

Federal Policies to Address Persistent Generic Drug Shortages

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JUNE 2023

ACKNOWLEDGMENTS

We would like to thank Wendy Edelberg, Lauren Bauer, Matt Fiedler, Josh Gotbaum, Erin Fox, Laura Bray, Rena Conti, and participants in the Hamilton Project Authors' conference for helpful comments on this proposal. We also thank The Commonwealth Fund for providing financial support for this project.

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June 2023

This policy proposal is a proposal from the author(s). As emphasized in The Hamilton Project's original strategy paper, the Project was designed in part to provide a forum for leading thinkers across the nation to put forward innovative and potentially important economic policy ideas that share the Project's broad goals of promoting economic growth, broad-based participation in growth, and economic security. The author(s) are invited to express their own ideas in policy proposal, whether or not the Project's staff or advisory council agrees with the specific proposals. This policy proposal is offered in that spirit.

BROOKINGS

Abstract

Generic sterile injectable or GSI drugs are the staple of hospital care, so shortages of these drugs can affect patients in emergency rooms, ICUs, cancer clinics, and outpatient elective surgery departments. Shortages of GSI drugs can have substantial adverse impacts through treatment delays, the use of inferior alternatives, and an increased risk of medication errors.

Market dynamics are at the heart of persistent GSI shortages. Hospitals primarily consider the price of competing GSI products because they can neither observe drug quality directly nor do they carry the full burden of patient harm resulting from shortages. Price pressures, coupled with FDA's inability to enforce strictly manufacturing quality standards, reduce a manufacturer's commitment to good manufacturing practices. When manufacturing quality problems are uncovered, often after FDA inspections, recalls and production stoppages can lead to shortages.

To reduce the incidence of GSI drug shortages, Wosińska and Frank propose policies that foster greater manufacturing reliability in GSI drug production. Their proposal combines push incentives to improve manufacturing infrastructure with the implementation of pull incentives through a pay-for-performance program that rewards hospitals for taking steps to prevent shortages before they occur. In addition, Wosińska and Frank propose a targeted government-funded buffer inventory to insure against supply chain shocks for drugs of particular public health import.

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Introduction

Nearly every hospital patient in the United States is treated with generic sterile injectable drugs (GSIs). Shortages of GSI drugs compromise patient care in emergency rooms and intensive care units, in cancer treatment, and during elective surgeries. Any such shortage can have substantial adverse impacts through treatment delays, the use of inferior alternative products, and an increased risk of medication errors.

What makes shortages of GSI drugs unique is that GSI shortages are disproportionately triggered not by exogenous factors, such as demand shocks or natural disasters, but rather by market-driven manufacturing quality problems.

To help address shortages of GSI drugs and the manufacturing quality problems that cause many of them, we propose a policy intervention with three components:

- **Component 1. Supporting Manufacturing Infrastructure Upgrades.** These are supply-side or push incentives to upgrade the GSI manufacturing infrastructure.
- **Component 2. Providing Incentives to Realign Hospital Purchasing.** These are demand-side or pull incentives to hospitals to procure from more-reliable manufacturers and to take other actions to prevent shortages.
- **Component 3. Buffering Through a Targeted Government-Funded Inventory.** This is a first-in-first-out buffer inventory that serves as a form of insurance for select critical drugs.

As we describe in this policy proposal, market forces have led to underinvestment in GSI manufacturing infrastructure. However, supply-side incentives alone, while proposed herein and important, would not be sufficient to address drug shortages. We therefore complement promotion of new investment with incentives for the demand side of the market. It is the demand side of the market, where hospitals pay disproportionate attention to price and far less attention to manufacturing reliability, that drives manufacturers to cut corners, thus increasing the chances of supply interruptions.

The demand-side incentives we propose include a pay-for-performance mechanism that rewards hospitals for taking steps to prevent future shortages during non-shortage periods, such as by building a buffer inventory and selecting vendors that are less likely to experience production disruptions. To support hospital decision-making, we propose ways for the US Food and Drug Administration (FDA) and other parties to provide information about manufacturer quality and reliability. In our proposal, we emphasize manufacturing quality, rather than just drug shortages, because compromised products can and do make their way to patients (Lupkin 2019).

Finally, we propose that the US Department of Health and Human Services (HHS) develop a targeted buffer inventory at the national level to complement hospitals' efforts. This first-in, first-out buffer inventories would serve as insurance for drugs the short supply of which would lead to dire health consequences. The government buffer inventories we propose would also help to allocate products to locations where they are most needed in a shortage.

The Challenge

In this section we describe GSI drugs shortages and the factors responsible for these shortages.

Manufacturing quality problems are a direct result of specific market dynamics and the regulatory environment. On the one hand, hospitals consider two versions of the same generic drug to be perfect substitutes. With the buy side of a drug highly consolidated, price pressures on manufacturers are significant. On the other hand, it is difficult for hospitals to observe quality or for FDA to enforce quality.

These dynamics contribute to manufacturing quality problems. With low prices and margins, firms lack incentives to upgrade facilities, may overuse their existing equipment, and may cut corners with respect to the tight manufacturing and quality control processes (Kansteiner 2023). Often only after being caught by FDA for violating current Good Manufacturing Practices (cGMPs), companies discard large batches of compromised product (Eglovitch 2022) or, worse, recall such batches after releasing them to the market (California State Board of Pharmacy 2023). To remedy persistent problems such as mold or metal shavings from machinery infiltrating product, manufacturers may have to shut down lines or even entire facilities temporarily to address problems (Cundell 2016). In some cases, they choose to close the sites permanently (Becker 2023). Any of these scenarios can lead to shortages.

GSI Drug Shortages

Shortages of GSI drugs first became a recognized problem in 2011 when an unprecedented 251 drugs went into shortage, of which 179 were GSI drugs (FDA 2013). A phenomenon long in the making began to create dramatic headlines in 2011, leading both the White House and Congress to address shortages through improved reporting of production disruptions to FDA and coordination within FDA in response to shortage threats.

