ASTCT
American Society for
Transplantation and Cellular Therapy

SUBMITTED VIA EMAIL

July 7, 2023

The Honorable Cathy McMorris Rodgers
Chair, Energy and Commerce
U.S. House of Representatives
2188 Rayburn House Office Building
Washington, DC 20515

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

Dear Chairwoman McMorris Rodgers and Ranking Member Crapo:

The American Society for Transplantation and Cellular Therapy (ASTCT) appreciates the opportunity to submit comments on the June 12, 2023 Request for Information (RFI) regarding the ongoing surge in drug shortages. As a professional membership association of physicians and healthcare workers in stem cell transplant, we have firsthand knowledge of the challenges faced during these shortages. It has been taxing on our community trying to navigate how best to serve our population of immunocompromised patients with limited resources. We are encouraged to see Congress taking an interest in the FDA supply chain issues we have been facing for quite some time.

The ASTCT is a professional membership association of more than 3,700 physicians, scientists, and other health care professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication, and clinical standards. Our Society's clinical teams have been instrumental in developing and implementing clinical care standards and advancing cellular therapy science, including participation in trials that led to current Food and Drug Administration (FDA) approvals for chimeric antigen receptor T-cell (CAR-T) therapy and hematopoietic stem cell-based gene therapies for genetic immune system and blood disorders.

We are pleased to present our answers to the questions put forth by your committees. ASTCT's Pharmacy Special Interest Group composed the following:

1. How would you define the scope and impact of the recent and ongoing U.S. drug shortages?
   a. For drugs currently in shortage, what percentage of their market is reimbursed through public payers, such as Medicare and Medicaid?

- **Currently the majority of drug shortages are impacting generic injectable drugs that are commonly used for Medicare and Medicaid patients receiving hospital care or infusion based therapies such as chemotherapy. The vast majority of drugs in shortage will have Medicare or Medicaid reimbursement. There have been a smaller percentage of oral medications**

for certain indications such as obesity or ADHD that likely have a lower percentage of Medicare or Medicaid reimbursement but also are likely being driven by different mechanisms such as increased demand or DEA quota limits.

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

- **Ongoing drug shortages continue to be a major issue in patient care and only seem to be getting worse. Specifically in oncology, when chemotherapy goes on shortage there are often few or no alternative evidence-based therapies. For example, Fludarabine, a lifesaving chemotherapy that is paramount for treatment in hematologic malignancies with hemopoietic stem cell transplant or chimeric antigen receptor t-cell (CAR-T) therapy, continues to be on shortage for over a year. ASTCT engaged directly with the FDA on the shortage and still did not receive enough of a supply that is still directly affecting our patient population.**
- **Many institutions have very limited or no supply of Fludarabine and were faced to make ethical decisions about which patients could receive therapy or what potential alternative could be used, with very limited data posing a major safety risk. Hundreds of patients have been unable (and continue to be unable) to be treated with standard of care, curative, chemotherapy regimens.**
- **The increased demand of available alternatives also often quickly leads to a cascade of drug shortages impacting multiple indications. Carboplatin, a chemotherapy agent that is used to treat and cure numerous types of cancer, has recently been placed on shortage. As a result, its sister drug cisplatin was used as an alternative and is now also on shortage. If both of these chemotherapy agents become unavailable, we are left with no alternative for many cancers, which otherwise would be curable.**
- **These two examples are by no means the only oncology-related shortages with recent methotrexate, a critical chemotherapy agent also used in many cancer types and often times has no alternative, is in short supply for the second time in the last 8 years. There have been critical shortages in etoposide and other agents have required difficult ethical dilemmas back to 2011. The American Society of Health System Pharmacists has a comprehensive list of over 150 medications that are currently on shortage, all of which impact varied avenues of patient care.**
- **The ongoing shortage goes beyond just the chemotherapy itself and affects many of the supportive care medications to help prevent or treat adverse effects we can see with many of our therapies. Most recently, hydrocortisone is on shortage. This critical medication is used throughout all medical practice and mitigation strategies have included pivoting to other IV steroids. The downstream affect is being seen on methylprednisolone, which**

is another critical medication used across all medical practices. There have been numerous ongoing, critical shortages with no end in sight. There is a lack of safety and efficacy data with use of alternative therapies in adult patients and even more paucity of data in pediatrics. As a result, difficult, ethical dilemmas have to be address by healthcare providers and institutions to decide what is best during a dire situation.

