Responses to Questions for the Record for Dr. Wosińska

following the 12/5/2023 Full Committee Hearing
of the U.S. Senate Committee on Finance

regarding

Drug Shortages: Examining Supply Challenges, Impacts, and Policy Solutions from a Federal Health Program Perspective

Thank you for the opportunity to testify at the December 5, 2023, hearing on drug shortages and to contribute further by answering these questions for the record.

My responses borrow extensively from what I have previously written or co-authored. The Appendix includes brief descriptions of these resources, along with links to them.

Question 1a: Your testimony recommends Congress create new performance-based payment incentives for hospitals related to drug shortage prevention and mitigation. Please list examples of specific measures that you recommend including in the scorecard along with a rationale for why each measure should be included.

Answer: Under the proposed program in question, CMS would score hospitals on purchasing based on vendor reliability and inventory practices during *non-shortage* times. The scorecard would then feed into an end-year payment adjustment based on a hospital's performance relative to its peers.

The Medicare drug shortage scorecard would reflect a combination of two measures: a hospital inventory index and a reliable manufacturer index. The inventory index would measure the level of buffering in which a hospital would engage in advance of potential shortages. The reliable manufacturer index is meant to shift the average reliability of manufacturers by rewarding those that are more reliable. The former would help mitigate shortages, the latter would get at the root of the problem, preventing shortages.

As described in the proposal, "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 group purchasing organization [GPO] private label program).

"At the end of each calendar year, hospitals would report inventory at [a trigger date determined at the end of the year by CMS, with FDA's input]. 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 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.

"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).

"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). 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."

Question 1b: How might these measures need to be adapted if the FDA Quality Management Maturity (QMM) Program is not fully operationalized?

Answer: As we describe in our proposal, Medicare could set up the scorecard based solely on the inventory and picked-right measures because GPOs already have various tools at their disposal to assess the likelihood of a supply disruption. We also anticipate rapid development of such tools if there is demand for them.

It might be, however, beneficial to give CMS flexibility to supplement the picked-right measures with additional indicators of quality. For example, CMS could work with FDA to develop a set of metrics for high-risk suppliers from which hospitals would be advised not to purchase. Such suppliers might include those that refused an FDA inspection, have no inspection history in last three years preceded by concerning inspection history, or a particularly problematic combination of violations (specific violations found during inspections, import alerts, and poor history of efforts to remedy problems).

As an outcome measure, the picked-right measure will remain the most accurate measure of performance because it encompasses all forms of vulnerability: manufacturing disruptions, reliability of vendors, risk of discontinuation, and vulnerability to natural disasters. For that reason, we recommend keeping it even if other measures (such as QMM) are developed.

Question 1c: What special considerations should Congress keep in mind to create a fair program for small independent and rural hospitals?

Answer: The proposed pay for performance (P4P) program has two features that make it a fair program for small independent and rural hospitals. First, it leverages the role that GPOs already play in assessing manufacturers during contracting process. Small hospitals using GPOs can benefit from these assessments, with the only decision left to the hospital is whether to follow those recommendations (as a reminder, the picked-right metric is about the share of volume procured from more reliable manufacturers). Small hospitals not affiliated with GPOs can leverage programs such as Civica Rx. Second, the payment is relative to performance of the hospital's peers. In this case, a small rural hospital would be compared to like hospitals, not large teaching hospitals part of a health system.

To further support the needs of smaller, independent hospitals, Congress should consider three additional flexibilities:

1. Give CMS flexibility to assign different weights in the scorecard for different peer groups. Large hospitals and systems should be weighted more on the picked-right measure, while smaller independent hospitals should be encouraged to buffer against shortages.
2. Allow the payment adjustment to deviate from prescription volume. For smaller entities, administrative costs associated with this P4P program may represent a greater share of participation cost than for larger entities than leverage sophisticated data systems and can spread administrative costs across many units.
3. Allow for a phased in approach, with peer groups that include small independent hospitals to be phased in a year or two later.

Question 1d: In addition, if Congress were to try to create a similar model for clinic and physician office settings, how might the scorecard and the specific measures you identify need to be adapted?

Answer: The pay-for-performance (P4P) model can be readily extended to the outpatient settings that are part of health systems and perhaps physician practice networks. Such systems and networks have integrated data, which improves adoption of the P4P program and lowers reporting costs. The same scorecard measures could work, but for drugs only used on the outpatient side of 340B entities, wholesalers would need to take over the assessment role from GPOs because of GPO prohibition in the 340B program. Motivating wholesalers to perform well for this narrow set of outpatient-only set of generic sterile injectable drugs would necessitate structuring outpatient payment peer groups with at least two major wholesalers per peer group (in addition to the two GPOs per peer group).