Drug shortages listed on FDA's website have dropped from the shortage peak in 2011 but have nevertheless persisted because reporting and coordination do not address the underlying market forces driving these shortages. Recent analyses suggest that shortages are again on the rise (US Senate 2023).

The January 2023 FDA drug shortage list included 77 GSIs, comprising 62 percent of all drugs then in shortage (FDA 2023a). Among those drugs in shortage were widely used products such as saline, morphine, and solutions used to dilute other drugs. The shortage list also encompassed medically necessary cancer drugs including leucovorin and cytarabine, crash cart drugs including epinephrine and calcium gluconate, anesthesia drugs including propofol, and hormones including oxytocin and somatropin.

Drug shortages have serious consequences for hospitals' ability to deliver care. According to a 2019 survey (Vizient 2019), virtually all hospitals experienced shortages in 2018, with close to two-thirds of hospitals experiencing more than 20 shortages at any given time. One study (Lin et al. 2022) found that the majority of the 30 most frequently used emergency department drugs experienced shortages between 2006 and 2019. Another analysis (McBride et al. 2013) found that a 2011 shortage of oncology drugs resulted in 93 percent of providers reporting delays in administration of the drugs or changes in treatment regimens, 16 percent reporting near-miss medication errors, and 6 percent reporting one or more actual medication errors.

Studies of specific drug shortages illustrate the serious effects of individual shortages on patient health outcomes. A 2011 shortage of epinephrine caused a 27 percent decrease in the use of the drug for septic shock; this was subsequently found to have led to a 3.7 percent increase in the rate of in-hospital mortality for that condition (Vail et al. 2017). The 2009 shortage of mechlorethamine led providers to use cyclophosphamide in treating Hodgkin's lymphoma in children, with the subsequent two-year survival rate decreasing from 88 percent to 75 percent (Metzger, Billett, and Link 2012). The 2014 shortage of the antibiotic piperacillin/tazobactam (PIP/TAZO) led to a 30 percent increase in the onset of *Clostridium difficile* infections (Gross et al. 2017).

Hospitals also lose out when shortages occur. Recent research suggests that hospitals incur about \$365 million yearly in extra labor costs and \$230 million in extra payments made to purchase substitutes (Vizient 2019). Hospitals sometimes have had to send patients to other hospitals because they did not have a drug available (Hantel et al. 2019). There may also be reputational effects and staff burnout.

However, these hospitals' costs are low in comparison to the resulting patient harm. One unpublished FDA analysis (Rosenberg 2018) used the value of a statistical life calculation to estimate a social cost of \$13.7 billion from increased mortality due to a single 2011 shortage of norepinephrine. This translates into over \$2 million per hospital. In contrast, the extra labor losses hospitals experience across *all shortages* in a year translate into only \$66 thousand dollars per hospital, 0.05% of average hospital budget. Even accounting for the harder-to-qualify costs to hospitals, there is an immense gap between the social and private benefits to having a reliable supply chain of drugs made to specification.

The Supply Side of the GSI Market

The market for GSIs differs significantly from the market for oral dose products (i.e., pills). There are about 300 to 400 different FDA-approved, physician-administered GSI drugs, in contrast to more than 2,000 generic oral dose drugs sold in pharmacies. The use of GSIs is much more specialized and therefore the markets are typically significantly smaller than the markets for oral dose products, on the order of 200 times (Frank, McGuire, and Nason 2021). These markets invite much less entry than oral dose products and, after accounting for exit, many end up highly concentrated (Frank, McGuire, and Nason 2021). Our analysis of the FDA Orange Book data (FDA 2023a) cross-walked with the FDA list of marketed products (FDA 2022b) suggests that about 20 percent of GSI molecules have only one generic manufacturer, or 15 percent if we account for active branded versions.

Manufacturing of GSIs

It is complex to produce GSIs because there is less room for error in the final production stage than in production of oral dose products. When drugs are taken orally, the patient's digestive system typically destroys harmful microorganisms and filters out impurities. Because sterile injectable drugs are injected into the body, often directly into the blood stream, it is extremely important for the drug to be sterile and free of particulates.

This lower margin for error requires that the final fill-and-finish manufacturing stage be done in specialized facilities with well-defined manufacturing processes and controls that employees follow. This ensures that the resulting product is free of contamination from all microorganisms and that it is also free of particulate matter.

A multitude of daily management decisions establishes quality assurance, including equipment selection, maintenance, quality of materials, staff

qualifications, supervision, process control, and thorough investigations of any manufacturing problems that arise (Woodcock and Wosińska 2013). But establishing the right controls can be challenging; many GSI production lines tend to repeatedly switch between products, with a single line being used for as many as 20 to 30 products over the year. Repeated manual interventions to clean lines between products and to address mechanical problems on heavily used and aging production lines raise the risks of introducing particulates and microbial contamination (Woodcock and Wosińska 2013).

Despite studies indicating plentiful sterile manufacturing capacity in the United States (Sardella 2022), supply is constrained in the short run for most GSIs for several reasons. First, a company must have an FDA authorization to market a product, and a manufacturing site must have FDA approval to make the product. Even when facilities have approval, many lines run 24 hours a day, 7 days a week, meaning that expanding production of one drug would mean having to postpone production of another product. Lastly, the ability to move products to other lines in the facility may be limited because production lines of GSI drugs are commonly dedicated to products with specific chemical properties, presentation form, and potential for cross-contamination (Woodcock and Wosińska 2013).

In the meantime, US GSI manufacturing infrastructure is deteriorating. Some large GSI manufacturers have self-funded upgrades (Blankenship 2020) or expanded facilities (Pharmaceutical Technology 2018) in the United States, but external financing options have been limited because returns on GSI investments are projected to be low. As a result, US plants continue to close (Becker 2023), while an increased number of sites are being opened in India with Indian government support (International Joint Ventures and Merger & Acquisitions 2020).

