The Pandemic and the Supply Chain: Gaps in Pharmaceutical Production and Distribution

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See also Erwin et al., p. 540, and the Fixing US Health Policy section, pp. 620–657.

The acute stress of the COVID-19 pandemic has laid bare a series of long-term weaknesses in the US public health system, including the fragility of our supply of essential medications.[1] The virus produced unprecedented shifts in demand for old as well as new drugs, while simultaneously introducing new uncertainties about the production and distribution of pharmaceutical products. COVID-19–related shortages extended beyond antivirals to include a range of drugs broadly used in intensive care and in general hospital management (Table 1). These shortages point to serious vulnerabilities in the pharmaceutical supply chain that compromise readiness for new waves of the current pandemic and crises that are yet to come.

PANDEMIC-RELATED DRUG SHORTAGES: MAIN DRIVERS

Drug shortages had become a visible threat to US public health well before the COVID-19 pandemic. At the onset of the COVID-19 emergency in January 2020, more than 100 drugs were in shortage according to the US Food and Drug Administration (FDA).[2] Most non-crisis shortages typically begin as manufacturing problems. Shortages triggered by the COVID-19 pandemic, however, have been driven by unexpected sharp increases in demand, exceeding manufacturers' production capacity. Many life-supporting drugs needed to treat COVID-19 patients are generic, low-cost products that were already at risk or had previously been in shortage.[2]

The globalization of pharmaceutical production over the past few decades complicates this challenge. Although drug manufacturing was once a primarily domestic industry, the United States now relies on a global supply chain for pharmaceuticals, with China, India, and Europe as the main suppliers.[2–5] These flows have been especially vulnerable during the COVID-19 pandemic, as national and international responses have disrupted the production and shipping of pharmaceuticals around the world because of lockdowns, understaffing, and travel and export bans.[2,4,6–8] At the same time, travel restrictions have limited the FDA's capacity to inspect drug-manufacturing plants overseas, reducing its ability to authorize new sources of medications.[9]

INCREASING SUPPLY CHAIN RESILIENCE

The FDA monitors and tracks nationwide drug shortages that are attributable to production problems, relying on information from manufacturers.[10] The COVID-19 experience underscores the importance of expanding the federal drug shortage surveillance system to capture shortages caused by demand surges, which can be regional or local. Doing so requires collecting, in times of crisis, information provided by drug purchasers such as hospitals and pharmacies on the week-to-week challenges procuring drugs at state and local levels. Several state proposals to address price gouging underscore the importance of local surveillance for potential scarcity.[11] Early identification of potential shortages at state and local levels would enable the FDA to more quickly deploy strategies to increase drug supply—such as expedited review of manufacturing changes, assistance in establishing new lines of production, and extended expiration dating—which may help prevent nationwide shortages.

The FDA has proposed establishing publicly available quality metrics for manufacturing practices, with higher scores for facilities that have a robust and resilient capacity.[12] With congressional authorization, the FDA could

TABLE 1— US Food and Drug Administration–Reported Drug Shortages During the COVID-19 Pandemic: January 31–August 31, 2020