3. What the regulatory challenges to manufacturing drugs in the United States, as compared to other countries?

- **This is a difficult question. The FDA in general has a reputation for having some of the highest standards across the globe although we do not have a direct comparison. However, tighter regulation is often appropriate to ensure the safety of medications reaching patients.**
- **In 2010-2011 HHS published a report stating that nearly all generic injectable drugs used in the U.S. were also manufactured in the U.S. although raw materials may be sourced internationally. At the time, the GAO cited manufacturing capacity as a potential major contributor to drug shortages. As a manufacturing facility encounters delays for maintenance or quality control, shortages inevitably would be a result of the reduced available supply. Now over 10 years later, this just-in-time manufacturing process remains unresolved and minor disruptions in manufacturing become major drug shortages. Quality seems to be a significant trigger to manufacturing delays and there continues to be no excess inventory to be able to cover the gap when there is a delay. After a facility has the manufacturing process paused, there is also a significant delay to acquire raw materials and get the manufacturing operating at capacity. This decade long of cyclical shortages has led to rumors of manufacturing pauses, which triggers consumers to attempt to buy enough inventory to cover the anticipated gap, which in and of itself creates a shortage.**
- **These shortages are likely worldwide but have not had news coverage as local shortages in the U.S.**

7. What role, if any, has growth in the 340B program played in drug shortage trends?

- **The 340B program was in place prior to the current, consistent drug shortages and the connection to 340B seems unclear. There may be less incentive for manufacturers to continue to produce generic drugs if discounting leads to products no longer being profitable. The removal of a manufacturer from the mix of generic products could create a shortage.**

9. 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 existing programs are likely not related to reimbursement rather than rebate programs. Currently if a manufacturer has to increase prices related to increased material costs, the Average Manufacturer's Price (AMP) will inevitably increase. If the AMP begins to exceed the inflation-adjusted, baseline AMP for a particular drug, the manufacturer will be required to pay a rebate to keep the drug "covered" and available to Medicaid beneficiaries. The proposed Inflation Adjustment Act creates a similar system for Medicare. In some cases, these systems may lead to slightly lower coinsurance for patients with the difference in payment coming from the manufacturer. It is unclear that this process impacts shortages but some may argue it may discourage manufacturing innovation or R&D.**

10. How might uncertainty in the drug coverage process, particularly as it relates to National Coverage Determinations (NCD) and coverage paradigms like Coverage with Evidence Development (CED), affect competition and, ultimately, the supply of drugs? What can be done to promote greater certainty in that process for FDA-approved drugs?

- **NCDs/LCDs may not directly impact drug shortages. Perhaps with stifled competition, if the policies are not appropriately updated with clinical practice or if the NCD/LCD requires the CED process to be done for the drug to be covered, could contribute. The CED process does create a barrier introduced to the FDA approval process, which may slow innovation. The CED process also may delay or prevent Medicare coverage if CMS requires CED completion prior to providing coverage to beneficiaries.**

12. 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 contacts contributed to the drug shortage issue we are seeing?

- **GPOs and Wholesalers have consolidated into 2 to 3 large organizations. GPOs awarding single source contracts and require failure to supply language as well as Wholesalers, thus driving down prices both likely contribute to fragile supply chains and deincentivize producing generic drugs.**

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ASTCT hopes that our answers to some of these questions provides clarity on the topics relating to drug shortages in the U.S. We strongly support any efforts to address these drug shortage issues to continue to allow us to serve our patients in the most clinically proper manner. The shortages have a direct impact on patient access to life-saving therapies and we thank you for your efforts in helping.

If you have any questions or need clarification please contact Alycia Maloney, the ASTCT's Director of Government Relations, at amaloney@astct.org.

Sincerely,

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