Less profitable GSI products are at a disadvantage when manufacturers shift production because there are meaningful costs to transfer technology from one site to another. Changes in the manufacturing process, whether a shift to a new site or upgrades to an existing line, may require validation, comparability studies, and technology transfer documentation (FDA 2004). Our conversations with manufacturers suggest that it may require a year or two to complete the tech transfer process for a GSI facility with a broad portfolio. Because the process is often burdensome and therefore costly, manufacturers may drop the less-profitable and generally older products from their portfolio if that portfolio is being transferred.

FDA Oversight of GSI Manufacturing

FDA regulates manufacturing standards and enforces those standards for facilities supplying the US market. A product cannot be manufactured until FDA approves the production facility as having met those standards. FDA's ability to enforce those standards and to ensure that all products are made to exact specifications is limited, however.

One reason limiting FDA's oversight is inspection frequency. Historically, FDA had to inspect US-based facilities at least once every two years, but there was no similar statutory requirement for foreign-based facilities. The Generic Drug User Fee Act (FDA 2023d) helped remedy that historical imbalance by providing additional resources to inspect facilities located abroad and shifting the inspection framework to focus on facilities at highest risk of noncompliance. Nonetheless, because almost all the foreign inspections are announced before they take place, the effectiveness of the risk-based inspection program is weakened. Between inspections, FDA relies on firms to be forthcoming about self-reporting any quality problems, which they do by issuing defect reports (FDA 2021).

During inspections, FDA relies on evaluation of a firm's manufacturing operations, including its system for quality management. The reliance on process review is particularly important in sterile operations because it can be difficult to detect defects in sterile injectable products, and therefore product sampling is not a reliable tool for assessing manufacturing quality (Woodcock and Wosińska 2013).

But perhaps the most significant challenge FDA faces is what might be referred to as a too-important-to-fail problem with the GSI facilities that manufacture a large share of medically necessary products. Because addressing developing quality problems requires slowing down or temporarily disrupting production, FDA must balance the short-term harm from creating a shortage with the potential impact of a manufacturing problem (Woodcock and Wosińska 2013). To enable continued distribution of the medically necessary drugs, FDA often uses regulatory flexibility in the face of looming shortages, which allows a manufacturer to depart from the requirements defined by current cGMPs (FDA 2023b).

Transparency of Manufacturing Quality

The intended audience for documentation produced by FDA staff during oversight of the manufacturing process and product quality is not the buyers or the public, but rather it is either other FDA staff or manufacturers. As such, what is publicly released is often redacted, released only after delays, and difficult to interpret.

FDA does not release commercial-confidential information, including information about which products

are made in which facilities. In contrast to the European Union, where directives require manufacturers to provide the location of the site responsible for release of the final product (European Parliament 2012), manufacturers selling in the US market have the option to either list which manufacturer the product is made by or which manufacturer it is made for (FDA 2009). If the product is identified as "made by," the pool of potential sites can be narrowed. Identifying it as "made for" leaves the field of possible facilities wide open.

On its website, FDA discloses many inspection reports, warning letters, and voluntary recalls, as well as import alerts (FDA n.d.). But in keeping with disclosure practices for commercial-confidential information, FDA redacts names of products when it releases inspection reports and other communication with manufacturers. In addition, there are frequently delays in posting documents on the FDA website. And, because the redaction process requires resources, not all documents are posted.

The Demand Side of the GSI Drug Market

Annual spending on physician-administered GSI drugs in the United States is about \$15 billion (BioSpace 2022). For most GSI drugs, the primary purchasers are hospitals, followed by clinics. There are around 6,000 hospitals in the United States (American Hospital Association 2022), with a wide range in size, from rural hospitals with 25 beds or fewer (American Hospital Association n.d.) to New York Presbyterian Hospital with 2,600 beds (New York-Presbyterian n.d.).

GSI drugs are a staple of hospital care. Our conversations with hospital pharmacists suggest that GSIs can represent three-quarters of hospital pharmacy drug volume. These drugs include crash cart drugs, antibiotics, electrolytes, anesthetics, and controlled substances. Of the 33 million annual inpatient stays (Agency for Healthcare Research and Quality n.d.), almost every stay includes treatment with at least one GSI drug.

Most hospital payment arrangements for GSI drugs encourage hospitals to minimize spending on inputs into treatment like GSI drugs. Medicare, the largest payer for hospital stays, bundles reimbursement for GSI drugs with other hospital services provided during an inpatient stay, which gives hospitals incentives to keep bundle input costs low. Such incentives also exist when GSIs are separately reimbursed in outpatient settings. If the daily drug cost is under \$135, the drugs are bundled as they are in the inpatient setting. If the daily drug cost is over \$135, payment rate is based on the average cost across manufacturers, providing incentives to buy the lowest cost version (CMS 2023a). Other payers create similar reimbursement schemes.

Hospital Purchasing Practices

From a clinical perspective, different presentations of the same drug molecule increase the risk of medication errors if they look different or if they must be administered differently. To avoid medication errors, hospitals prefer to buy a single version of a drug from a single manufacturer. However, pharmacy costs represent a significant cost center, so hospital pharmacies are under constant pressure to keep costs down. With limited leverage over purchase prices of patented branded products, hospitals pay a lot of attention to GSI prices.

To obtain low GSI drug prices, hospitals pool their bargaining power. Almost all hospitals use group purchasing organizations (GPOs) to negotiate for a variety of supplies—from masks, gowns, and cleaning supplies, to drugs, surgical supplies, and medical equipment (Definitive Healthcare 2023). The top three GPOs collectively represent hospitals that account for more than 80 percent of hospital beds (Definitive Healthcare 2023), which gives them substantial collective purchasing power to negotiate prices. Vizient holds the largest share of the market with 37 percent of hospital beds, followed by Premier with 28 percent, and Health Trust with 15 percent. If we exclude federal hospitals, those companies' shares are even greater.