When it comes to smaller independent outpatient providers, such an arrangement is more complicated operationally and would benefit from a different arrangement that would focus solely on buffering. This focus is appropriate because with small market power, independent outpatient clinics and physician practices are less likely to influence the quality equilibrium in the market. This could be done by strengthening the authority previously used for the domestic N95 mask rule. In my written testimony, I recommend Congress adjusts Sections 1886(d)(5)(I) and 1833(t)(2)(E) of Social Security to cover not just the Medicare share of qualified expenses, but all the qualified costs that relate to supply chain resilience.

One consideration is whether the outpatient setting requires financial bonuses or penalties. Unlike under a DRG payment, doctors and clinics under Medicare Part B collect margins on their purchases, not even considering 340B. This means that there is less concern with resilience requirements leading to financial losses and therefore policy instruments may reasonably encompass both bonuses and penalties.

A final consideration is how Medicaid inflation rebates may affect the effectiveness of the program on the outpatient side. Medicaid inflation rebates (and by extension the 340B discounts that follow) penalize manufacturers on any cost increases beyond CPI (which for a low-cost product might be on the order of a few dollars or less). The P4P, if implemented on the outpatient side, could change hospital behavior, but the impact on manufacturer behavior may be limited as there is no incentive to invest in reliability if those costs cannot be passed on to buyers. To address this structural problem, my written testimony includes the recommendation to exclude multisource generic sterile injectable drugs from Medicaid inflation rebates.

Question 2: Are there unique challenges around shortages for controlled substances we should consider from a Finance Committee perspective?

Answer: The policy challenge with controlled substances used for treating ADHD or pain is that there is, at the same time, both "overuse" (inappropriate use) and "underuse" of these products. This complicates responses to shortages and public health policy generally. To address overuse and underuse, policymakers need to distinguish appropriate from inappropriate use and then develop mechanisms that steer utilization towards the former and away from the latter.

In the opioids context, CMS addressed Medicare Part D over-prescribing by instituting a set of utilization management "edits" to its approval of prescription drug payment processes. Simple indicators related to dosages and durations of prescriptions were used to create the edits and the result was a significant reduction in high-risk prescribing. Likewise, some commercial and state Medicaid health plans have instituted requirements that for controlled substances (like stimulants for ADHD) that were initiated via telehealth, a face-to-face visit take place within a prescribed period.

Because reducing inappropriate use when a shortage arises serves to boost the effective supply of the product, similar approaches hold promise for improving appropriate use of controlled substances generally and when shortages arise. The impact of above-described efforts should be more fully assessed, pointing way towards broader implementation of such tools.

Question 3: Given the persistence and scale of drug shortages, does there need to be more transparency within the supply chain? If so, by whom and how could this improve the situation? If not, who in the supply chain should do more with the information they have to address drug shortages?

Answer: The first step toward transparency is assessing who needs which information and for what purpose. Not all information sharing is equally useful and, in some cases, could be counterproductive.

There are many stakeholders we could consider, but here I discuss two key ones: the federal government and hospitals and providers.

On the federal government side, there are two areas of need I would like to highlight.

First, FDA would benefit from greater transparency into when manufacturers face a demand spike to implement prevention or mitigation efforts. I describe my recommendations on such notifications in my response to Question 8a below.

Second, the federal government needs better transparency into the vulnerability of various supply chains, so that it prioritizes where to engage, thereby maximizing the maximizing the impact on taxpayer dollars. In my response to Question 12 below, I describe my recommendations regarding strategic approach should be deployed and the role that Congress should play there.

On the hospital and provider side, I would distinguish between three different needs.

First is the need to know how the shortage is likely to progress and when it is likely to end. This need however is difficult to fulfil because shortages are dynamic, potentiated through panic buying, and with the path to recovery often taking weeks if not months to assess by the companies involved. Congress could improve what FDA can share by improving the transparency of the notifications that manufacturers currently submit to FDA under 21 USC 356c. I further describe this recommendation in my response to Question 8b below.

Second is the hospitals' interest in early warning systems that identify impending shortages. This kind of transparency, however, is one that policymakers should be extremely cautious about providing. It is critical that FDA knows as early as possible that a manufacturer has a disruption in production so it can

work with that manufacturer to restore production and with others. It would be important for wholesalers to know the same so they could put product on allocation. However, to a hospital, an early warning signal of shortage is a signal to start stockpiling, precipitating the shortage.

