



March 14th, 2013

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA--2013-N-0124: Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the *Food and Drug Administration Drug Shortages Task Force and Strategic Plan*. BIO appreciates that FDA opened this comment period in an effort to obtain public insight as it seeks to develop and implement the drug shortages strategic plan as per Section 1003 of the recently enacted Food and Drug Administration Safety and Innovation Act (FDASIA, Pub. L. 112-144).

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

The biotechnology industry is committed to the discovery and development of new, novel treatments for serious and life-threatening diseases, and drug shortages that prevent patient access to needed treatments stand counter to our driving mission to extend and enhance the life of patients. BIO shares the FDA and public's interest in the recent documented increase in prescription drug shortages, as these shortages can create significant concerns for patients seeking to maintain a treatment regime for their disease or condition. These shortages can even delay or halt clinical trials necessary to bring new therapies to market.

BIO applauds FDA's commitment to finding new tools and approaches to prevent and mitigate drug shortages. Currently, critical shortages are most acute for off-patent

sterile injectable products, including certain chemotherapy agents, total parenteral nutrition (TPN) electrolytes, and anesthetics¹, and therefore most resources and analysis have been focused on these products and markets. The factors contributing to drug shortages are complex and multi-faceted, and the relevant economic, logistical, and scientific factors can vary significantly among different sectors of the pharmaceutical industry, including branded and generic manufacturers. Consequently, there is no one-size-fits all solution to this issue and only a sustained multi-faceted approach that engages all stakeholders will advance the goal of preventing or mitigating shortages.

While biotechnology products represent a small minority of overall drug shortages, BIO recognizes that, in recent years, there have been shortages of a handful of these products. Companies invest, on average, more than \$1 billion over a decade or longer to produce a new biologic² and have a limited time (patent life) to recoup this investment. A manufacturing delay can cause significant adverse economic impact to companies, secondary to lost or reduced production of patented biologics. These economic realities incentivize biotechnology companies to invest in highly qualified manufacturing experts, top-of-the-line manufacturing facilities, robust quality systems, and extensive quality control.

We agree with Janet Woodcock, et al.'s recent article in *Nature* cautioning against applying the conclusions of sterile injectable drug shortage analysis to other drug shortages as "branded manufacturers have a greater incentive to invest in quality systems and to maintain spare capacity in case production unexpectedly has to be shut down."³ Many of the current biologic shortages are either due to increases in demand, leading to the need to ramp up production, or unanticipated manufacturing problems. Given the complexity of biologic manufacturing processes, addressing either of these causes takes time. When a manufacturer had difficulty ramping up the process or encounters unexpected difficulties producing a pure and potent final product, it works exhaustively to address the issues and restore manufacturing capacity.⁴

In the experience of many biotechnology companies, FDA staff work constructively and collaboratively with the manufacturer in the event of a shortage to help resolve the problem and restore patient access to needed therapies as soon as possible. In our December 2011 comments, BIO proposed several additional steps that the Agency could take to help further bolster the ability of both FDA and manufacturers to prevent and respond to drug shortages. These include expedited review of manufacturing

¹ Food and Drug Administration, *A Review of FDA's Approach to Medical Product Shortages*, October 31, 2011, available at: <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm277755.pdf>.

² Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is \$1.2 Billion, According to Tufts Center for the Study of Drug Development," November 9, 2006, www.csdd.tufts.edu.

³ J. Woodcock and M. Wosinka, *Economic and Technical Drivers of Generic Sterile Injectable Drug Shortages*, *Nature*, Vol. 93, No. 2, February 2013.

⁴ See *ibid*, noting that "when production disruptions occur [with branded products], they tend to be resolved faster."

supplements, prioritized re-inspections of facilities, joint and harmonized inspections, and guidance on continuity of supply chain and risk mitigation.⁵ BIO also offers the following specific responses to questions posed by the FDA in the Federal Register Notice and would welcome the opportunity to serve as a resource to the Agency as it continues to enhance its efforts to work with manufacturers to prevent and mitigate shortages.