The contracts GPOs negotiate, which typically have terms of one to three years, are binding to the manufacturer on price, but generally do not specify purchase guarantees. GPO contract prices are generally attractive relative to other options, and GPOs give some financial incentives to hospitals to buy products through GPO contracts, but finding lower prices from another manufacturer can result in a hospital buying off-contract. Hospital pharmacists report that they are willing to undergo the needed IT system changes if the resulting savings would be as little as \$5,000.

Hospitals can buy off-contract because participation in a GPO is voluntary. While GPOs assist hospitals with pricing negotiation, hospitals purchase from wholesalers that distribute the product and often engage in logistical support around inventory management. A wholesaler will load the hospital's GPO contract to its portal, but it will also provide other options. Just as grocery vendors pay extra for prominent product displays at the end of the aisle, manufacturers can provide discounts for being part of a wholesaler vendor program.

There are three major wholesalers, collectively representing about 90 percent of the wholesale drug distribution in the United States (Seeley 2022). A given hospital will contract with one wholesaler. Unlike in the retail market, wholesalers are not aligned with GPOs, so there is variation in the wholesaler-GPO pairs.

Hospitals generally do not purchase directly from manufacturers because they value the one-stop shop of using a wholesaler and do not want to incur the

costs of holding and managing inventory. The exception is in times of shortage, when some of the larger manufacturers switch to shipping directly.

During shortages, hospitals typically attempt to raise their inventory levels by increasing their orders well above their expected needs (Hantel et al. 2019), which can then further exacerbate a shortage. Ultimately, wholesalers and manufacturers apply allocation schemes, often based on historical purchase patterns; nevertheless, it can be challenging to recover from a period during which buyers hoard supply. Manufacturers expect to experience a bullwhip effect (Inturn n.d.), where changes in demand are amplified through the supply chain; they expect their sales to drop substantially, as hospitals draw down their inventories post-shortage or as they switch permanently to alternatives. This situation can reduce incentives for manufacturers to ramp up production.

Between shortages, hospitals tend to rely on just-in-time deliveries from wholesalers, although anecdotal evidence suggests that they will carry higher inventories of drugs such as protamine, a drug that is used in highly profitable cardiac surgeries, as an inadequate supply can result in serious revenue losses for hospitals.

Efforts to Address Shortages

The persistent shortages of GSIs have elicited a variety of responses from GPOs, wholesalers, and hospital systems; third parties have not responded, however, because federal regulations, such as the Prescription Drug Marketing Act (FDA 2022c) and the Drug Supply Chain Security Act (FDA 2023c), limit prescription drug arbitrage through reselling.

Holding buffer inventory is one way to improve continuity of supply. Both GPOs and wholesalers have created new contract options for their hospital clients. Hospitals now can pay wholesalers to hold allocated inventory (Ten2Eleven Business Solutions n.d.). GPOs have begun to expand their private label programs (Vizient 2022), which include buffer inventories. Nonprofit ventures such as Civica Rx have been stood up. Civica Rx signs five-year fixed-price fixed-quantity contracts that include six months of inventory. Civica Rx members, consisting of several large health systems, identify which products at high risk of shortage Civica Rx should contract for.

Identifying and limiting contracts to reliable manufacturers is another way that buyers can improve continuity of supply. As discussed in the section "The Supply Side of GSI Market," transparency of manufacturing quality information is limited, but GPOs can compel manufacturers to share confidential business information if there is competition in manufacturing supply, and to use this information to inform their

contract selection. Civica Rx also vets the manufacturers with which it signs long-term agreements.

Several start-up efforts have sprung up to improve visibility of supply chains. The US Pharmacopeia (USP) has brought together multiple data sources, including its information on drug substance monographs, to create the USP Supply Chain Map (USP n.d.). A start-up venture called RISCS has developed a rating system for sterile injectable manufacturers on their resilience efforts for specific products (RISCS n.d.).

Although promising, the efforts listed in this section have not been widely adopted because hospitals are reluctant to pay for resilience. The members of the Civica Rx cooperative represent a third of hospital beds, but fewer than 10 percent of GSI sales go through Civica Rx. Standard GPO contracts might include a review of reliability, but a higher contract price would drive hospitals to buy off-contract. The supply-chain visibility efforts are also realizing limited uptake.

The Proposal

Our policy proposal to bolster resilience in the GSI market has three interrelated components:

1. Supporting manufacturing infrastructure upgrades.
2. Providing incentives to realign hospital purchasing.
3. Buffering through a targeted government-funded inventory.

The first component includes financial and regulatory supply-side push incentives to improve the GSI manufacturing infrastructure. The second involves demand-side pull incentives, using the Medicare hospital payment systems to encourage hospitals to internalize more of the social benefits from improved reliability in supply. FDA plays a key role as a party that generates critical information so that hospitals and their purchasing agents can observe which manufacturers have greater reliability of supply.

As we have noted, manufacturing quality problems are primarily driven by employees who do not follow quality assurance processes. Deteriorated infrastructure is making it increasingly difficult to follow those processes, however. Component 2 proposes ways that would drive demand to more reliable manufacturers, stabilizing their demand and allowing them to carry a price premium, but the existing financing options make access to capital difficult in a market that is not yet stable.

To the extent that policymakers want to improve the domestic GSI base, they would need to supplement the critical demand-side reforms with supply-side investments.

Our proposal also includes buffer inventories on two levels. The first level is credit for hospital inventories as part of the Medicare payment policy (component 2), and the second is a separate buffer inventory program, overseen and funded by the federal government, which serves as a form of insurance during the transition period to a more stable GSI marketplace (component 3).

Component 1: Supporting Manufacturing Infrastructure Upgrades

We propose two-part support for infrastructure investment, particularly among smaller manufacturers; we also propose FDA regulatory support to encourage those investments.

Funding to Modernize Manufacturing Infrastructure

To address the challenges of the current financing environment, we propose that HHS offer targeted low-interest loans to smaller manufacturers so they can invest in upgrading infrastructure that will lead to improvements in manufacturing quality and reliability. Instead of funding a specific technology, HHS should fund proposals that show how the company would use capital investments to support a quality operation in recognition that different GSI facilities require different investments to improve operations.

