July 6, 2023

The Honorable Cathy McMorris Rodgers
Chair, House Energy & Commerce Committee
1314 Longworth House Office Building
Washington, DC 20515

The Honorable Mike Crapo
Ranking Member, Senate Finance Committee
239 Dirksen Senate Office Building
Washington, DC 20510

Dear Chair Rodgers and Ranking Member Crapo:

Thank you for the opportunity to respond to your request for information dated June 12, 2023. As your committees work to examine the causes of and solutions to drug shortages, the Association for Clinical Oncology (ASCO) stands ready to assist. ASCO represents more than 45,000 oncology professionals who care for people living with cancer. ASCO works to ensure that all individuals with cancer have access to high quality, equitable care; that cancer delivery systems support optimal cancer care; and that our nation supports robust federal funding for research on the prevention, screening, diagnosis, and treatment of cancer. ASCO and a robust group of stakeholders formulated both long-term and short-term policy recommendations to mitigate drug shortages. In this response we highlight some recommendations of particular importance but encourage broad consideration of all our recommendations.[1][2][3]

How would you define the scope and impact of the recent and ongoing U.S. drug shortages?

For years, the medical community has experienced shortages of critical drugs that are used to treat a variety of conditions. However, today's shortages are the worst we have seen in decades. These shortages are caused by a multitude of factors, including quality issues, manufacturer business decisions, disruptions to raw ingredients and excipient supplies, natural disasters, and other

[1] https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2023-JG-CEC-Testimony.pdf
[2] https://www.ashp.org/-/media/assets/advocacy-issues/docs/Recommendations-Drug-Shortages-as-Matter-of-Natl-security.ashx)
[3] https://www.ashp.org/-/media/assets/news-and-media/docs/Healthcare-Supply-Chain-Recommendations

emergencies that take place in countries that house critical drug manufacturing facilities. In recent years, the U.S. has experienced shortages in broadly used essential products such as saline and morphine, in addition to products critical to patient populations affected with cancer. These shortages are nationwide, impacting both rural and urban areas and large and small practice settings.

For drugs currently in shortage, what percentage of their market is reimbursed through public payers, such as Medicare and Medicaid?

Approximately half of newly diagnosed cancer patients are over 65 years old, which makes Medicare the largest single payer of cancer care in the country.[4] A study published in 2022,[5] based on data from 2010 – 2014, found that for patients aged 18-64 years newly diagnosed with cancer, 72.9% were covered by private health insurance. Other coverage included Medicaid (11.2%), Medicare (7.2%), and dual Medicare/Medicaid (2.1%). At the time of diagnosis, 6.7% of patients were uninsured.

If the assumption is made that the need for specific drugs in shortage is spread evenly across populations with different insurance plans, it would appear that Medicare and Medicaid combined pay for well over half of the drugs in shortage. However, we should caution that these are very general estimates based on past statistics of insurance coverage, and do not factor in the reality of how drugs in shortage are actually allocated, the fact that patients in certain demographics suffer disproportionately from more advanced disease at time of diagnosis, and that the distribution of cancer diagnoses shifts over time.

What are the impacts of recent and recurring shortages of generics and other critical medicines on patient care?

Within the oncology pharmaceutical supply chain, patients and providers continue to face shortages of potentially life-saving treatments. A recent survey of U.S. oncology pharmacists found that oncology drug shortages occurred frequently in 2020 due to procurement issues from the COVID-19 pandemic and led to delays in chemotherapy and changes in treatment or omission, complicated clinical research, and increased risk of medication errors and adverse outcomes.[6] The study also reported that the most difficult oncology drugs to obtain at the time were vincristine, vinblastine, intravenous immunoglobulin, leucovorin, and Bacillus Calmette-Guerin.

Currently, there are 12 oncology drugs in shortage, a majority of which are generic sterile injectables, according to the Food and Drug Administration's (FDA) website.[7] Frequently the patients affected are those who rely on these drugs for curative-intent therapies. A typical example is the cytotoxic chemotherapy drug fludarabine which remains on the FDA drug shortage list and has been on the list throughout the COVID-19 pandemic. Many large volume cancer centers across the U.S. have completely run out of the drug, which is a critical component of induction prior to curative treatment with CAR T-cells. The centers have been forced to choose between offering an inferior replacement induction chemotherapy or using CAR T-cell therapy in a less effective fashion. Because the CAR T-cell treatment is a genetically modified cellular product from the immune system of the patient who receives the treatment, this treatment can often not be repeated due to cost, logistics, and cancer related factors.

