis	Victoza	Lantus SoloStar	Xarelto	Advair Diskus	Januvia	Humalog KwikPen	Spiriva HandiHaler	Trulicity	Symbicort	Levemir FlexTouch	Restasis	Eliquis	Lantus	Humalog	Advair Diskus	ProAir HFA	Toujeo SoloStar	Trulicity	Myrbetriq	Novolog FlexPen	Breo Ellipta	Jardiance	Xarelto	Tradjenta	Januvia	Jardiance	Breo Ellipta	Advair Diskus	Novolog FlexPen
	Drug Firm	Bristol Myers Squibb	Novo Nordisk	Sanofi-Aventis U.S.	Janssen	Glaxo Smith Kline	Merck Sharp & Dohme	Lilly	Boehringer Ingelheim	Lilly	Astra Zeneca LP	Novo Nordisk	Allergan	Bristol Myers Squibb	Sanofi-Aventis U.S.	Lilly	Glaxo Smith Kline	Teva Respira-tory	Sanofi Pharma-ceuticals	Lilly	Astellas	Novo Nordisk	Glaxo Smith Kline	Boehringer Ingelheim	Janssen	Boehringer Ingelheim	Merck Sharp & Dohme	Boehringer Ingelheim	Glaxo Smith Kline	Glaxo Smith Kline	Novo Nordisk
Up Stream Supply Chain	Key Starting Materials	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	API Manufacture	Switzerland	Denmark	Germany	Germany	France UK Singapore	Italy	USA-PR	Germany	Ireland	France	Denmark	USA	Switzerland	Germany	USA-PR	France UK Singapore	Ireland	Germany	Ireland	Ireland Japan	Denmark	UK Singapore	Germany Italy	Germany	Germany Italy	Italy	Germany Italy	UK Singapore	France UK Singapore	Denmark
	Finished Drug Manufacture	USA-PR	Denmark	Germany Italy	USA-PR	UK Spain	UK	Italy France	Germany	Italy USA	France	Denmark	USA	USA-PR	Germany Italy	Italy France	UK Spain	Ireland	Germany	USA	Ireland Japan	Denmark	UK	Germany Mexico	USA-PR	Mexico USA	UK	Germany Mexico	UK	UK Spain	Germany
	Pack & Label	USA	NR	Italy USA	USA	USA	USA	Italy	USA	USA	UK	USA	USA	USA	Italy USA	Italy	USA	Ireland	Germany	USA	NR	NR	NR	Germany Mexico	USA	Mexico USA	USA	Germany Mexico	NR	USA	NR
Down Stream Supply Chain	FDA Sponsor (BLA | NDA | ANDA)	USA NDA	USA NDA	USA BLA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA BLA	USA NDA	USA BLA	USA NDA	USA NDA	USA BLA	USA NDA	USA NDA	USA NDA	USA BLA	USA BLA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA	USA NDA
	Manufactured for:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Marketed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Distributed by:	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Whlse & GPO Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Pharmacy Stock	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA
	Patient	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA

- USA
- USA-Puerto Rico
- No. America (Mexico & Canada)
- Europe
- Asia
- India
- Not Reported

* **90%** (27/30) of **API Manufacture** are **Foreign Sources** (European)
* **80%** (24/30) of **Finished Drug Manufacture** are **Foreign Sources**
* **53.3%** (16/30) of **Packing & Labeling** are **Foreign or Unknown Sources**

The U.S. Drug Supply
(Both Brand & Generic)
is Heavily Dependent Upon Foreign Sources



Impact of COVID-19 on Drug Shortages

COVID-19 Exposed Long-Standing Vulnerabilities in the Drug Supply Chain


The New York Times

Essential Drug Supplies for Virus Patients Are Running Low

Medicines to alleviate breathing difficulty, relieve pain and sedate coronavirus patients are in very high demand, depleting stock around the country.


