



AMERICAN SOCIETY OF HEMATOLOGY

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Dear Dr. Woodcock,

On behalf of the American Society of Hematology (ASH), thank you for convening the U.S. Food and Drug Administration's (FDA) public workshop to address drug shortages on September 26, 2011. The Society appreciates the opportunity to share its concerns regarding the increasing problem of shortages of life-saving drugs. ASH's comments will describe how drug shortages are adversely affecting hematologists and the patients we treat. In addition, these comments offer several recommendations for strategies FDA could implement for preventing or mitigating shortages. There is a critical need for changes in policies and practices to prevent patient harm and disruptions in patient care caused by shortages and ASH urges FDA to work with stakeholders, including the Society, to identify and implement effective strategies.

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases, including blood cancers such as leukemia, lymphoma, and myeloma and a number of nonmalignant illnesses such as anemia (including sickle cell and thalassemia), thrombosis (including venous thrombosis, heart attack and stroke), and bleeding disorders. The patients our members treat have been especially adversely affected by recent shortages.

Although physicians have dealt with national drug shortages before, the increasing number of shortages of drugs in the United States has become critical and life threatening. Each year the total number of new shortages identified increases. Between 2006 and 2010, the number of new drug shortages tripled. What is even more alarming is that we continue to see increasing numbers of shortages this year, with close to 200 national drug shortages already reported as of August 31, 2011, compared to the overall total of 211 shortages reported in all of 2010.

The increasing number of drug shortages has significantly affected the practice of hematology because the standard therapies frequently used include older, sterile injectable products that are particularly vulnerable to production, marketing, and business factors. Fewer firms manufacture these products, the products require complex manufacturing processes, companies may be tempted to redirect resources to more profitable products, and financial return may not justify corrective action when problems occur.

Over the past year, ASH has received frequent calls from hematologists, pharmacists and patients who experienced drug shortages and who requested help in finding supplies of the drugs or asked for guidance on alternative therapies. A spectrum of therapies has been involved, but the Society has heard the most concerns and questions about drugs used to treat multiple myeloma, lymphomas, and leukemias. In addition, a shortage of supportive care drugs has further complicated the lack of chemotherapy drugs.

The drug shortages already have had a profound impact on the care of some patients and, if not addressed, have the potential to place even more patients at risk. At a minimum, patients with serious hematologic diseases have been distressed if their treatments are delayed, even if this is for a very short time and not clinically significant. More significantly, physicians have had to choose initial therapies that are not their usual first-line of therapy standard treatment or have had to change therapies mid-treatment. Some institutions and practices have established policies to prioritize and ration the use of certain drugs during temporary periods of drug scarcity.

A widespread problem for hematology patients has been the shortage of cytarabine, part of standard therapy for certain leukemias and lymphoma. An ASH member recently shared his experience with the Society about a case involving a 50 year old male with primary refractory large B-cell lymphoma who was receiving chemotherapy to prepare him for a bone marrow transplant. The patient received the first part of the chemotherapy and was responding well. The treatment schedule called for cytarabine to be included in the second dose of chemotherapy, but because it was not available at the time, the physician was forced to choose an alternative therapy that was more toxic. The patient was not able to receive the transplant and died from complications.

This story is only one example of several cases that have recently been described to ASH about physicians having to give patients less effective or more toxic alternative treatments not because of a lack of coverage, prohibitively costly treatment, progression of disease, or lack of knowledge about how to treat, but, rather, because the standard treatment was not available.

The interruption in treatment caused by shortages puts vulnerable patients at risk. Physicians have been forced to send some of their most fragile patients to hospitals, pharmacies and clinics in geographically inconvenient locations to access remaining supplies of their therapy. Another ASH member reported several cases at his institution involving patients with pernicious anemia who were receiving monthly B12 shots. Because there was a shortage of the injections, the patients were faced with a multi-month interruption in their treatment, which exposed them to the risk of neurological damage and worsening anemia. The patients had the option to take oral B12 pills, but for most of them this was not a viable option because they were unable to absorb the alternate therapy through their digestive tract. Practice management has also been affected. Practices typically hear about shortages when they order the therapy and find out that the supplier does not have the product in stock. Consequently, practices have had to spend significant time tracking drugs for patients who are scheduled for admission in the upcoming weeks. In addition, support staff and physicians are forced to constantly monitor multiple sources to track new and ongoing shortages. There has often been different information provided by the FDA, drug companies, and medical societies. Sorting through this information takes time away from direct patient care.

The cost implications of such shortages can be considerable. Traditionally, practitioners have been proactive in controlling health care costs by using generic drugs. However, because of shortages, practices have been forced to choose more expensive alternative treatments.