Name	Therapeutic Category	Day Posted	COVID-19 Relation
Pindolol tablets	Cardiovascular	Feb 21, 2020	Relation unknown
AVYCAZ (ceftazidime and avibactam) for injection, 2 g/0.5 g	Anti-infective	Feb 26, 2020	ICU care
Amoxapine tablets	Psychiatry	Mar 9, 2020	Relation unknown
Rifapentine tablets	Anti-infective	Mar 25, 2020	Relation unknown
Nizatidine capsules	Gastroenterology	Mar 27, 2020	Relation unknown
Chloroquine phosphate tablets	Anti-infective	Mar 31, 2020	COVID-19 treatment
Hydroxychloroquine sulfate tablets	Anti-infective; other; rheumatology	Mar 31, 2020	COVID-19 treatment
Hydrocortisone tablets, USP	Endocrinology/metabolism	Apr 2, 2020	Indirect
Midazolam injection, USP	Anesthesia; neurology	Apr 2, 2020	ICU care
Furosemide injection, USP	Cardiovascular	Apr 7, 2020	ICU care
Cisatracurium besylate injection	Anesthesia	Feb 4–8, 2020	ICU care
Dexmedetomidine injection	Anesthesia	Apr 10, 2020	ICU care
Etomidate injection	Anesthesia	Apr 10, 2020	ICU care
Propofol injectable emulsion	Anesthesia	Apr 10, 2020	ICU care
Azithromycin tablets	Anti-infective	Apr 14, 2020	COVID-19 treatment
Continuous renal replacement therapy solutions	Renal	Apr 22, 2020	ICU care
Sulfasalazine tablets	Gastroenterology	Apr 24, 2020	Relation unknown
Hydroxypropyl (Lacrisert) cellulose ophthalmic insert	Ophthalmology	May 1, 2020	Indirect
Famotidine tablets	Gastroenterology	May 4, 2020	ICU care
Famotidine injection	Gastroenterology	May 5, 2020	ICU care
Lithium oral solution	Psychiatry	May 6, 2020	Relation unknown
Vecuronium bromide for injection	Anesthesia	May 6, 2020	ICU care
Dimercaprol (BAL in Oil) injection USP	Hematology; other	May 11, 2020	Relation unknown
Amifostine injection	Oncology	May 21, 2020	Relation unknown
Sertraline hydrochloride oral solution, USP	Psychiatry	May 26, 2020	Indirect
Sertraline hydrochloride tablets	Pediatric; psychiatry	May 29, 2020	Indirect
Timolol maleate ophthalmic gel-forming solution	Ophthalmology	May 29, 2020	Indirect
Timolol maleate ophthalmic solution	Ophthalmology	May 29, 2020	Relation unknown
Doxycycline hyclate injection	Anti-infective	Jul 10, 2020	ICU care
Leuprolide acetate injection	Endocrinology/metabolism; oncology	Jul 24, 2020	Relation unknown
Chlorothiazide (Diuril) oral suspension	Cardiovascular; pediatric	Aug 12, 2020	Relation unknown
Tobramycin lyophilized powder for injection	Anti-infective; pediatric	Aug 24, 2020	ICU care
Hydralazine hydrochloride injection, USP	Cardiovascular	Sep 8, 2020	ICU care

Note. FDA = US Food and Drug Administration; ICU = intensive care unit; USP = US Pharmacopeia. COVID-19 treatment = a drug that can be used in the direct treatment of COVID-19 infection; indirect = a drug whose shortage has been described as triggered or related to the COVID-19 pandemic, although not because of the direct treatment of COVID-19 infection; ICU care = a drug commonly used in treatment of critically ill patients, such as patients with severe COVID-19 illness; relation unknown = drugs that were listed by the FDA on the shortage list during the COVID-19 pandemic but that lack clear evidence attributing this shortage to the pandemic itself.

Source. Information extracted from the FDA Drug Shortages Database (https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm) on August 31, 2020.

develop and publicize such metrics, allowing drug purchasers such as pharmacies and wholesalers to choose manufacturers that are less likely to experience shortages. Additionally, competitor manufacturers may choose to enter the market if all available products have poor quality ratings. A quality metrics system would create

incentives for manufacturers to self-correct and would help improve product quality, reducing shortage risks.

An additional strategy to strengthen production capacity would be to expand a mutual recognition agreement that allows the FDA and European regulators to recognize each other's inspections of manufacturing facilities within each other's borders.[13] Given the supply chain's high reliance on China and India, the agreement should be revised to cover inspections of global manufacturing facilities conducted by either European regulators or the FDA and to cover inspections of manufacturing plants that produce active pharmaceutical ingredients (APIs) as well as those that produce finished products. Alternatively, new agreements with countries with capable inspectorates, such as Australia and Japan, could be sought.

The FDA could also be charged with maintaining an evolving list of approved API sources of generic drugs. Most generic manufacturers purchase APIs for their finished products from an equally globalized web of producers; when these products experience sudden increase in demand, it can be difficult for manufacturers to quickly find alternative API sources. A list of approved API suppliers could accelerate the process of identifying new API sources and help the generic supply chain be more flexible and resilient without sacrificing quality. Such a list should be API and drug specific and should reflect the latest updates in FDA inspections, approvals, and manufacturing changes.