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318119/
[5] https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21732
[6] https://ascopubs.org/doi/full/10.1200/OP.21.00883
[7] https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

Thus, the lack of this critical chemotherapy drug could result in relapse and death among patients, who would otherwise be cured.

More broadly, the current cisplatin and carboplatin shortages may impact as many as 500,000 Americans a year. In 2022, approximately 100,000 Americans were diagnosed with ovarian, bladder and testicular cancers, curable cancers where treatment requires cisplatin or carboplatin. In addition to ovarian, testicular and bladder cancers (the FDA-approved indications for the platinum drugs), these agents are also commonly used in cervical, endometrial, lung, head and neck, bladder, esophageal, gastric, breast and more cancers.

It has been widely reported that 50% of the cisplatin used in the U.S. came from the Intas plant in India, and that the current shortage can be most directly traced to disruption of its production after an FDA inspection found significant failures in quality control.[8] Despite that identifiable, singular event in this specific case, it should be emphasized that this is not an isolated instance. These events have and will recur again and again, with different acute exacerbations layered on top of existing chronic shortages of scores of lifesaving drugs. Patients will be impacted every day by shortages until we institute policies that strengthen the resilience of the generic drug market.

Shortages impact children with curable cancer, as well. Pediatric cancer drugs were amongst the drugs in shortage during the 2010-2011 shortage spike, and from 2010 to 2020, eight of the 10 most frequently used drugs to treat acute lymphoblastic leukemia - the most common childhood cancer - were at some point temporarily unavailable.

How do existing inflation penalties in Medicaid and Medicare create additional barriers for generic manufacturers, leading to drug shortages? How does the discretion given to CMS to reduce or waive these penalties for drugs on the FDA's Drug Shortage list, as well as certain drugs facing severe supply chain disruptions, introduce additional uncertainty into drug development, and what can be done to remedy that uncertainty?

The U.S. market for sterile generic injectable drugs is broken. The Medicare formula for reimbursement of physician-administered drugs under Part B, established by the Medicare Modernization Act (MMA) of 2003, reimburses physicians at the average sales price (ASP) plus six percent ("ASP+6") for drugs bought for use in their practices. There is a 6-month lag between the time the manufacturers submit their ASP data and when changes in sales prices are reflected in the Centers for Medicare and Medicaid Services' (CMS) reimbursement files. This time lag has the practical effect of making it difficult for manufacturers to raise their prices more than 6% in any 6-month period. This leaves little flexibility for prices to adapt to free-market supply and demand. As was noted in an early (2012) editorial,[9] the MMA was implemented in 2005 and shortages in chemotherapy drugs began to escalate within a year and have increased dramatically since 2008.

An Assistant Secretary for Planning and Evaluation (ASPE) report[10] published 12 years ago helped illustrate the relationship between prices and shortages: it showed that that drugs that had not been in shortage had stable or increasing prices during the period under study, whereas drugs that had gone into

[8] https://www.washingtonpost.com/business/2023/06/27/cancer-drug-shortage-generics/
[9] https://ascopubs.org/doi/10.1200/JCO.2011.41.0936?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[10] https://aspe.hhs.gov/reports/economic-analysis-causes-drug-shortages-0

shortage almost universally witnessed their prices decrease before the shortage period, as competition and market factors drove prices down.

It has been highlighted since 2010 that the supply chain for pharmaceuticals is opaque. While the FDA has information on finished product manufacturers and active pharmaceutical ingredients (APIs), the agency does not necessarily know which API supplier(s) is being used by which manufacturer; additionally, visibility into earlier steps in the supply chain, such as key starting materials (KSMs) and refined chemicals is even more limited. ASCO and others have advocated for years for more insight into this supply chain, including requiring manufacturers to report more actionable information to the FDA and to give the FDA an earlier and more holistic picture of the actual and anticipated supply of any given drug.

In addition to the existing opacity of the supply chain, the market for prescription drugs is incredibly complex and likewise lacking in transparency. Many institutions and practices join group purchasing organizations (GPOs) which negotiate drug prices on their behalf. Because they can leverage the purchasing power of multiple entities, GPOs can often obtain more favorable pricing than that available on the "open" market. The specifics of each contract are confidential and proprietary and often involve the "bundling" of drugs and rebates for specific preferred drugs. Manufacturers may sell certain drugs at very thin margins, or even at a loss, to procure guaranteed purchasing for other drugs. Finally, much of this purchasing power has been consolidated into just three GPOs, which serve most of the market, giving them yet more leverage. All these forces are at work behind the scenes, compounding the "race to the bottom" inherent in our current generic market competition. This reduces the competition and resilience in the underlying supply chain and market.