We further propose that part of the loan be forgivable when a company achieves agreed-on milestones that reflect the quality management maturity (QMM) principles of establishing the proper employee processes and controls that are required in a quality operation. In addition, greater loan forgiveness could be tied to setting aside, contractually, a certain percentage of production to manufacture older GSI drugs that are more vulnerable to shortage.

We propose \$2 billion in loans of which we propose up to half be forgivable. Funding requirements would vary from company to company, ranging from several million dollars to \$250 million for major updates to large sites (Palmer 2013). Relatedly, costs of recent non-GSI sterile injectable plant expansions have ranged in cost from \$10 million to \$150 million (Van Arnum 2022), and a new fill-and-finish facility can cost upwards of \$500 million (Pfizer 2018).

This kind of whole package proposal is already used in the HHS's Administration for Strategic Preparedness & Response (ASPR) Industrial Base Expansion (IBx) Connect, which is a program focused on

expanding the manufacturing base for medical countermeasure preparedness (Biomedical Advanced Research and Development Authority n.d.). Funding infrastructure investments would require either modifying the IBx program to include products not limited to countermeasures or setting up a parallel program at FDA. Both these pathways would require congressional appropriations and new authorities.

Regulatory Support for Technology Transfer

We recommend an improvement to FDA's approval process of manufacturing supplements, which companies must file with FDA if they want to make manufacturing changes to already approved drugs. FDA currently gives higher priority to changes in production lines for drugs in shortage, including GSI drugs. When it comes to production line improvements or moving to newer lines, we recommend that FDA give the same priority to changes related to GSIs that are not in shortage but that are at high risk of being in shortage. Regulatory support is an important tool that FDA could use to lower the cost of technology upgrades and transfers that may jeopardize the manufacturer's willingness to continue producing older, less-profitable GSI drugs.

Component 2: Providing Incentives to Realign Hospital Purchasing

Component 2 is the core component of our proposal. It creates pull incentives for hospitals to take actions that prevent shortages by procuring from more-reliable manufacturers and by using inventory buffering strategies.

Medicare, whose beneficiaries represent almost half of all inpatient stays (Healthcare Cost and Utilization Project n.d.), is well positioned to influence hospital behavior. We propose that Medicare develop a hospital drug shortage scorecard that rates hospitals on their efforts to prevent shortages. The drug shortage scorecard would serve as a basis for yardstick competition among hospitals, where a given hospital's scorecard is compared to scorecards from a group of peer institutions. Medicare would also create a schedule of payment adjustments to the total spending associated with GSIs that would be based on a hospital's relative performance.

The Centers for Medicare & Medicaid Services (CMS) uses similar schemes to motivate Medicare Advantage plans to provide quality care (Fuglesten Biniek et al. 2022); Community Behavioral Health Centers to supply crisis and integrated care services (HHS

2023); and hospitals to curb readmission (CMS 2023a), health-care errors that cause patient harm (CMS n.d.a), and hospital-acquired conditions (CMS 2023b).

Transparency on Manufacturing Quality and Reliability

Before we describe the hospital drug shortage scorecard and the CMS payment mechanism, we describe the data and measures needed to support the scorecard. We describe two such areas: increasing accessibility of existing cGMP compliance data, and development of new QMM measures.

Increasing Accessibility of Existing cGMP Compliance Data

FDA can support hospital buyers' efforts to assess cGMP compliance in three ways. First, FDA should provide guidance for hospital buyers that explains the oversight process and describes what information is exchanged with companies, so that hospital buyers know what information to ask for and at what stage in the process they should ask for it. Second, FDA should refine and publicly share inspection facility ratings (Unger 2019) and ratings used in the new inspection protocol project (Center for Drug Evaluation and Research Office of Pharmaceutical Quality n.d.) established for sterile injectable drugs (Gottlieb 2018). Third, FDA should make the inspection reports easier to interpret. For example, FDA could add a severity matrix to inspection reports similar to what the Joint Commission does in hospital assessments (Joint Commission n.d.).

Although these efforts will help buyers assess manufacturer compliance with cGMPs, buyers must still be able to map products to facilities; such mapping is a data element that is currently considered to be proprietary and so is redacted from inspection reports. Congress is best positioned to address this information gap by requiring manufacturers to disclose the location of the facility in which the final product is manufactured. Manufacturers frequently raise supply-chain security considerations for keeping information private, yet they comply with such disclosures in the European Union (European Medicines Agency 2022) without apparent meaningful harm.

In the absence of congressional action, we recommend that FDA assess what information it could additionally disclose under the FOIA Improvement Act of 2016 (US Department of Justice [DOJ] 2016). This act requires that agencies withhold information under the FOIA "only if the agency reasonably foresees that disclosure would harm an interest protected by an exemption" or "disclosure is prohibited by law" (DOJ 2016). There are strong benefits to sharing many

elements of supply-chain information, while the harm from such sharing is probably limited. For example, FDA may find that the FOIA Improvement Act allows them to publicly narrow down the pool of facilities in which the product might be manufactured, for example to determine which firm-owned facilities are able to produce sterile injectable products.

Congress would need to fund this and other FDA initiatives.

Standing Up the QMM Program

The disclosures we describe above relate to cGMP records, which are lagging indicators of the quality of manufacturing operations. FDA is also developing leading indicators of manufacturing quality under the QMM program (CDER 2023). Given the importance of manufacturing quality signals in addressing GSI shortages, we encourage FDA to focus the development of that program on fill-and-finish in facilities that manufacture GSI drugs.

As envisioned under the QMM program, FDA would rate active pharmaceutical ingredients and finished dose facilities on a scale that reflects the level of QMM (Maguire et al. 2023). QMM is reflected in the facility's leadership and governance, knowledge management, continual improvement, workforce engagement, stakeholder engagement and satisfaction, and operations. According to FDA, "Mature quality systems promote proactive detection of vulnerabilities, prevent problems before they occur, and foster a culture that rewards process and system improvements (Maguire et al. 2023, p. 14)."