Third is transparency to hospitals about which manufacturer is reliable. More transparency on this front is a common recommendation, as review of literature suggests. I agree that information about manufacturing quality can be improved and have proposed various ways FDA can help on that front with support of Congressional appropriation. But I emphasize that currently there is sufficient information available to enable resilience purchasing. Individual hospitals do not directly contract with manufacturers, but the GPOs that contract on their behalf can leverage their market power, can compel manufacturers to share confidential business information that is otherwise not publicly available. Similarly, GPOs can do the homework on behalf for hospitals by tapping into reliability and risk measures through syndicated sources such as Redica Systems, Medicine Supply Map, or RISC Ratings. Hospitals can also rely on the vetting (and contracting) of organizations such as Civica Rx.

Much relevant information already exists, but it is underutilized because hospitals are reluctant to pay for resilience. Congressional priority, especially with Senate Finance, should be on incentivizing hospitals to utilize the wealth of information and the programs that already exist. Only then will additional transparency measures help. For recommendations on priority transparency measures that FDA should provide, please see Federal policies to address persistent generic drug shortages | Brookings.

Question 4: Drug companies harden their manufacturing facilities to be resilient against natural disasters like hurricanes and tornadoes. What role do drug companies have in preparing for drug shortages caused by economic factors or a pandemic? Do they do enough to prepare for the unexpected?

Answer: Perhaps the most basic premise in economics is that rational economic actors balance the costs and benefits of the actions they take. Along these lines, it is rational for companies to balance the costs and benefits of investing in risk mitigation against potential supply chain disruptions.

This cost-benefit calculus looks very different for manufacturers of branded and generic drugs. For high-margin branded products, losing production capacity for any reason means lost profits in the short term and a potential longer-term loss of market share to competitors. In contrast, for generic products, foregone profits due to productions disruptions of low-margin products would not be significant.

For these reasons, branded manufacturers work to lower the risk of disruptions by investing more in manufacturing quality oversight than their generic counterparts. Manufacturers also buffer supply chains of branded products more: they will vet their suppliers more closely, diversify their supply chain with multiple suppliers and multiple production sites, carry greater inventory of raw materials and finished product, and maintain a lower utilization rate on production lines. But the low margins resulting from price competition makes these kinds of steps economically prohibitive for manufactures of generic drugs.

Given the impact that shortages have on patients, their families and communities, it is also worthwhile to compare the manufacturers' risk calculus with that from a social perspective. For one, neither branded manufacturers nor generic manufactures fully internalize the harm that results from poor supply chain resilience. Private manufacturers also do not internalize such concepts as national security.

To the extent that policymakers want manufacturers to make their supply chains more resilient than their economic circumstances dictate, they will need to provide economic incentives. They can be in the

form of subsidies or penalties, but it is important to consider that penalties (requirements) imposed on low-cost producers can lead to market exit if those additional costs make production unprofitable.

Question 5: Can alternative payments for drugs under Medicare reduce the number of shortages?

Answer: To address the persistent shortages of generic sterile injectable drugs, we need to change how hospitals buy such drugs. By modifying how CMS pays for drugs most at risk for shortage, CMS can steer hospitals away from their heavy emphasis on price and towards reliability of supply.

It matters greatly how Congress implements such programs – not every alternative payment system will be equally effective or could be made functional in the same time frame. Some proposals could even make things worse. For example, paying hospitals more when drugs are in shortage would do nothing to encourage hospitals to buy from more reliable manufacturers. In fact, hospitals might see buffering and other prevention efforts not worth the effort when the hospital can get a higher payment during a shortage.

The payment models needed to improve reliability of generic sterile injectable supply are procurement-based. In that way, they differ standard alternative payment models (APMs) that give an added incentive payment to provide high-quality and cost-efficient care. Ultimately preventing shortages is about preventing patient harm but designing proper quality measures would be challenging given adverse health outcomes vary greatly for each of the many dozens of drugs in shortage, with outcomes often not observable in the time frame observed within a hospital.

There are two primary proposals for how to incentivize hospitals to buy reliably: an add-on payment for purchasing from reliable manufacturers and a pay-for-performance program that adds a year-end payment based on hospital's relative performance on shortage prevention and shortage mitigation measures.

