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Reshoring Debate Continues As COVID-19 Drives New Wave Of US Drug Shortages

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Executive Summary

As the response to another wave of COVID-19 infections continues, fill rates of critical medicines such as methylprednisolone are dropping. But experts say the answer is not to concentrate manufacturing in US facilities, which could lead to further risks if US supply is disrupted.

COVID-19-RELATED MANUFACTURING HAS LED TO SHORTAGE OF CRITICAL DRUGS *Source: Alamy*

Fill rates of critical medicines are dropping as manufacturers focus resources on producing COVID-19-related vaccines, treatments and supplies, according to data from Premier Inc., a hospital group purchasing, consulting, and advocacy organization.

While drug shortage numbers fluctuate over the years due to various factors, Premier confirmed that of the 162 drugs currently on the US Food and Drug Administration's shortage list, at least eight critical medications have been directly affected by COVID-related manufacturing constraints, including:

- 0.9% sodium chloride;
- Methylprednisolone acetate;
- Metronidazole/sodium chloride;
- Potassium chloride;
- Potassium phosphate, m-basic-d-basic;
- Sodium chloride;
- Water for injection, bacteriostatic; and
- Water for injection, sterile.

The FDA has touted overreliance on foreign sources as the major threat to pharmaceutical supply chain security. (Also see "Real-Time Manufacturing Volume Reporting Could Help Prevent Drug Shortages, Woodcock Tells Congress" - Pink Sheet, 31 Oct, 2019.)

The agency has proposed reshoring manufacturing to the US along with increased use of advanced manufacturing technologies as ways to decrease reliance on foreign-produced medications and strengthen supply chains. However, it's unclear whether these measures would address the current shortages.

Shortage Data

Fill rates are essentially a calculation of supply versus demand, with the number of units of a drug ordered compared with the number received. Historically, a 90% fill rate is considered a healthy level, while rates falling into the 80% range signal a need for further investigation, according to Soumi Saha, vice president of advocacy at Premier.

Throughout the pandemic, Premier has tracked about 300 drugs deemed to be critical for patient care or that are used in the treatment of COVID-19 patients, and in the past four months has seen fill rates of several critical medicines slip well below the 80% threshold.

“No one is arguing that vaccine production doesn't need to be prioritized,” Saha said, but when such items are placed on the backburner, “what is the downstream impact to patient care?”

“What we tried to do is highlight about eight of those products where we’re starting to see the shortages and starting to see some impact. And we unfortunately anticipate that more will be forthcoming,” she said.

Medicine Fill Rates

Source: Premier Inc.

Generic Name	Product Category	Baseline Fill Rate	October 2021	November 2021	December 2021
0.9% sodium chloride	Injection	98.4%	50.5%	34.8%	21.6%
Methylprednisolone acetate	Injection	97.4%	63.5%	50.1%	39.9%
Metronidazole/sodium chloride	Injection	95.6%	63.2%	19.3%	40.6%
Potassium chloride	Injection	95.3%	20.4%	7.8%	6.0%
Potassium phosphate, m-basic-d-basic	Injection	97.3%	75.6%	61.5%	63.2%
Sodium chloride	Injection	90.9%	60.0%	60.5%	11.1%
Water for injection, bacteriostatic	Injection	99.4%	98.5%	47.5%	10.0%
Water for injection, sterile	Injection	98.8%	78.3%	28.6%	16.1%

Share

More Complicated Than It Appears

Rather than affecting new drugs, the shortages are concentrated in lower-cost generics that have been on the market for many years, and due to their low profit margins may have only one or two manufacturers. Such manufacturers may not desire or have the capital to invest in advanced technologies or build extra production capacity and safety stock. (Also see "Will Continuous Manufacturing Mean Continuous Generic Delay? FDA Hears AAM's Warning" - Pink Sheet, 4 Dec, 2017.)

Additionally, some experts believe that relocating manufacturing to the US isn’t an ultimate solution.

Michael Ganio, the senior director of pharmacy practice and quality at the American Society of Health-System Pharmacists, said that having a global supply chain keeps the industry from relying on one region that could be susceptible to disruption.

“There's good quality manufacturing in United States and Canada, and in Europe. Even in China and India there are instances of strong manufacturing. So there's really no reason to on-shore everything. Certainly, having the capacity and the ability to manufacture here is good,” he said, “but we do believe that a global supply chain is the answer. It helps spread out the amount of redundancy in manufacturing.”

Ganio also pointed to Schedule II controlled substances such as morphine and fentanyl, which have experienced “significant supply chain disruptions” in the past several years despite being manufactured in the US.

“We’re not immune to problems for drugs that are made strictly here in the United States,” he said.

Saha echoed Ganio’s points.

“Premier’s stance has always been that global diversity and supply chain is what you need,” she said. She mentioned that she sees a healthy supply chain in thirds, comprising a third domestic, a third near-shore, defined as within all Americas, and a third off-shore production.