The QMM program need not be mandatory for it to support our proposal. Voluntary participation would work here because component 2 in our proposal gives reasons for higher rated manufacturers to not only participate but to disclose their rating. But to level the playing field for manufacturers, FDA should consider releasing the first batch of QMM ratings to participating manufacturers at the same time and then publicly posting ratings for manufacturers that choose to disclose their ratings.

Once developed, we recommend that manufacturers that are willing to disclose their QMM ratings attach them to products made in that facility. In other words, a specific National Drug Code would have its own QMM rating, representing the facility at which it was made. With that code in place, our proposal works within the existing confines of business confidentiality, with no need to disclose which products are made at which facility. It is rare for GSIs to be made in multiple facilities owned by the same manufacturer, but, if that is the case, companies should assign distinct National Drug Codes that are facility specific.

The QMM program is the most important and the most involved FDA initiative we propose. It will require

additional appropriations. Because of its importance in supporting demand-side initiatives, it should take priority over other time-intensive transparency efforts in this space listed in the cGMP data transparency discussion above.

Because a QMM rating system may take time to establish, FDA should provide informal guidance to GSI drug buyers on what QMM-related information to invite in requests for proposal (RFPs) and how to interpret incoming data. For example, reliance on paper records instead of on electronic laboratory information management systems may be a strong indication that the facility is not capable of proactive quality monitoring, and therefore information about recordkeeping systems might be something worth asking for in RFPs. Similarly, high staff turnover and low training investment could mean that staff are not being trained properly. Such an informal guidance would support the implementation of the drug shortage scorecard ahead of QMM being fully functional.

Drug Shortage Scorecard

The Medicare drug shortage scorecard would reflect a combination of two measures: (1) a hospital inventory index and (2) a reliable manufacturer index.

Hospital Inventory Index

The hospital inventory index would measure the level of inventory when a supply disruption occurred. This index would be a retroactive measure for shortages added to the FDA's drug shortage website in the relevant year. The eligible inventory would be inventory held at the hospital, committed wholesaler inventory (other than historical allocation), or committed inventory held by the contracted manufacturer (as in the case of Civica Rx or through a GPO private label program we described in the "Hospital Purchasing Patterns").

At the end of the relevant year, hospitals would report inventory at a date specified by Medicare. That trigger point date, different for each shortage, would be the earlier date of the manufacturer's report of disruption to FDA in 21 USC 356c (FindLaw 2018) or other public signals of the shortage. We recommend that Medicare structure the index with greater weights for drugs that are used more and for drugs that do not have therapeutic substitutes.

Reliable Manufacturer Index

The reliable manufacturer index we propose is a composite measure comprising two elements: whether a hospital is picking manufacturers that are not having production disruptions (picked right) and whether a

hospital is procuring product from manufacturers rated above a certain level of the yet-to-be-developed FDA QMM measure (QMM measure). Both measures relate to reliability of manufacturers, but they differ in construction, in the level of responsibility and behaviors they encourage, and in the timing of their implementation.

Like the hospital buffer inventory index, the picked-right measure would look back to the trigger point date of an FDA-listed shortage and then assess the share of purchases that the hospital procured from manufacturers other than the one triggering the shortage (as reported under 21 USC 356c; FindLaw 2018). In some cases, there may be no at-fault manufacturers (as with a demand shock) or there could be multiple (as with an active ingredient shortage). In contrast, the QMM measure would apply to all GSI drugs throughout the full year, irrespective of whether any of them ends in shortage, also looking at the share of sales coming from QMM manufacturers rated above a certain level.

The picked-right metric places more responsibility on the hospital, and by extension on the hospital's GPO, to use existing and proposed information sources to identify which manufacturers are more reliable. In turn, the QMM procurement measure places responsibility on FDA to develop and validate QMM metrics and the extent to which they are predictive of reliability in manufacturing products to specification.

Both measures are important, however. The QMM measure drives hospital purchasing practices toward manufacturers that have high QMM of the fill-and-finish facility. The picked-right measure is broader: it rewards hospitals for procuring from manufacturers that have a combination of quality operation and supply-chain resilience through strategies such as dual sourcing, redundant capacity, or higher raw materials and finished product inventories (RISCS n.d.).

The picked-right measure would shift the weight that hospitals place on price versus reliability of supply, in turn incentivizing GPOs and wholesalers to weigh these more heavily. The metric would induce greater vetting of manufacturers to assess their supply-chain resilience and paying more for the higher level of reliability or quality. Hospitals could leverage existing GPO, wholesaler, or Civica Rx programs we described in the section above, "The Challenge." This metric could fuel efforts such as the nongovernmental RISCS rating system mentioned above or USP's Medicine Supply Chain Map (USP n.d.).

The Medicare drug shortage scorecard would necessarily need to be rolled out in phases because the QMM rating is not yet available through FDA. Initially, Medicare would set up the scorecard based solely on the inventory and picked-right measures and would introduce the QMM procurement measure later. Once those measures are available, Medicare could choose whether to weigh the reliable manufacturer

measures equally or to weigh one more than the other based on public stakeholder input and assessment of past hospital responses to the drug shortage scorecard measures.

To support hospital decision-making, Congress should allow public disclosure of which manufacturer had a production disruption that triggered a shortage. Because the scorecard creates measures based on multiple shortages—in recent years around 30 to 40 a year—our proposal minimizes inadvertent disclosure of what could be considered business-confidential data. Congress should formalize disclosure by CMS of the shortage trigger, however, so that there is a feedback mechanism to hospitals for when they picked right and when they did not.

Payment Adjustments

Our proposed payment adjustment leverages two lessons learned from multiple pay-for-performance programs. First, it is important for the payment scheme to be continuous in order to avoid payment cliffs. Second, the benefits of participation must outweigh the cost of participation in the program, including penalties.