The add-on payment would apply to manufacturers qualifying as reliable. The effectiveness of such an add-on payment in preventing shortages would depend on CMS's (or FDA's) ability to identify which manufacturers are reliable. The better the predictive power of such measures, the greater the impact of an add-on payment program tied to such a list. If those measures are not reliable, CMS would be increasing government spending without making a difference on the shortage front.

Currently no validated measures of supply reliability exist. FDA has been developing a set of forward-looking metrics. However, even with funding (which FDA does not currently have), that system will likely take several years to develop and would only be a general facility measure and not the specific product supply reliability measure that is needed. Another alternative is to use FDA compliance records to construct a measure of reliability. Just as with QMM, the predictive ability of such measures would need to be established.

An alternative mechanism – one that I explained in my written testimony – is a pay-for-performance program, under which hospitals are scored on their behavior on two measures: what share they buy from what turned out to be (in retrospect) reliable manufacturers and did they buffer their inventory for the affected drugs. Hospitals would be measured on their performance retroactively, on their behavior *before* the first signal of each shortage that occurs. The scorecard would then feed into an end-year payment adjustment based on a hospital's performance relative to its peers. Hospitals should largely expect to cover their participation costs, with payments to top performing hospitals exceeding those costs.

Unlike an add-on payment where CMS needs to identify which manufacturers are reliable, the pay-for-performance program harnesses market ingenuity. To start purchasing from reliable manufacturers, hospitals could leverage current but underutilized programs that assess manufacturers on reliability, including those done by their GPOs. Greater interest from hospitals in identifying which manufacturers are reliable would also drive development and utilization of new tools. The program would also incentivize greater adoption of currently underutilized programs that hold buffer inventory through wholesalers or manufacturers (as in the case of Civica Rx or through a GPO private label program).

I should also add that any drug shortage resilience project should be separate from other hospital quality programs. It would be possible, perhaps, to expand the Hospital Value Based Payment (HVBP) program to encompass procurement measures. Bundling shortage with other measures would lower the visibility that the shortage measures deserve and require. Also, HVBP is budget-neutral, but the shortage proposal needs a strong financial boost across the board.

Question 6a: Do you agree that the current GPO business model is ultimately unsustainable and weakens the drug supply chain in the long run?

Answer: Because generic versions of the same drug are therapeutically equivalent and therefore can be readily substituted, buyers can place tremendous pressure on manufacturers to lower price. The resulting race-to-the-bottom leads manufacturers to shift production to lower cost environments and challenges manufacturers' ability to invest in maintenance, upgrades, staffing, and oversight. This dynamic leads to a fragile supply chain, with potential for highly disruptive drug shortages.

GPOs play a significant role in driving prices down, enabled by the market power they represent – three GPOs represent around 80 percent of hospital beds. Generally, the contracts GPOs negotiate neither provide a purchase guarantee to the manufacturer nor do they fix the price over the contract term. Instead, the contracts frequently include best-price guarantees that allow the contract price to drop if the GPO finds a better price elsewhere.

It is important to note that GPOs are incentivized to weigh price heavily over reliability of supply because their hospital customers demand that. Currently, while GPOs assess supply reliability of many manufacturers, they will be hard pressed to contract with a higher priced but more reliable manufacturer because GPO contract participation is voluntary for hospitals. Hospitals can and do buy off-contract if they find a lower price. GPOs try to incentivize hospitals to buy through the contract (which is the way the GPO makes money) but the strongest tool GPOs have for contract compliance is securing the lowest price possible.

Question 6b: Is it possible to find a balance between keeping costs down for providers and using the GPOs' market leverage to enforce the resiliency of the drug supply chain? What would that look like?

Answer: Under the pay-for-performance proposal described in my written testimony, hospitals would not need to take the responsibility for identifying which manufacturer's products are less likely to be in shortage, instead relying on their GPOs to do this work for them. GPOs already conduct such assessments but have strong financial incentives to continue heavily weighing low-cost producers because otherwise hospitals buy off contract. If hospitals weigh reliability more, they will change GPO's incentives for how to award contracts to manufacturers. By putting at least two GPOs in each hospital peer group, GPOs would be incentivized to perform better on predicting reliability and securing product through quantity commitments.

Leveraging GPO's market power is helpful in that three GPOs can do the assessment for virtually all hospitals and then compete for hospital business by excelling at these assessments.

Question 7: Some individuals have asserted that the 340B program is causing drug shortages. (…) In your testimony the drugs you state are most commonly in shortage are generic sterile injectables. 340B purchases make up only 7% of total U.S. purchases of generic sterile injectables. With such a low volume of overall drug spending, is there evidence that 340B has a direct effect on drug shortages?