Drug shortages have also adversely affected clinical trials that are pivotal in research and treatment efforts. Trial activation has been suspended and patient accrual halted, ultimately slowing the pace of clinical research. For instance, a recently opened large Eastern Cooperative Oncology Group (ECOG) randomized clinical trial in Acute Myeloid Leukemia involving cytarabine and daunorubicin could not accrue patients and delayed the research.

ASH understands that the causes of drug shortages are multiple and complex. There is not a single solution. As different remedies are considered, there must be forethought to anticipate and prevent unintentional consequences of legislation or over-regulation. ASH recognizes that FDA cannot force a manufacturer to produce a product. Currently, FDA's ability to address drug shortages is compromised because of limited authority and resources. FDA cannot require manufacturers to notify it of all potential or pending shortages or impose penalties for not doing so; FDA has no authority to require companies to increase production of a drug during a shortage; FDA cannot impose an allocation plan when a shortage causes life threatening conditions; and FDA has limited ability to post timely information on its website for healthcare professionals and patients regarding reasons for shortages and timelines for resolution. Therefore, ASH believes it is critical that FDA have greater authority and resources and offers the following recommendations:

- **Increase FDA Authority** – ASH recognizes that the FDA currently does not have the authority to address many issues that cause drug shortages. *The Preserving Access to Life-Saving Medications Act* (S. 296/H.R. 2245) was recently introduced and proposes an expansion of FDA's authority.

The legislation would give FDA the authority to require early notification from pharmaceutical companies when a factor arises that may result in a shortage. These factors may include changes made to raw material supplies, adjustments to manufacturer production capabilities and certain business decisions such as mergers, withdrawals or changes in output. The legislation would also direct the FDA to provide up-to-date public notification of any shortage situation and the actions the agency would take to address them. In addition, the legislation would require the FDA to develop evidence-based criteria for drugs vulnerable to a shortage; and would require FDA to collaborate with manufacturers of drugs vulnerable to a shortage to establish continuity of operations plans for medically necessary drugs. The legislation would also require FDA to develop an enforcement mechanism for non-compliance. This legislation would not fully solve the drug shortage problems we are experiencing, but it would be a significant step towards reducing the magnitude of the problem.

- **Improve FDA Communication with Stakeholders** – Information provided by the FDA, pharmaceutical companies, and medical societies about shortages frequently varies. The inconsistencies can be confusing to stakeholders and can complicate the management of patients. ASH recommends that the FDA increase its current communication with the pharmaceutical industry and medical societies to ensure that timely and accurate information is being delivered to all stakeholders. One basic way to improve and enhance communication would be to develop specialty-specific listserves. Any information that the FDA receives about a potential shortage could be filtered through the relevant listserve to all stakeholders. Also, if drug companies and medical societies are circulating information, they could share this information through the relevant listserve as well. This should include information regarding specific drugs in shortage, length of time, and ways physicians may access therapies in short supply. This practice would ensure that all stakeholders receive accurate information in real time.

- **Examine Impact of Current FDA Requirements on Shortages** – Since approximately 42% of the 2010 drug shortages were caused by product quality issues, ASH recommends that the FDA examine how new testing methodologies involving more sensitive assays may contribute to the problem of shortages. While ensuring safety standards is paramount, FDA also needs to determine if its evaluation of product quality is accurate.
- **Develop a National Drug Registry** – ASH recommends that FDA develop a registry for older and medically-necessary drugs to better track quantities and availability of these drugs. A registry would facilitate FDA’s ability to monitor potential shortages, share information with physicians and pharmacists, and assist providers in locating supplies of drugs in a more efficient way than through the current process.
- **Expand “Orphan Drug” Status to Incentivize the Continuous Production of Generics** – Many shortages have occurred because manufacturers are having a difficult time maintaining a profit margin under the current system. In an effort to encourage manufacturers to continue producing single source, older generic drugs, ASH recommends FDA consider classifying these therapies as “orphan drugs” and creating incentives for companies to manufacture these products.

The current drug shortage situation in the United States is unacceptable. The shortages have caused medical treatment to be delayed and compromised, research to be slowed or halted, and increased costs. Most significantly, shortages have caused patients to suffer. It is critical that FDA have expanded authority to mitigate drug shortages. ASH urges the FDA to work with stakeholders to identify and implement solutions as soon as possible.

Thank you for your consideration of ASH’s comments and recommendations. The Society looks forward to working with you on this urgent and most important issue. Please contact ASH Government Relations Manager, Stephanie Kaplan (skaplan@hematology.org or 202-776-0544), if we can provide additional information or expertise.

Sincerely yours,

A handwritten signature in black ink, appearing to read "J. Evan Sadler". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

J. Evan Sadler, MD, PhD
President, American Society of Hematology