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March 14, 2013

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-2013-N-0124; Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments in response to the proposed rule implementing provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) as signed into law on July 9, 2012. In the Tuesday, February 12, 2013 Federal Register, the Food and Drug Administration (FDA) solicited input related to Section 1003 of FDASIA that requires the FDA to form a task force to develop and implement a strategic plan to enhance the Agency's response to preventing and mitigating drug shortages.ⁱ ASHP is the national professional organization whose over 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in hospitals, health systems, and ambulatory clinics. For 70 years, the Society has been on the forefront of efforts to improve medication use and enhance patient safety. ASHP was instrumental in developing these provisions and having them included in FDASIA as enacted into law.

Since 2006, shortages of primarily generic injectable drugs have dramatically escalated, increasing from 70 seven years ago to 299 in 2012.ⁱⁱ These drugs, which are fundamental and essential to care, affect this nation's hospitalized and most vulnerable patients. Without access to the preferred or most clinically appropriate drug treatment, health care professionals must use alternatives, which may be less effective or associated with increased risk of adverse outcomes.

TOGETHER WE MAKE A GREAT TEAM

ASHP partnered with several health care, provider and safety-related groups to hold a drug shortages summit in November 2010 that was aimed at defining the causes of drug shortages and identifying potential avenues to address the problem through legislation, regulation and within the marketplace itself.ⁱⁱⁱ One finding was that the causes of drug shortages are many and complex. The causes of a vast number of drug shortages can be traced to manufacturing issues, most significantly product quality issues that result in production halts or recalls, as well as unavailability of active pharmaceutical ingredients (APIs) or other raw materials, and product discontinuations.

In the Federal Register notice referenced above, the FDA solicited responses to the following questions about issues related to the development by the Task Force of the strategic plan to address drug shortages. Wherever possible, ASHP provides recommendations as to whom to engage for questions that are outside the expertise of the Society.

1. In an effort to address the major underlying causes of drug and biological product shortages, FDA is seeking new ideas to encourage high-quality manufacturing and to facilitate expansion of manufacturing capacity.
 - a. To assist in the evaluation of product manufacturing quality, FDA is exploring the broader use of manufacturing quality metrics. With that in mind, FDA would like input on the following issues:

What metrics do manufacturers currently use to monitor production quality?

This question is outside of the scope of ASHP's expertise.

To what extent do purchasers and prescribers use information about manufacturing quality when deciding how to purchase or utilize products?

Buyers assume that FDA approved drugs and biologics are of high quality due to cGMP adherence requirements and FDA regulation, inspection, and oversight.

What kinds of manufacturing quality metrics might be valuable for purchasers and prescribers when determining which manufacturers to purchase from or which manufacturers' products to prescribe?

All FDA approved drugs and biologics are assumed to be held to the same high standard of manufacturing and that products listed in the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations meet these quality standards. An additional factor in evaluation which manufacturer to choose is the manufacturer's record for meeting historical demand for their products. However, as a result of the serious impact of shortages on patient care and

significant expenditures by health care providers and organizations to manage shortages, we propose that purchasers and prescribers place a greater priority on the ability of a manufacturer to provide an uninterrupted supply of critical medications and would be willing to pay more for drugs with guaranteed availability. As quality issues are a major cause of shortages, a “failure to supply” metric might be a surrogate indicator for product manufacturing quality that is meaningful to the health care community. Such an indicator would require exceptions to avoid penalizing drug firms experiencing increased demand due to temporary or permanent departures of one or manufacturers from the market. However we believe rewarding reliability in supply indirectly incentivizes improved quality.

What kinds of manufacturing quality metrics might be valuable for manufacturers when choosing a contract manufacturer? How frequently would such metrics need to be updated to be meaningful?

This question is outside of the scope of ASHP’s expertise.

- b. The use of a qualified manufacturing partner program similar to one used under the Biomedical Advanced Research and Development Authority (BARDA) has been suggested as a potentially useful approach to expanding manufacturing capacity and preventing shortages. FDA recognizes that there are important potential differences between the BARDA program and the use of a parallel program to address shortages. For example, the BARDA program covers a relatively stable and limited number of products, but drugs at risk of shortage are many, may change rapidly over time, and are difficult to predict in advance. In addition, FDA does not have funding to pay manufacturers to participate in a drug shortages qualified manufacturing partner program or to guarantee purchase of the end product.

With these differences in mind, is it possible to design a qualified manufacturing partner program that would have a positive impact on shortages?

ASHP agrees that a qualified manufacturing program, such as BARDA, could be useful in addressing the need to expand manufacturing capacity. The Society recognizes the funding limitations of the Agency, and that the FDA is not in the position to fund such a program or guarantee purchase of drugs produced by participants in a qualified manufacturing program. ASHP is aware of the Accelerated Recovery Initiative (ARI) currently in development by the Generic Pharmaceutical Association (GPhA) and encourages the FDA to determine whether or not this program could meet the goals of a qualified manufacturing program.