“If you move everything 100% back to the US, you continue to create an over-reliance on a single geographical area,” she said.

API Manufacturers and Market Share Are Important

Ganio and Saha explained that in addition to the number of suppliers, the number of active pharmaceutical ingredient manufacturers and the market share of each supplier are also important.

Saha mentioned propofol, which has multiple manufacturers but only three API suppliers.

“So you may think there’s a lot of diversity, but once you start going upstream, there’s actually very little,” she said.

Saha also referenced a class of antibiotics, cephalosporins, for which almost all of the API comes from one source.

Ganio brought up the 2019-2020 shortage of vincristine, a chemotherapy treatment for leukemias, lymphomas and brain tumors in adult and pediatric patients.

Because vincristine can be curative in many regimens, there was an outcry when one manufacturer stopped producing it, he said. However, that manufacturer had only 3% of the market share, while the other manufacturer that made the majority of the product was having quality issues. (Also see "Teva Defends Vincristine Discontinuation Decision" - Generics Bulletin, 21 Oct, 2019.)

“There’s more than just how many manufacturers there are, you have to look at market share,” he said.

Recommendations For Supply Chain Changes

In December 2021, ASHP and four other health groups released recommendations for drug supply chain improvements. The other four groups were the American Medical Association, the American Society of Anesthesiologists, the Association for Clinical Oncology and US Pharmacopeia.

The groups' recommendations include:

- Incentivize advanced manufacturing technology and develop new continuous manufacturing technology for critical drugs and active pharmaceutical ingredients in both domestic and foreign manufacturing facilities;
- Improve the function and composition of the Strategic National Stockpile, including incentivizing the creation of private-sector reserves of essential medicines, medical devices and supplies not adequately provided by the SNS;
- Improve multinational cooperation on supply chain resilience;
- Incentivize quality and resilience; and
- Replicate requests for critical drug manufacturing transparency and oversight for medical devices and ancillary supplies (e.g., personal protective equipment), meaning extend CARES Act provisions and reporting requirements to include medical devices.

Many drug shortages are due to quality issues, said Ganio, especially for older sterile injectable generic drugs. That's where continuous manufacturing could be useful, because the quality control is better and such technology can adapt to address shortages more rapidly.

"These new technologies are more expensive and therefore hard to adopt for some generics manufacturers. But there's a way through regulation or legislation to incentivize the adoption of these technologies, and it'll help reduce the risk of some of these disruptions due to quality concerns," he said.

Actions That Have Been Taken

In April 2020, the Association for Accessible Medicines proposed measures to build on the March 2020 Coronavirus Aid, Relief and Economic Security (CARES) Act and provide more manufacturing incentives for generics and biosimilar producers. (Also see "Generic Firms Want Congress To Build On CARES Act To Prevent Critical Drug Shortages" - Pink Sheet, 30 Apr, 2020.)

The measures included price- and volume-guaranteed contracts for high-priority essential medicines that would be purchased by the government, but the measures so far have not been included in legislation.

On 29 October 2021, the FDA also announced that manufacturers are expected to begin reporting manufacturing production volumes via the NextGen portal starting on 15 February 2022. The requirement stems from a CARES Act provision intended to gain insight into the pharmaceutical supply chain. (Also see "How US FDA Wants Pharmaceutical Production Volumes Reported For Drug Shortage Prevention" - HBW Insight, 3 Nov, 2021.)

Saha said that the CARES Act volume reporting will be useful to understand upstream visibility in manufacturing, and it's valuable that API manufacturers will also need to report shortages to the FDA. "We think that's critical in order to start catching some of these shortages more upstream, and be able to proactively address them, versus waiting until they hit the patient care level," she said.

Another CARES Act requirement is the creation of risk management plans for life-saving drugs. However, industry representatives have said that the FDA's definition of "life-saving" is so broad that it could encompass 90-95% of the prescription drugs in an organization's portfolio, and that creating risk management plans for all of them would be an undue burden. (Also see "Industry Fears Report-Writing Burden From Supply Chain Risk Guidance US FDA Is Drafting" - Pink Sheet, 9 Nov, 2021.)

In response, Saha said that that "we absolutely understand" and "it's going to be a lift in the beginning," but that the hope is that it's an initial effort to start creating the plans and get the initial volume reporting in, and thereafter it would become part of a routine reporting process to the FDA along with current regulatory reporting requirements.

"We think the benefit of having this information is absolutely critical, given the 200-plus drugs that we can see on a drug shortage list at any given moment in time, COVID or non-COVID. That's just the way the market has been for about 20 years now, and we need to change that dynamic," she said.

"There's no silver bullet to drug shortages, there's a multitude of reasons why they occur, and there's going to have to be a really holistic approach to addressing them."