As in the Medicare Value-Based Payment program (CMS n.d.b.) we propose that Medicare set up yardstick competition payments based on the drug shortage scorecard performance of a hospital relative to its peer group average. We propose to establish peer groups in a way that accounts for differences in drug mix, hospital size, scope of services, and geographic location. Such construction of peer groups sets aside the impact of common shocks, thereby preserving the yardstick competition incentives. It is important, however, that peer groups include hospitals affiliated with different GPOs in order to extend the competition to those GPOs.

Unlike the Medicare Value-Based Purchasing program, which is budget neutral, we propose that the pay-for-performance program presented here makes additional payments for improved reliability and quality that would not be budget neutral. It is important that the program provides enough support to cover the cost of participation.

We propose that Medicare estimate the payment adjustment on the cost of participation in the program plus any additional payments necessary to motivate adjusting GSI purchasing arrangements.

We do not possess sufficiently detailed data to assess average participation costs. We anticipate that Medicare would be able to estimate product-specific costs, such as carrying inventory or paying a price premium for resilience by looking back at the prior year, using inventory level data provided by hospitals, and assessing the price differential between reliable and unreliable manufacturers. Other participation

costs would likely accrue to GPOs or entities such as Civica Rx, which would do the manufacturer vetting on behalf of hospitals. As such, these compliance costs would be spread across many hospitals, thus limiting those costs.

An initial assessment based on discussion with industry sources suggests this would likely require additional revenues that are 5–20% above current hospital spending on GSIs in competitive manufacturer markets. Assuming financial incentives would need to entail a 20% increase in revenues over the estimated \$15 billion in annual spending on all physician-administered GSI drugs in the United States, the expected total increase in federal spending would be \$3 billion per year.

Component 3: Buffering Through a Targeted Government-Funded Inventory

The Medicare drug shortage scorecard would encourage hospitals to carry higher levels of inventory or to have wholesalers or manufacturers hold inventory on their behalf. Hospitals would have an incentive, however, to select buffer inventory levels based on probability of shortage instead of on the value of the drug to patients. Because the social costs of even short supply interruptions for some drugs are so significant, public intervention through a government buffer inventory is likely socially efficient.

Another reason for creating a government buffer inventory is that reallocation of product already inventoried on the hospital level is difficult during a shortage, making recovery from uneven demand or supply shocks more challenging. Reallocation also has an equity angle in that, left to their own devices, hospitals in a better financial position would be more likely to invest in buffer inventory.

To address the high value and reallocation problems, we propose that HHS directly pays for inventory buffers to be carried either by manufacturers or by wholesalers, which can then be sold on the first-in, first-out basis if the buffer is maintained, while allowing for a separate allocation scheme if demand exceeds supply and the buffer starts to get drawn down. The default allocation would be the usual past purchasing behavior, but the government could set aside a portion to allocate otherwise.

In this proposal, HHS would select a list of high-value GSI drugs that could not otherwise be accessed from the Strategic National Stockpile unless there is an

explicit public health emergency announcement. Good candidates for the buffer inventory include drugs that have no substitutes, those whose unavailability leads to immediate and significant adverse health outcomes, and those for which supply chains are vulnerable. Crash cart drugs appear to fit all three criteria, as do many of the older GSIs used for treating cancer.

The development of this list should complement the design of the inventory scorecard. For example, if the CMS scorecard weighs inventory shortages equally, hospitals will inventory lower volume products since the same amount of dollars would provide insurance across more markets. This in turn would mean the smaller volume markets may be better protected, suggesting a different strategy for the government buffer inventory. Determining criteria for selecting products to inventory is a good place to invite stakeholder input, given that the existing FDA's List of Essential Medicines, Medical Countermeasures, and Critical Inputs (FDA 2022a) does not include some high-value products such as cisplatin (SGO 2023) or water for injection (ASHP 2018).

HHS should develop allocation plans for the inventoried drugs, considering most likely scenarios. For example, to the extent that oncology community clinics lose out to health systems during shortages, HHS could set aside a certain percentage of cancer drugs to be allocated to specific clinics. HHS could also consider allocation schemes in response to local supply-chain shocks that may affect hospitals unevenly. Determining appropriate allocation schemes for GSI drugs to be inventoried is another good place for stakeholder input.

To promote manufacturing reliability in the market, HHS should purchase GSI products for the buffer inventory from manufacturers that are rated high on QMM, if such product is available, or should be required to meet other cGMP quality standards. HHS would also need to have participating wholesalers or manufacturers build inventories slowly enough so that such buildup does not cause shortages.

Because government buffer inventory supplements hospital inventory efforts, its size will depend on hospital performance in addressing shortages. The government buffer inventory is more important initially, as the market moves to a higher-quality equilibrium. The cost of inventory for selected drugs will have start-up and ongoing costs. The start-up cost will depend on the volume and price point of selected drugs. The ongoing cost would be replenishing inventory for the select drugs that may go into shortage as well as the typical inventory holding costs that HHS would have to pay those holding the inventory.

Questions and Concerns

In this section, we discuss questions that may arise with those reviewing this proposal.

Will this proposal alter hospital behavior?

As with any CMS incentive, a hospital is likely to compare the cost of participating with the value of the incentive. For example, it has been documented that many hospitals are not taking any positive steps to avoid the readmission penalty (Advisory Board 2021). Anecdotally, such hospitals are assessing the cost of compliance and concluding that the cost is greater than the penalty afforded by the law.

For this reason, Congress should enable CMS to properly fund the incentive program we propose.

Will the transition increase the number of shortages in the short run?

If the proposal works as intended, more-reliable manufacturers will face an increase in demand, possibly exceeding their short-run capacity. If orders for the reliable manufacturer's products exceed deliveries, the specific product will appear as a shortage on the ASHP drug shortage database (ASHP n.d.). We do not expect that less-reliable manufacturers will exit the market in the short run, however.

We recommend that both FDA and ASHP consider adapting their communications around shortages to mitigate the perception that the program is having the opposite effect of the one intended.

Which elements of the proposal require legislative authority?