The Washington Post

Coronavirus raises fears of U.S. drug supply disruptions

Many pharmaceuticals' active ingredients are made in China


FiercePharma

Drugmakers struggle to meet demand for antidepressant Zoloft amid COVID-19


CBS NEWS · May 7, 2020, 8:31 AM

Pandemic exposes drug supply shortages doctors have grappled with for "more than two decades"


CNN BUSINESS

The coronavirus exposed the US' reliance on India for generic drugs. But that supply chain is ultimately controlled by China

By Priyali Sur, CNN

Updated 9:28 PM ET, Sat May 16, 2020


tracelink

NETWORK FOR GREATER GOOD

COVID-19 is the Pharma Supply Chain's "Apollo 13" Moment

Impact of COVID-19 Pandemic on Drug Supply

Triple Play: Demand ↑, Supplies ↓ & Vulnerabilities Exposed

Increased Demand

- **Global & U.S. Spread of COVID-19 Infection**
- **Increased Number of COVID-19 Cases, Hospital Admissions, Ventilator Use & ICU Care**
- **Non-Evidence-Based Claims of Effectiveness → Irrational Demand** (e.g., Hydroxychloroquine)
- **Fear of Shortages → Hoarding Behavior** (e.g., Toilet Paper, PPE & Drug Shortages)