Fundamentally, the generic market must be stabilized so that manufacturers do not continue to exit due to the unfavorable market conditions described above. They need a healthy market in order to have the necessary resources to invest in physical plant upgrades and to move to advanced manufacturing technologies. How policymakers can accomplish that without causing unintended or inadvertent consequences in the rest of the market is always a challenge, but we believe it is possible. Among the many interesting or promising solutions put forward, we urge consideration of a reserve or buffer of critical drugs outside of the Strategic National Stockpile (SNS) that would focus on drugs at risk of shortage; creating tax incentives or restructuring the reimbursement system for generics; encouraging the federal government to participate in long-term contracts with a variety of generic manufacturers for the programs it oversees directly; waiving or decreasing the generic drug user fee in specific situations; and making more supply chain information available to the FDA and the public. For this last suggestion, the point has been made that purchasers of generic drugs have little to no visibility into any quality issues manufacturers may be having and that providing these purchasers with more information related to quality manufacturing assurances or plans may provide valuable information beyond only the price of a drug for purchasers to base their decisions on.

What are the regulatory challenges to manufacturing drugs in the United States, as compared to other countries? Please specify which agency issued and enforced such regulations.

The FDA inspects facilities and reviews manufacturing processes to ensure the safety of drugs. These inspections sometimes result in adverse findings, which may require temporary stoppage of production for the manufacturer to come back into compliance, recall of drug, or other facility upgrades.

ASCO and other stakeholders have put forward recommendations[11] for regulatory action that creates incentives for manufacturers to improve drug and device manufacturing quality. For example, requiring the FDA to provide ratings of the quality management processes of medication and device manufacturers that are predictive of supply chain and manufacturing vulnerabilities and to make the ratings publicly available; and identifying key starting materials, active pharmaceutical ingredients and finished dosages forms of essential medicines, that have domestic manufacturing capacity to improve the resilience of the U.S. drug supply and incentivize their production without limiting access to foreign sources of the product.

How can federal agencies, such as the Centers of Medicare and Medicaid (CMS), better address the economic forces driving shortages? Are these agencies using their current authorities effectively?

CMS is constrained by statute in how it pays for drugs. We believe an effective use of the agency's authority would be to investigate innovative reimbursement structures for sterile generic injectable drugs under the Center for Medicare & Medicaid Innovation's (CMMI's) current authority.

How does the current generic drug reimbursement structure in federal programs, including those programs' mandatory discounts and rebates, contribute to drug shortages, and what solutions exist?

The Inflation Reduction Act (IRA) requires drug manufacturers to pay a rebate to the federal government if prices for *single-source drugs* and biologicals covered under Medicare Part B increase faster than the rate of inflation (CPI-U). For Medicare Part D, nearly all covered drugs are included in this rebate provision. In oncology, the most troublesome and pervasive shortages occur with sterile generic injectables, which are largely not covered by the IRA rebate provision affecting Part B. While we would not expect this IRA provision to have a material impact on generic drug prices, we are still left with the underlying problem of the inability of generic drug prices to reflect adjustments in market demand, due to the pre-existing market conditions described above.

As the agency implementing the rebate provisions, CMS has recognized that there will be a potentially troublesome intersection between the rebate requirements and drug shortages. This could impact both drugs actively in shortage, and those at risk of going into shortage, with no sure way for the market to identify this latter set of drugs. CMS issued an RFI specifically on this topic, soliciting stakeholder feedback on approaches to adjusting the rebate requirements for drugs in shortage, without inadvertently creating market conditions where there is an incentive for manufacturers to have a drug designated as a drug in shortage. Historically, it is not common to have brand-name, single-source drugs in shortage, with the well-publicized exceptions due to circumstances like spiking demand (e.g., semaglutide) or pandemic conditions. In our response, we urged CMS to carefully monitor generic drugs with fewer manufacturers and to consider the circumstances driving the shortage (or anticipated shortage) when making any adjustments to rebates.

Given that supply chain issues can trigger manufacturing delays and disruptions that result in shortages, are further incentives necessary to address manufacturing issues?

We recommend that policymakers develop incentives for drug manufacturers to have contingency or redundant production plans for their pharmaceutical products on the critical drug list. The back-up plan should include prioritizing the most medically necessary products, qualifying third party suppliers across

[11] Healthcare-Supply-Chain-Recommendations (ashp.org)

their network, and increasing production and inventory for API and finished goods. However, we recognize the investment required to implement this policy and its success would also be contingent upon the rise of generic sterile injectable drug prices and their profitability.