Each proposed component has an element that will require legislative authority. Component 1 requires a new financing program. Component 2 requires that a new authority is given to CMS to set up a pay-for-performance program and new transparency authorities, including public disclosure of which manufacturer had a production disruption and where final product is manufactured. Component 3 requires a new authority for setting up a government-funded first-in, first-out buffer inventory.

The key FDA recommendation, which is the development of QMM, does not need new authorities but it does require funding.

How will paying hospitals more translate to manufacturers?

Our proposal works by driving demand toward more-reliable manufacturers. To the extent that supply for reliable manufacturing is constrained, it also enables prices to increase up to the point that is worthwhile to hospitals under the CMS plan.

Which elements are essential?

The proposal has three components that work together to stabilize GSI markets. However, components differ in the extent to which they can be scaled down.

The development of the CMS program cannot be scaled down because insufficient incentives to hospitals will prevent their participation. Without sizable participation, the market will not move toward the higher equilibrium quality that is needed to prevent shortages. Without significant changes on the demand side, GSI markets cannot stabilize.

Scaling of the funding support for the other elements comes with trade-offs. The greater the government buffer inventory, the greater the insurance against shortages. The greater the support for building infrastructure, the more sites there are to create quality alternatives. The greater the support for FDA's efforts, the faster the agency will be able to support the shift to a more stable GSI market.

Will buy side concentration create bunching of hospital results?

We note that, with three large GPOs and three large wholesalers, we might expect bunching of scorecard results, conditional on product mix. This bunching occurs because hospitals rely on those parties, particularly on the GPOs, to conduct supplier vetting. But this bunching need not be problematic—it will be a strong incentive to the GPO falling behind the curve to improve its assessments and to shift contracting

practices accordingly. But, to benefit from GPO competition, at least two large GPOs must be present in each peer group.

How would this program affect new entrants?

This question becomes relevant when QMM metrics are incorporated into the drug shortage scorecard. Because QMM ratings incorporate leadership and culture, they may not be available to new facilities or new entrants, potentially disadvantaging their market entry. One solution would be to subtract their units from the QMM procurement index so as not to penalize purchases from them. Another solution would be to give facilities a temporary provisional measure based on the initial inspection record, sophistication of technology, and QMM scores of other facilities in the firm's portfolio.

Does this proposal encourage or discourage diversification?

The picked-right measure in our proposed scorecard encourages diversification because it is structured not

as a discrete variable, but rather as a share of sales from manufacturers that are not directly responsible for the supply disruption. To minimize risk, hospitals may find it beneficial to select two reliable manufacturers to supply any one product. We recognize, however, that diversification on a hospital level may not be desirable from a medication error perspective.

How significant would the hospital reporting burden be?

To support the payment mechanism, hospitals would need to report their GSI spending either through a new reporting mechanism or through a new field on existing hospital cost reports (CMS 2021).

To support data collection for the drug shortage scorecard, hospitals could use wholesalers to collect core data that supports the QMM procurement rate as well as the picked-right measure. Hospitals may need to supplement the data with direct purchases from manufacturers. Hospital inventory infrastructure is quite sophisticated, which enables the requisite reporting of inventory.

Conclusion

The social benefits from GSI supply-chain resilience greatly exceed the private benefits of reliability to manufacturers and hospitals.

For a manufacturer, a shortage means lost sales of low-margin products and perhaps weakened market position relative to its competition, but only in the short run. For a hospital, a shortage means additional labor costs to manage shortages and additional costs to purchase alternatives. But these costs pale in comparison to the cost faced by patients.

We should not expect private parties to internalize these costs without additional incentives. Manufacturers have fiduciary responsibilities to their shareholders and therefore have a drive to seek cost advantages that come with foreign sourcing, carrying limited inventory, forgoing excess capacity, and keeping the make-up of their supply chains confidential. Hospitals, GPOs, and wholesalers each face a set of economic incentives that keep them from fully internalizing the patient impact.

To close this gap, our proposal aims to realign incentives of hospital buyers and, by extension, of GPOs and wholesalers, thus enabling the market to reward

manufacturing quality and reliability, and, with that, addressing the key manufacturer incentives. As a complement to altered pull incentives we suggest the development of targeted push incentives in the service of modernizing manufacturing of GSIs.

Our proposal emphasizes manufacturing quality, rather than just drug shortages, because compromised products can and do make it to patients. If drug shortages were the only issue of concern, our solution would be to create sufficient buffers through inventories. Although we propose buffer inventories as part of our proposal, we are especially focused on manufacturing quality to lower the possibility that products that were not made to specification are used to treat patients.

Realigning those incentives requires involvement of multiple government agencies, supported with new funding, and, in some cases, with new authorities. But without a serious, coordinated effort on multiple fronts, policymakers will fail to change the dynamics and the unacceptably high number of costly shortages will persist.

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Generic sterile injectable or GSI drugs are the staple of hospital care, so shortages of these drugs can affect patients in emergency rooms, ICUs, cancer clinics, and outpatient elective surgery departments. Shortages of GSI drugs can have substantial adverse impacts through treatment delays, the use of inferior alternatives, and an increased risk of medication errors.

Market dynamics are at the heart of persistent GSI shortages. Hospitals primarily consider the price of competing GSI products because they can neither observe drug quality directly nor do they carry the full burden of patient harm resulting from shortages. Price pressures, coupled with FDA's inability to enforce strictly manufacturing quality standards, reduce a manufacturer's commitment to good manufacturing practices. When manufacturing quality problems are uncovered, often after FDA inspections, recalls and production stoppages can lead to shortages.

To reduce the incidence of GSI drug shortages, Wosińska and Frank propose policies that foster greater manufacturing reliability in GSI drug production. Their proposal combines push incentives to improve manufacturing infrastructure with the implementation of pull incentives through a pay-for-performance program that rewards hospitals for taking steps to prevent shortages before they occur. In addition, Wosińska and Frank propose a targeted government-funded buffer inventory to insure against supply chain shocks for drugs of particular public health import.