SPECIFIC COMMENTS:

BIO provides the following responses to FDA's questions posed in the Federal Register Notice:

Question One:

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

Manufacturing quality is a critical factor in providing customer satisfaction in that patients expect a reliable supply of drugs that will perform as described. BIO and its member companies work closely with the FDA to ensure that the United States' drug supply is safe, secure, and reliable, and that Americans can be confident that when they use an FDA-approved prescription drug or biologic, the medicine will be safe and effective and work as intended. FDA's regulatory standards for drugs and biologics are among the most rigorous in the world and BIO's members will continue to comply with the requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA or the Act) and the Code of Federal Regulations, including good manufacturing practice (cGMPs) that ensure the safety of prescription drugs.

⁵ BIO, Comments on Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage, December 23, 2011, available at: <http://www.bio.org/sites/default/files/2011-12-23%20BIO%20Drug%20Shortages%20Comments%20FINAL.pdf>.

Manufacturers use a variety of metrics to monitor production quality. BIO looks forward to working with the Agency to evaluate which metrics and potential summary information are appropriate to assess drug shortages and provide increased confidence to consumers and prescribers regarding manufacturing quality.

While metrics must be considered in context, and companies may define terms differently, examples of internal metrics include:

- Error rates as identified by non-conformances or deviations are a component in monitoring production quality. For companies that employ a tiered scale for these events, one could consider the most serious category(ies). A higher error rate could be evidence of poor process control, poor training of operators, poor oversight by supervisors, poorly maintained equipment and facilities, or poor product and process characterization.
- Product disposition cycle times serve as an indicator of the level of control under which a plant operates. Longer cycle times may be evidence that there are more errors and product failures that must be identified, documented, investigated, remediated and closed before a lot or batch can be released. A shorter cycle time may represent a facility operating in a higher state of control.
- Process and product performance index (P_{pk}) values are indicative of an optimal control strategy supported by an in-depth understanding of the causes of variability for both products and process.
- Complaint rates (complaints per million units sold) also indicate the robustness of the manufacturing process and control strategy in addition to product and process design controls. However, the nature of the complaint, should also be considered.
- Regulatory agency inspection outcomes with particular emphasis on major and critical observations.
- Manufacturing Success Rates: The percent of lots that meet specification and are released indicate if processes and products are robust and can be consistently made in a state of control.
- Critical Inventory and Backorder Report: Measure of available product to ship versus pending orders.
- Right First Time: Ability to produce batches that do not require rework, reprocessing or major deviations.
- Schedule Attainment: Ability to achieve scheduled production for a set window of time. The measure is calculated on a weekly basis (versus latest version of schedule) and reported monthly.

- Field Actions: All field actions encompassing field corrections and removals for all product(s) that have left the companies' control either as marketed product or under pre-market evaluation or clinical investigation.
- Adherence to maintenance programs.
- Re-capitalization of facilities, utilities, and equipment.

Metrics used to choose and evaluate a contract manufacturer are, in general, identical to those that companies use internally to monitor their own operations, and are usually provided for and detailed in specific contract arrangements. Quality metrics related to contract manufacturing facilities, including the frequency of updating, will vary by product and Sponsor need, but may include facility maintenance metrics and the on time performance of preventive maintenance and equipment calibration. Another possible proxy of quality may be overall corporate financial health and good governance.

- 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?*

BIO encourages FDA to explore possible qualified manufacturer program designs that support the construction of facilities, development of next-generation robust manufacturing processes, and back-up suppliers for critical and medically necessary products in order to positively impact shortages. While it may be possible to develop a BARDA type program, without funding and resources it may be difficult to encourage the requisite levels of participation required to have a positive impact on shortage in a timely and efficient manner. In addition, any such program should provide necessary intellectual property and data protections.