INCREASING DOMESTIC PHARMACEUTICAL PRODUCTION

Expanding domestic production of pharmaceuticals has been the focus of multiple policy initiatives during the COVID-19 pandemic. However, the "Made in the USA" stamp alone will not solve the US drug shortage crisis; it is not realistic to relocate all pharmaceutical production. Instead, it is in the best interests of US public health to focus domestic investments where they will produce the greatest benefit while maintaining a robust global supply chain for essential pharmaceuticals, such as those on the essential medicines list of the World Health Organization.

Congress should establish a legislative framework to define and sustain the activities to increase domestic production of critical medications. Such a framework could specify the characteristics of eligible drugs, applicable circumstances, and eligible institutions for contracts with domestic manufacturers, especially when emergencies threaten further shortages. Importantly, this framework should contain provisions to address safety failures, effectiveness, and target product supply. A payment structure to avoid price gouging should also be an important component of this framework. Support for facilities that can pivot to making a number of different medications based on national needs should be considered.

California recently passed a law aiming to have the first state-sponsored generic drugs label.[14] This initiative would allow California to establish its own drug-manufacturing capability. The initiative aims to increase competition in constrained markets, reduce drug costs, and improve public health. California's initiative would also increase the state's supply chain resilience, helping mitigate drug shortages, including in public health crises. Crucial to the success of state-sponsored drug manufacturing is the establishment of robust potential markets. Congress could support such initiatives by providing tax credits for state-sponsored drug-manufacturing programs, and federal agencies such as the US Department of Health and Human Services could help create new markets for these products, for example by prioritizing drugs of state-sponsored manufacturing in federal purchasing commitments.

FACILITATING DRUG SUPPLY REALLOCATION

The COVID-19 pandemic has revealed that the US health care system has no functional means to coordinate and direct sharing drug supplies across institutions in different regions facing different burdens of disease. Rather, the distribution of limited medical supplies has relied largely on pharmaceutical wholesalers that use proprietary algorithms to allocate supplies according to their contracts with hospitals and other purchasers. Because drug inventories are confidential, it is not possible to ascertain whether scarce resources are being distributed equitably and to prioritize areas and facilities of higher demand. COVID-19 has exposed a US health care system that has placed individual states and cities in competition with each other for scarce medical supplies.

To avoid this type of competition, the federal government should lead a comprehensive effort to assess and manage the US pharmaceutical supply chain during an emergency, including measuring the adequacy of available supplies, purchasing additional supplies and distributing them from a government stockpile, and allocating supplies across markets based on levels of need. Such an effort could defer to regional solutions where possible or assume the principal responsibility of ensuring

access to critical supplies when necessary. Congress should make clear that these activities should largely be restricted to declared emergencies but could be used in extraordinary circumstances in the setting of life-threatening drug shortages.

To prepare for an emergency system of distributing medical products, competing hospital systems in the same state or region could create joint allocation frameworks on the model of Maryland's framework for allocation of ventilators and other medical resources.[15] In this model, a central triage center would collect information on hospitals' inventory for scarce medications and would develop a ranking system that determines which facilities and patients should receive the limited drugs first.

CONCLUSIONS: SURVIVING THE NEXT STRESS TEST

Like a stress test of the human cardiovascular system, the COVID-19 pandemic can be seen as challenging the US pharmaceutical supply chain, accentuating the critical spots of strain, the mismatches of supply and demand, and the risks of failure and collapse. This acute stress reveals a series of chronic weaknesses in pharmaceutical production, distribution, regulation, and oversight, which need to be remedied—and remedied soon—if the United States is to emerge from the present pandemic and the divisive 2020 election prepared to face the waves to come.

Ideally, the new administration and Congress can come together to learn the lessons of the COVID-19 pandemic for the supply chain. With only a slim majority in both houses of Congress, successful policy efforts will likely emphasize the areas where the executive branch can act on its own authority through rulemaking and the areas where bipartisan agreement on pharmaceutical supply as a matter of national security can be achieved. Importantly, the federal government must meet the crucial challenge of balancing the need to improve the quality of the global pharmaceutical supply chain while incentivizing domestic drug-manufacturing capabilities as well as developing systems to improve transparency in the pharmaceutical supply chain in the United States and abroad. AJPH

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