Answer: Because of lack of data transparency around the 340B program, there are no well-designed studies of the impact of that program on drug supply chain resilience and drug shortages. This does not mean, however, that there is not a problem.

It is indeed the case that drug shortages disproportionately affect generic sterile injectable drugs used in the inpatient setting. But this is due to the preponderance of those drugs in that setting, not the fact that somehow outpatient generic sterile injectable drugs are at less risk.

Just like inpatient generic sterile injectable drugs, outpatient generic sterile injectable drugs (including generic injectable cancer drugs) can face fierce price competition, with prices trending towards marginal cost. However, outpatient drugs face an additional pressure: manufacturers of those drugs are limited in their ability to pass on cost increases, including input costs increases driven by supply shocks, and infrastructure improvements, maintenance, quality oversight, and staffing investment.

With low margins, manufacturers have little ability to absorb these costs, and with 340B, they have limited ability to pass on costs, however legitimate they might be. The cost increases need not be high to hit the penalty threshold – the penalty threshold can be less than $1 for a $20 generic sterile injectable drug. The penalty will then apply not to the 7% mentioned in the question, but to the drug's volume of 340B sales. For a cancer drug, a third or half of volume could be going through the 340B program – a potentially consequential financial hit that could lead the manufacturer to phase out and ultimately discontinue the product. This in turn makes the market more vulnerable to future shortages.

The inability of manufacturers to pass on legitimate costs becomes even more consequential if Congress attempts to change the hospitals' existing emphasis on price towards reliability of supply. The only reason that paying hospitals more for reliability helps prevent shortages is that such a system enables manufacturers to differentiate therapeutically equivalent products on reliability, carrying a price premium for that added reliability. However, in the outpatient setting, a manufacturer cannot pass any quality improvements onto the prices of 340B products.

To address this structural problem that constrains generic manufacturers from passing on legitimate costs, my written testimony recommends excluding multisource generic sterile injectable drugs from Medicaid inflation rebates.

On the hospital side, the potential financial losses to 340B entities are lower than the 7% volume statistic might suggest. First, single-source generic sterile injectables should not be included in the calculation because those are not included in my recommendations to Congress. Second, the loss in the 340B dollar savings will be less after adjusting for the fact that per unit 340B savings on a $10K drug will quite likely be much larger than on a $20 drug. Third, relevant losses should net out compliance burden relating to 340B requirements, particular in mixed use areas such as emergency rooms. Fourth, the losses would be even lower if Congress were to eliminate the GPO 340B prohibition for drugs that are exempt from Medicaid inflation rebates. In that case, hospitals would be swapping 340B savings for GPO rebates.

Given the limited financial consequences for improving supply chain resilience, I strongly question the rationale for the strong pushback from 340B providers regarding Medicaid inflation rebates for multiple-source generic sterile injectable drugs.

Question 8a: My legislation, the Drug Shortages Prevention and Quality Improvement Act, would require manufacturers to notify the FDA no later than 30 days after the manufacturer knows of an increase in demand for a drug that is likely to lead to a shortage. How would this kind of authority impact the drug shortages and wholesale alerts?

Answer: Notifying FDA about supply or demand shocks is helpful to the extent that it gives FDA time to work with manufacturers to restore or ramp up production.

Demand increase reporting (or rather reporting in the number of orders a given manufacturer receives) can be grouped in two categories. First are across-the-board demand increases, such as what we saw with ventilator drugs in early COVID or with amoxicillin early last year. Second are spillover demand increases when orders for a given manufacturer's product increase because another manufacturer (for the same drug or a substitute drug) had a supply disruption. In the latter case, manufacturers that experienced disruptions should be reporting, but reporting of spillover can serve as backup and another market signal.

To maximize the effectiveness of the demand notification requirement, I would recommend that FDA be authorized to require that a manufacturer reports when orders exceed by a certain level what the manufacturer can fulfill. This is different from reporting a demand increase within 30 days because the signal to the manufacturer can occur much earlier than 30 days. If a manufacturer waits the full 30 days, the information might not be useful to the FDA. Congress should determine the level which triggers reporting in consultation with FDA and industry.

I am not aware of the existence of wholesaler alerts from the FDA to wholesalers or vice versa. However, FDA would benefit from information sharing from wholesalers when they see unusual order patterns. I would recommend FDA sets up a pilot program to test this kind of information sharing.