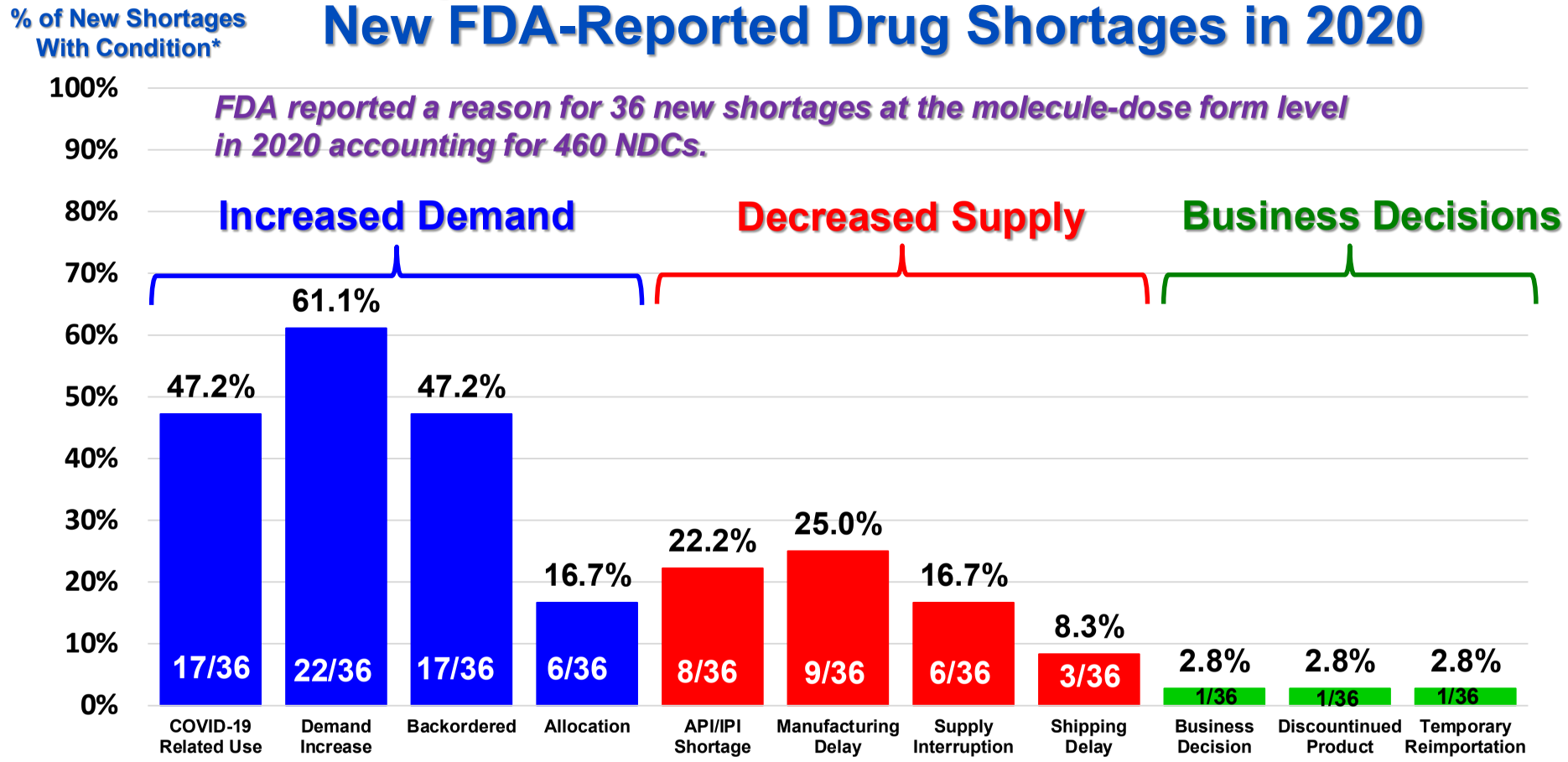
Disrupted Supply Chain

- **Disrupted API Supplies: Factory Shut Downs, Port Closures & Other Shipping Disruptions**
- **Export Bans on API & Finished Drug Products**
- **Depleted Inventories at Manufacturers & Wholesalers**
- **Drug Product Allocation Limitations by Manufacturers & Wholesalers**

Systemic Vulnerabilities Exposed

- **Manufacturers using "General Contractor" model rather than in-house manufacturing**
- **Aging & poor quality manufacturing facilities & processes**
- **Concentrated manufacturing including geographic, economic & sourcing issues**
- **Disparate regulatory environments & enforcement and limited inspection capacity**
- **Lack of transparency in the medicines supply chain**