- c. Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and/or to create other conditions to prevent or mitigate shortages?

We recommend that the FDA engage manufacturers to ascertain if there are incentives that could encourage manufacturers to operate in such a way that could prevent or mitigate drug shortages. Such incentives could include accelerated approval of an ANDA for products in short supply or incentives to increase capacity in exchange for production of products in short supply.

2. In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies.

Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?

We recommend that the FDA engage manufacturers to ascertain if there are incentives other, Agencies outside of the FDA, which could encourage manufacturers to operate in such a way that could prevent or mitigate drug shortages. We encourage the FDA to coordinate with the Drug Enforcement Administration (DEA) to address shortages of controlled substances and to work with other departments to identify additional incentives related to increasing capacity and upgrading production capital.

3. When notified of a potential or actual drug or biological product shortage, FDA may take certain actions to mitigate the impact of the shortage, including expediting review of regulatory submissions, expediting inspections, exercising enforcement discretion, identifying alternative manufacturing sources, extending expiration dates based on stability data, and working with the manufacturer to resolve the underlying cause of the shortage.

Are there changes to these existing tools that FDA can make to improve their utility in managing shortages? Are there other actions that FDA can take under its existing authority to address impending shortages?

Revisions to the United States Pharmacopeia (USP) requirements may result in quality variances due to a higher standard for a current product or more sensitive testing methods that yield a greater number of out of range results. We recommend that the FDA use enforcement discretion to allow more time to correct for cGMP violations if

there is no evidence of patient harm or quality problems with GMP-produced products that are in shortage.

ASHP recommends that the FDA identify potential drugs and biologics as candidates for importation and contact foreign manufacturers in advance if the drug is critical and therapeutic alternatives are few or nonexistent.

4. To manage communications to help alleviate potential or actual shortages, FDA uses a variety of tools, including posting information on our public shortages Web sites and sending targeted notifications to specialty groups.

Are there other communication tools that FDA should use or additional information the Agency should share to help health care professionals, manufacturers, distributors, patients, and others manage shortages more effectively?

ASHP believes that manufacturers should provide a more accurate timeframe of when production of a drug in short supply will resume and become available. The Society notes that information provided to the Agency by manufacturers often does not match reports from our members.

The FDA should consider developing a confidential reporting portal, similar to the reporting function on the ASHP website which allows for simultaneous distribution to relevant parties. A similar mechanism would allow for distribution to the various FDA staff or offices that need the information and avoid confusion regarding who should receive reports at the Agency. It would also limit potential miscommunication of information within the FDA.

Are there changes to our public shortage Web sites that would help enhance their utility for patients, prescribers, and others in managing shortages?

ASHP believes there are enhancements that can be made to the FDA website on drug shortages. The Society looks forward to working directly with staff in the Office of Drug Shortages to identify ways to improve the FDA website.

5. What impact do drug and biological product shortages have on research and clinical trials?

For some disease states (e.g., oncology), standard-of-care drugs that are used in the control arm of a study population may be in short supply which has unintended consequences on research. For further information see:

<http://www.medscape.com/viewarticle/762488>

What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?

The reasons for shortages of standard-of-care drugs in clinical trials are systemic and should be addressed as part of the larger plan to reduce generic injectable shortages.

What other actions or activities should FDA consider including in the strategic plan to help prevent or mitigate shortages?

Any actions that return manufacturing capacity, ranked by firms and lines that produce the most critically needed products, should be seriously considered by the Agency.

We encourage the FDA to continue to aggressively pursue activities that they have identified in the past, including:

- 1. Expedited review of submissions from manufacturers*
- 2. Identification of additional sources of supply or alternative manufactures that can initiate or increase production*
- 3. Identification of new or additional sources of API*
- 4. Consultation with sponsors on resolution of quality or manufacturing issues, and*
- 5. Discretion on temporary importation of a non-U.S. product.*

The Society appreciates the opportunity to provide input into the Task Force's strategic plan to address drug shortages. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,



Christopher J. Topoleski
Director, Federal Regulatory Affairs

ⁱ Federal Register Volume 78, Number 24629 Pages 9928 – 9929

ⁱⁱ University of Utah Drug Information Service

ⁱⁱⁱ American Society of Anesthesiologists, American Society of Clinical Oncology, American Society of Health-System Pharmacists, and the Institute for Safe Medication Practices, Drug Shortages Summit Summary Report: November 5, 2011 (issued Jan. 10, 2011), available at <http://www.ashp.org/drugshortages/summitreport>.