Question 8b: Are there other data gaps that exist regarding the causes of drug shortages that would be important for providers to have as they plan to care for patients who may need a drug that is in shortage?

Answer: Congress should improve the transparency around the causes of shortages. FDA knows the precipitating events leading to each shortage, but they are unable to share them publicly because it interprets the information as business confidential. Instead, FDA discloses what category specified in 21 USC 356c the manufacturer chose to select. Those categories, however, are not helpful, especially the "Other" category.

Enabling FDA to share more information could help providers plan better for patient care. Such sharing would also be important for supporting the pay-for-performance program that I presented in my written testimony. It is possible for CMS to protect manufacturer confidentiality and score hospitals on whether they picked-right across 30-50 shortages, however, hospitals and GPOs should have a clear feedback mechanism for whether they are indeed picking right.

Question 9a: In a 2019 report from the FDA on drug shortages, the agency notes that FDA heard from stakeholders that some contracts currently include "low-price clauses" that allow group purchasing organizations to unilaterally walk away from a contract if a competing manufacturer is willing to supply the same product or bundle of products for a lower price. How do practices like "low-price clauses" impact drug shortages?

Answer: Those kinds of contracts may exist for hospital and retail drugs alike but given the focus of FDA's drug shortage report on generic sterile injectables, I will focus my answer on the latter. I am unable to comment on the frequency with which such contracts (sometimes called best-price clauses or MNF clauses) are deployed for drugs administered in hospitals, but I have heard those contracts exist.

Standard economics suggests such contracts terms would push prices down between contract cycles. They also decrease demand predictability for manufacturers because a manufacturer may not be able to match the lower price. Without guarantees for stable demand, manufacturers have little incentive to buffer their supply chains. Frequent changes in demand for specific products also lead to more frequent changes on production lines, which is a key risk factor in manufacturing.

I should note that the importance of "low-price" provisions is lower than it would be if hospitals were committed to buy though GPO contracts. But GPO contracts are not binding, so hospitals can and often will buy off-contract if they find a more attractive price. If "low-price" provisions were banned from GPO contracts, hospitals would simply buy off-contract if a more attractive price were available elsewhere. For this reason, elimination of such provisions would be consequential for manufacturers only if hospitals were also prohibited from buying off-contract.

Question 9b: Now we hear that some PBMs have chosen to start group purchasing organizations even as PBMs use group purchasing organization services. How might these relationships impact drug shortages, particularly patients' ability to access low-cost drugs that typically do not provide much profit to manufacturers?

Answer: The GPOs that have been set up by PBMs are very different than the GPOs that operate in the hospital setting. In the hospital setting, GPOs negotiate contract terms on behalf of hospitals, which hospitals then can use to purchase products at negotiated prices or can buy off-contract if they find a better price through the wholesaler. In turn, the role of the retail GPOs is not well understood. The ongoing FTC Section 6b study will hopefully shed more light on those new entities.

Question 10: Can you comment on how consolidation among purchasers of generic drugs has led to "race to the bottom pricing" and is driving drug shortages?

Answer: Price competition in the generics industry can be fierce. At the heart of this competition is therapeutic equivalence, meaning that different manufacturer's versions of the same drug can be readily substituted. Using therapeutic equivalence, buyers can play manufacturers against each other to obtain better prices and better contract terms. Concentration on the buyer side, be it through GPOs, wholesalers, pharmacy chains, or mail pharmacies, means that buyers have more bargaining power in that negotiation.

This price competition drives manufacturers to cut costs. The price pressures create incentives to move operations to lower cost environments. They also create a dynamic where there is little room for and return on investing in facilities, staffing, and oversight.

These price pressures, however, have different consequences for injectable and oral dose generics.

With generic sterile injectables, there is little room for error in the final production stage. The drugs are injected into the body, often directly into the blood stream, and therefore they must 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 employees following complex manufacturing processes and controls.

In contrast, oral dose products, by definition, need not be sterile because our digestive system can rid of most microbes and impurities. The manufacturing footprint is less concentrated and the manufacturing technologies more fungible. Even if manufacturing problems arise and a facility must close, the supply chain for these products is more resilient and can absorb the manufacturing disruption.

For these reasons, generic oral dose products are less likely to be in shortage due to manufacturing problems than generic sterile injectable products. On the other hand, vulnerability to geopolitical disruptions may not differ much between oral dose and injectable products because key starting materials for all drugs primarily are sourced outside of the United States.

