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February 16, 2012

Margaret A. Hamburg, MD
Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA-2011-N-0898; Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements – Discontinuance

Dear Dr. Hamburg,

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) on the Interim Final Rule (IFR) Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements – Discontinuance as announced in the Federal Register (FDA-2011-N-0898) on December 19, 2011. ASH commends the FDA for developing the IFR and taking an important step to address the urgent problem of drug shortages. ASH supports the changes included in the IFR and believes they will help improve FDA's ability to prevent and mitigate the impact of imminent drug shortages by increasing the scope of information that the agency receives regarding discontinuances. ASH agrees with the Agency that the broader reporting resulting from the IFR will enable FDA to improve its collection and distribution of drug shortage information to physician and patient organizations and to work with manufacturers to respond to potential drug shortages. However, the Society has several comments concerning the IFR and specific recommendations that are provided below.

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 disease 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. For example, last year a national shortage of cytarabine, an irreplaceable chemotherapy drug essential to the cure of acute myeloid leukemia (AML), was reported. (Cytarabine cures forty percent of patients with AML; without cytarabine, the cure rate is zero percent. This shortage affected thousands of patients who were diagnosed with AML and treated in the approximately 6-month period when cytabine was out of stock.) Currently, we are experiencing critical shortages of additional drugs for the treatment of leukemia, including: methotrexate injection and daunorubicin. Scores of other leukemia, lymphoma and myeloma patients also faced shortages of other life-saving treatments and our sickle cell patients have struggled with a lack of access to hydroxyurea, the only approved drug used to treat this disease.

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 other business factors that lead to shortage. 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.

A. *Discontinuance*

ASH supports the changes to broaden the definition of discontinuance contained in the IFR. ASH believes this rule will increase the number of manufacturers reporting, which will allow FDA to improve communications to physicians and patients as well as to work in a more informed manner with manufacturers to reduce the impact of drug discontinuances and prevent potential shortages. The Society, however, notes that recently we experienced a drug shortage due to the transfer of the drug application between firms, and consequently recommend amending the language to include this type of circumstance.

ASH Recommendation:

> **ASH recommends adding a *merger of firms* or *transfer of a drug application to a new firm* to the list of circumstances that would trigger notification to the FDA of a discontinuance of a drug product subject to 506C.**

ASH is also concerned that the IFR does not address the need to improve FDA's communication with stakeholders. Key to FDA's stated goal of expanding collection and distribution of information on the discontinuance of certain drugs is having an effective communications strategy. Currently, however, information about drug shortages provided by the FDA to stakeholders varies and is often delayed, complicating the management of patients.

ASH Recommendation:

> **ASH recommends that the Final Rule include a plan to improve communications with the pharmaceutical industry, medical Societies, physicians and patients.**

For example, one way to improve and enhance communication would be to develop specialty-specific listservs. Any information that the FDA receives about a potential shortage could be filtered through the relevant listserv to all stakeholders. If drug companies and medical societies are circulating information, they could share this information through the relevant listserv as well. This should include information regarding specific drugs in shortage, the expected duration of the shortage, and ways physicians and patients may access therapies in short supply. This practice would ensure that all stakeholders receive accurate information in real time.

B. *Sole Manufacturer*

ASH is pleased that the IFR expands the definition of the sole manufacturer to include "an applicant that is the only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities." The Agency further clarifies that a manufacturer will be considered a "sole manufacturer even if other manufacturers hold an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for the same product, if the other applicants are no longer manufacturing (or have never manufactured) the product for sale in the United States." The Society is concerned, however, that the expanded definition may not cover situations in which there are multiple manufacturers of the same critical product, but if one discontinues there is a severe

disruption. For example, the severe 2011 shortage of cytarabine involved three manufacturers, which would not qualify under this definition and therefore would not need to be reported; similarly, there are multiple manufacturers of methotrexate, but when one had to discontinue, the others could not make up the shortfall.

ASH Recommendation:

> **ASH recommends that the Final Rule mandate reporting for drugs that are deemed "critical," but may have multiple manufacturers and may not meet the definition of sole manufacturer.**

Another concern for the Society is that the determination of sole manufacturer status is made by the manufacturer. The IFR states that "A manufacturer is responsible for determining if it is a sole manufacturer under this regulation. There is commercial information available to help with this determination. If an applicant is unsure if it is a sole manufacturer of a drug product subject to section 506C, FDA's drugs shortages staff may be able to work with it to help it determine whether it is or is not the sole manufacturer of the drug." ASH is concerned that this process for individual determination will result in inconsistent adherence.

ASH Recommendation:

> **ASH recommends that the Final Rule require the FDA to have the responsibility of designating sole manufacturer status.**

While ASH supports the IFR and believes that it is a good start in supporting the FDA's ability to address drug shortages, additional FDA authority and resources are needed to support the Agency's efforts. As the Society prepares to submit this letter, the country is experiencing an increasing number of shortages, including a life-threatening shortage of methotrexate. Hematologists across the United States have reported they are out of preservative-free methotrexate or have a very low supply and they are struggling to figure out how to treat their patients with insufficient information about when additional product will be released. Consequently, the Society concludes the impact of the IFR is limited and clearly more must be done beyond this rule to prevent and mitigate future drug shortages.

While ASH recognizes this is outside of the scope of this regulation, the Society continues to advocate for the following to further strengthen the FDA: enforcement authority to penalize a manufacturer for non-compliance with reporting requirements; authority to examine the impact of current regulations on shortages; authority to better track drugs vulnerable to shortages; and authority to provide economic incentives to manufacturers of critical drugs.

Thank you for your consideration of ASH's comments and recommendations. The Society hopes to continue to work with the FDA on this most critical issue. Please contact ASH Government Relations Manager, Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544), if the Society can provide additional information or expertise.

Sincerely,

Armand Keating, MD
President