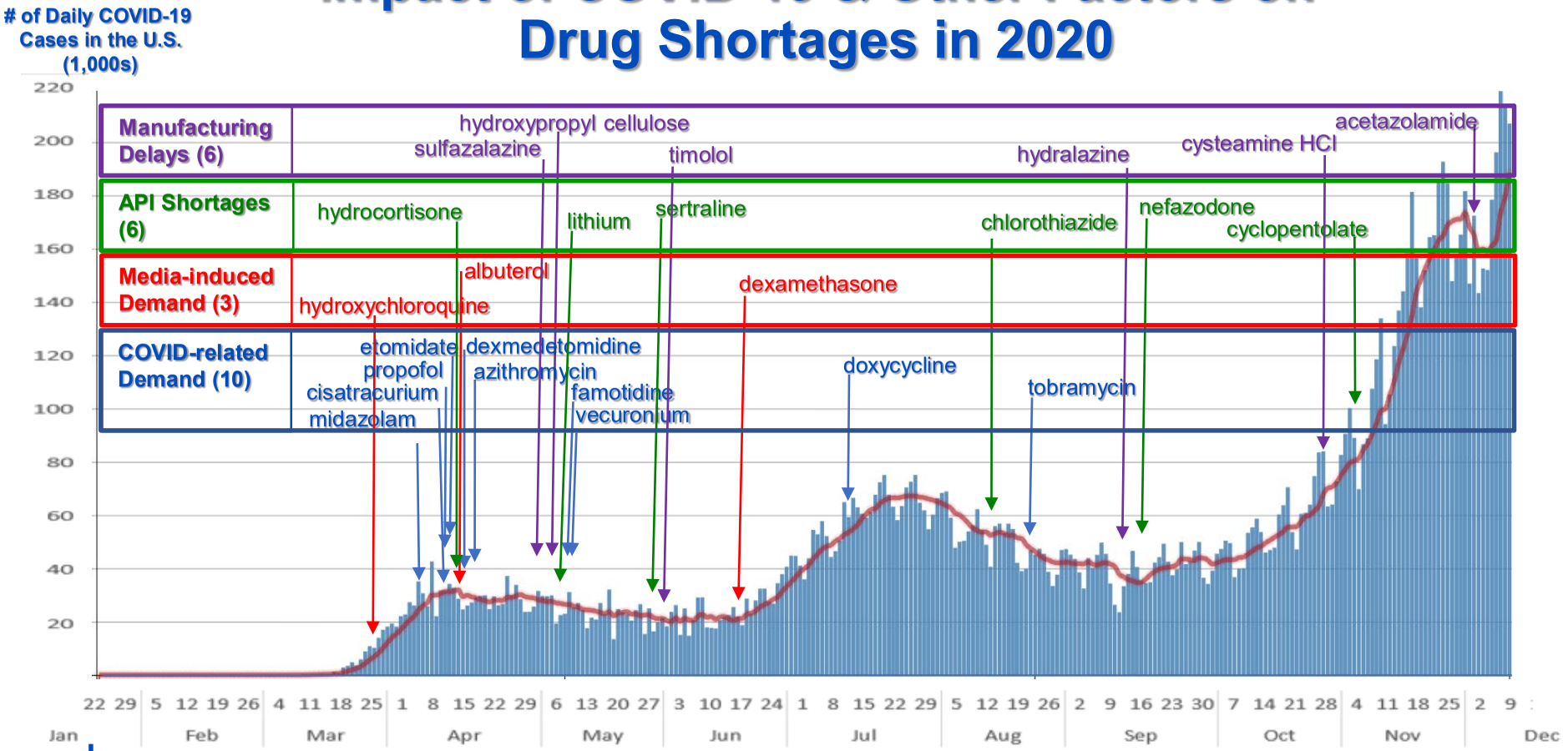
Impact of COVID-19 & Other Factors on New FDA-Reported Drug Shortages in 2020



* Shortages may have multiple factors so these percentages total to more than 100 percent.

Source: Based on data from FDA's Drug Shortage web site found on Dec. 5, 2020 at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

Impact of COVID-19 & Other Factors on Drug Shortages in 2020



Daily # of COVID-19 cases in the U.S.; seven-day average # of cases;

Source: CDC COVID Data Tracker, Trends in Number of COVID-19 Cases and Deaths in the US Reported to CDC, found on Dec. 5, 2020 at CDC web site: https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases. Drug shortage data is based on data from FDA's Drug Shortage web site found on Dec. 5, 2020 at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm. Based on preliminary analysis of factors related to each drug shortages.

Recommendations for Ensuring a Resilient Drug Supply

- The U.S. should have a national process and infrastructure for analyzing, predicting, managing, and preventing shortages of critical medications.
- An in-depth map of the US drug supply chain is needed.
- Congress should authorize and fund a national entity to:
  - Build the US Drug Supply Map
  - Make drug supply chains more transparent, and
  - Coordinate development of relevant national policy.
- This national entity may be a new or an existing organization such as:
  - US Pharmacopeia Convention (an independent, scientific, non-profit organization)
  - National Institute for Pharmaceutical Resilience (*new entity at NIH*)
  - Prescription Drug Policy Review Commission (*new entity*)
  - Existing entity such as NIH, NLM or FDA
- Establish an ongoing research program on resilience of the US drug supply chain including, but not limited to:
  - Development of a sentinel system that can predict and prevent supply chain disruption
  - Reduction of the number of drug shortages and
  - Response to shortages if they do happen.

Beyond COVID-19:

* Move Drug Shortages from:
  - "A Fail & Fix Framework" to
  - "A Predict & Prevent Paradigm"
* Reduce & Eliminate Drug Shortages

Questions ?
&
Discussion . . . !

Resilient Drug Supply Project
University of Minnesota

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

PRIME Institute
University of Minnesota