Question 11a: In a 2019 House Energy & Commerce Committee Hearing, the FDA outlined competitive cost "advantages" that China and India have over the U.S. (…) Would speeding up implementation of advanced manufacturing approaches in the pharmaceutical manufacturing industry help lower drug prices?

Answer: The short answer is no for branded products and highly unlikely for generics.

As for any product, manufacturers of branded products set prices based on demand elasticity, which reflects how sensitive buyers are to price changes. Because branded products are patent protected, they do not have close substitutes and therefore face inelastic demand, with profit maximizing prices far above the cost of production. Changing the marginal cost of production for patent protected brand name products could increase profit margins for those manufacturers but would have no discernable impact on drug prices.

In turn, manufacturers of generic products face highly elastic demand, which drives prices close to marginal cost. In this setting, lowering marginal cost would drive prices down. However, advanced manufacturing – continuous manufacturing in particular – does not, in its current state, appear to provide a cost advantage in manufacturing of generics. For one, the technology has great advantages when used continually for one product. But this advantage does not translate well to generic manufacturing, where the unstable nature of the demand can lead to 20-30 products being run on a single line over a course of a year, leading to frequent switchovers. The upfront costs of these technologies are also prohibitive at this stage, making the return on investment quite unclear.

For more information about the potential role of advanced manufacturing technologies in addressing generic drug supply chain resilience, please see the summary from the proceedings of a workshop, which colleagues and I organized in March 2023.

Question 11b: What can we to do encourage [the implementation of advanced manufacturing], and are there other ways to help reduce the cost of manufacturing drugs?

Answer: Given the offshoring context of this question, I presume the question is about making domestic manufacturing sustainable, whether through lowering the cost of production in the U.S. or through other means.

As I describe in my response to Question 12 below, economics is what has driven production offshore, so countering these economic forces would require the U.S. government to subsidize any reversal of offshoring. Similarly, as described in my response to Question 11a, manufacturers lack economic incentives to adopt technologies that would improve reliability of manufacturing (for which advanced manufacturing is oft touted) – the return on investment is not there for them. For these reasons, if policymakers want greater supply chain resilience, they will need to subsidize manufacturers, ultimately passing on the cost either through higher taxes, higher healthcare premiums, or higher generic drug prices.

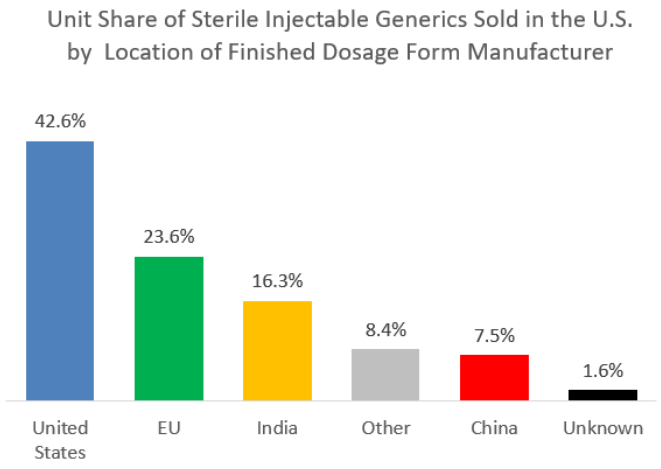
There are many ways to do it, but all with come with a cost. First, the government can provide grants or loans for upgrading or building new infrastructure, keeping in mind that sometimes the highest return on investment can be through relatively low-cost improvements and not through sophisticated advanced manufacturing technologies. Second, even with subsidies of fixed costs, manufacturers may struggle to keep the marginal cost of production competitive and therefore may require marginal subsidies. In my written testimony, I describe how the statutory provisions used to create the N95 domestic mask rule could be leveraged in this space if Congress were to enhance those provisions. The government could also strategically use direct purchasing (such as through the VA or DOD) to support domestic manufactured products or to fund buffer inventories of drugs using domestic manufacturers (all these with the caveat that those manufacturers meet appropriate manufacturing quality standards).

Question 12: What are additional authorities that the U.S. government can use, similar to how the Defense Production Act is being used, to bolster the domestic manufacturing of pharmaceuticals?

Answer: Before considering authorities, it is critical that we first establish the role that domestic manufacturing should play in creating greater supply chain resilience. This analysis will then inform possible policy solutions and whether and which new authorities are needed.

In that context, it is important to distinguish between current persistent drug shortages of generic sterile injectable drugs and potential shortages due to geopolitical conflicts.