Additionally, policymakers could investigate developing a system of paying suppliers to hold inventory, perhaps similar to the system employed by the U.S. Department of Defense (DoD) Defense Logistics Agency. Consider partnering with the DoD to create contractual leverage with drug manufacturers for civilian hospitals.

Furthermore, policymakers could explore incentivizing manufacturers to work with the FDA to repackage pharmaceuticals according to the amount of medication commonly used to reduce waste. (E.g., it can be wasteful to only offer a 30 mL vial of a drug when most common volume needed is 5 mL.)

Are there any guardrails that Congress should consider related to demonstration projects, including via the CMS' Innovation Center, that would help protect against drug shortages? Are there any proactive demonstrations that would prevent drug shortages?

Based on several factors, we are deeply concerned that shortages are going to get worse. First, FDA inspections during the COVID-19 pandemic lagged. They are quickly picking back up and it is highly likely that additional problems will be uncovered at inspected sites. Second, one of the largest generic manufacturing firms, Teva, has announced its intent to significantly reduce its footprint in the U.S. generic market, and it is unknown how quickly remaining manufacturers will be able to fill that deficit. Third, none of the underlying problems plaguing the market have been addressed, leading to continued patterns of generic drugs dropping in price until continuance of their manufacture becomes financially untenable resulting in fewer resources and/or incentives to invest in improved physical plants or manufacturing processes, and ultimately rational business decisions to switch to more profitable drugs.

CMS could consider using its authority with CMMI to develop innovative reimbursement models that would focus *specifically* on sterile generic injectables in shortage, at risk of shortage, or with a history of shortage. The market must be stabilized to ensure both continued savings to patients and the healthcare system provided by generic drugs, while providing sufficient financial incentives to manufacturers that they are willing to stay in the market.

How has consolidation among Group Purchasing Organizations and Prescription Drug Wholesalers led to less redundancy in the drug supply chain? Has this consolidation contributed to drug shortages, especially among generic drugs? Have business practices, such as just-in-time deliveries and limited-source contracts contributed to the drug shortage issue we are seeing?

The market for prescription drugs is heavily consolidated. This consolidation gives a small handful of powerful purchasers the ability to negotiate favorable pricing, which is effective in lowering prices. In the context of sterile generic injectable shortages, however, it has the effect of making their manufacturing less and less appealing. End users of these drugs (hospitals, clinics, etc.) should be incentivized to purchase drugs based not on price alone, but instead based on price and quality and reliability of supply. ASCO has long advocated for a framework in which quality and reliability of supply is reflected in drug pricing; the current FDA pilot programs in quality management maturity (QMM) is a step in the right direction of laying the groundwork.[12]

[12] https://www.fda.gov/drugs/pharmaceutical-quality-resources/cder-quality-management-maturity

What factors would lead to a generic drug receiving approval but not coming to market?

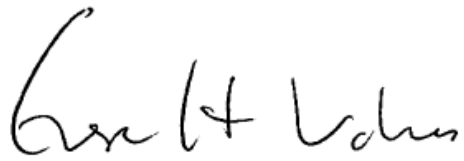
One obvious factor is return on investment. If a manufacturer sees a competitive market where the margin for that drug is very small, it makes sense for that manufacturer to consider producing an alternate drug with higher profit margins.

Are there any other issues leading to drug shortages that we have not considered in this RFI?

While other countries also experience drug shortages, in many countries, the shortages are not as widespread as those impacting the U.S. Countries in Europe, for example, pay less for reference/brand name drugs than the U.S., but pay up to 30% more for generic drugs and suffer much less in the way of shortages. It is notable that those countries that have long-term, stable contracts for generic drugs set at higher prices tend to maintain supplies compared to markets (such as ours) which are driven solely by (lowest) pricing, without factoring in quality or reliability of supply.

Thank you for the opportunity to provide our comments, concerns, and solutions to strengthen our oncology drug supply chain. We would welcome the opportunity to engage with your committees in a meaningful dialogue about these issues. ASCO is open to advancing a comprehensive solution to drug shortages via any viable legislative vehicle and hopeful to address these issues quickly. If you have any questions, please contact Megan Tweed at megan.tweed@asco.org.

Sincerely,



Everett E. Vokes, MD, FASCO
Chair of the Board
Association for Clinical Oncology