Generic sterile injectable shortages are primarily caused by manufacturing quality problems at the final stage of production. As indicated in the graph below (courtesy of USP Medicine Supply Map), that stage of production for generic sterile injectable drugs is primarily done in the United States, followed by Europe. Although the recent cancer shortage was caused by a production disruption at site in India, U.S. facilities, which produce 2.5 times as many units of generic sterile injectable drug units, are also plagued by manufacturing quality problems that lead to shortages.



Sources: USP Medicine Supply Map, IQVIA Sales Perspective eaches (Jan-Nov 2023)

Building more domestic capacity in the U.S. is not an appropriate solution to the persistent shortages of generic injectables but improving the existing U.S. infrastructure can be. Even there, improving infrastructure with government support will be reversed if there is no change in how hospitals buy drugs. For this reason, changing how hospitals buy should take precedence in addressing persistent shortages of generic sterile injectables, with some

supplemental infrastructure funding. For more information, I recommend reviewing the discussion of infrastructure funding in this report: Federal policies to address persistent generic drug shortages | Brookings.

In turn, addressing potential geopolitical threats requires a different approach. A major geopolitical conflict could expose many more supply chains, potentially quite different from the ones currently at high risk of shortage. It may also expose production sites along many different stages of production, unlike the more limited set of finished dose facilities that are at the heart of most current shortages.

Decreasing reliance on countries that pose geopolitical threats is key to lowering the risk of shortages that could result, but how it is done matters greatly. The pharmaceutical and chemical industries are immense and global. We have many thousands of drug products, each with dozens of inputs made in facilities spanning the globe.

Economics is what drove this expanding web of production, so countering these economic forces would require the U.S. government to subsidize any reversal of offshoring. But given the size of the pharmaceutical industry and the chemical industry that feeds the key starting materials for drugs, government subsidies should be based on a highly strategic approach—otherwise, with limited resources, government intervention can easily become a feel-good strategy that does little to lower geopolitical risk to supply chain resilience where it matters most.

The strategic approach requires the following:

1. **Reconsidering which supply chains to support**. The FDA Essential Medicines list focuses on pandemics and CBRN treats, but our healthcare system could be readily disrupted if drugs or components not on the list were unavailable.
2. **Thinking about all stages of production.** Much attention has been given to Active Pharmaceutical Ingredients (API) but moving API production to the U.S. will not address geopolitical risks if all the key starting materials and reagents still come from a country with high geopolitical risk.
3. **Supporting strategic diversification**. Lowering geopolitical risk means lowering exposure to certain countries, not moving all production onshore. Not all countries have the same risk, and therefore a proper risk mitigation strategy would consider the differential risk across countries. Friend-shoring and near-shoring should be an integral part of U.S. government strategy in response to geopolitical threats.
4. **Not assuming that domestic production equates with quality**. The economic incentives to drive costs down for generic drugs exist for domestic manufacturers as well, especially if they continue to compete with manufacturers from lower-cost environments. For this reason, any government subsidies to bolster domestic manufacturing should come with strings attached on quality outcomes.

The recently announced HHS Supply Chain Coordinator is in best position to lead this strategic approach to U.S. government engagement, helping to implement a data analytic approach to prioritizing supply chains for intervention (an approach we describe in A Framework For Prioritizing Pharmaceutical Supply Chain Interventions | Health Affairs). However, to be effective, this role will require Congressional support through a statutory mandate and resources. The MAPS bill is an important step in that direction.

In terms of authorities, my written testimony includes a discussion on why tax credits are a *less effective* tool for accomplishing greater supply chain resilience than loans or grants.

Appendix: Recommended reading

Marta Wosińska's testimony before the Senate Finance Committee | Brookings: describes actions the SFC can take to address drug shortages, including establishing a pay-for-performance program, eliminating Medicaid inflation rebates for multisource sterile injectable generics, and expanding authorities used in the N96 domestic mask rule; discusses why tax credits are not an effective tool relative to loans and grants

Federal policies to address persistent generic drug shortages | Brookings: in depth analysis of generic sterile injectable shortages and what CMS, FDA, and ASPR can be doing to address them with support from Congress (various committees)

A Framework For Prioritizing Pharmaceutical Supply Chain Interventions | Health Affairs: framework for how the U.S. government should prioritize supply chains for intervention

Workshop summary: Technology solutions for improving the resilience of generic drug manufacturing | Brookings: placeholder for the forthcoming meeting summary on the potential role of advanced manufacturing technologies in addressing generic drug supply chain resilience