- 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?*

There are potential incentives that FDA can provide to manufacturers to mitigate or prevent drug shortages. For example, FDA could also consider waiving or reducing the

establishment user fee under the Prescription Drug User Fee Act (PDUFA) in exchange for the availability and maintenance of redundant manufacturing capacity. Other potential incentives include:

- Faster and more streamlined approval of new technologies (such as isolator technology for parenteral filling operations) and redundant manufacturing facilities or raw material suppliers that have a positive impact to reduce potential and real drug shortages. This would include both faster review of filings and expedited GMP inspections where deemed necessary.
- Faster and streamlined approval of new products for companies that the Agency has determined are compliant and have adequate risk mitigation plans to prevent drug shortages.
- Expedited review and approval time for supplements to add additional (or replacement) manufacturing facilities that don't ordinarily qualify as CBE or CBE-30.
- For companies with a good compliance status and adequate risk mitigation plans to prevent drug shortages, FDA could reduce regulatory oversight / requirements including: downgrading filing categories for other filings such as site transfers or, assay improvements, increased use of extended comparability protocols, and reduced validation requirements.

Question Two:

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?

Greater clarity and transparency regarding inter-agency actions and process may help industry work better with FDA to prevent and mitigate shortages. For example, it would be helpful to have a greater understanding of if and when the Agency refers (1) to the Centers for Medicare and Medicaid Services (CMS) and how reimbursement would be handled for alternative products during a shortage; (2) to the Drug Enforcement Agency (DEA) where controlled substances are impacted and it may be necessary to increase DEA quotas to overcome the loss to active pharmaceutical ingredients (API) due to re-development, rejection, or recalls; and (3) to U.S. Customs for issues at the border. FDA should consider a partnership with U.S. Customs to prevent shortages, including collaboration with Customs and Border Control to streamline entry of drugs into the U.S.

We also note that the Centers for Disease Control and Prevention (CDC) plays a primary role in tracking and addressing vaccine shortages and we continue to encourage appropriate coordination between CDC and FDA with respect to these unique products.

Question Three:

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?

FDA has taken very strong and diligent actions in exercising enforcement discretion and identifying alternative manufacturing sources. BIO also encourages the Agency to provide guidance to Industry on engagement with the Agency regarding the use of existing tools and processes to mitigate shortages. And, as discussed above, there is need for improvement in expediting review of regulatory submissions and inspections.

The Agency may also want to consider:

- Expedited approval for Sponsors adopting advanced technologies, or adding redundant manufacturing sites that could prevent or mitigate against potential drug shortages. This would include both filing review and GMP inspections if necessary.
- Expedited review for Sponsors that implement second sourcing for raw materials as a means of preventing future drug shortages.

BIO also suggests the Agency consider leveraging their Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership, to drive convergence of regulatory expectations for drugs in short supply, which would allow for FDA to expedite review of pending or approved PIC/S country submissions.

Question Four:

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

Timely and consistent communications with various stakeholders is essential to the successful management, mitigation, and prevention of drug shortages. The FDA's drug shortage web page and emails to interested stakeholders are informative and timely. We strongly encourage FDA to continue in this manner. We also encourage FDA

investigate the use of social media (i.e., Twitter ‘#shortage’ or ‘#drugname’) or mobile applications, along with the necessary guidelines and controls, as a means of timely communication to share information with health care professionals, manufacturers, distributors, patients, and others, and to manage drug shortages more effectively.

However, FDA should be strategic and judicious in its public communications regarding a *potential* shortage in order to prevent unnecessary public alarm or contribute to a hoarding situation that can exacerbate the existing shortage. In these situations, targeted outreach to relevant stakeholders may be more appropriate than a broad public announcement.

Question Five:

What impact do drug and biological product shortages have on research and clinical trials? What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?

Because many clinical trials evaluate the use of combinations of marketed medicines with other marketed products or with an investigational medicine, drug shortages may delay or halt clinical trials necessary to bring new therapies to market. Actions that may help alleviate a shortage’s impact on research and clinical trials may include: (1) a dedicated approval mechanism for the consideration of alternative treatment protocols or modification to existing clinical trial designs for trials impacted by a shortage; (2) increased communication with Sponsors regarding the expected duration of the shortage in order to better manage available resources, including site maintenance; and (3) working with Sponsors to assess if an alternate product is available.

Question Six:

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

FDA may want to consider more proactive and transparent engagement with other international health authorities during a shortage. BIO encourages FDA to continue the global cooperation initiatives to enable registration of contingency manufacturing sites. Also, since many Sponsors outsource portions of the manufacturing process to contract manufacturing organizations (CMOs) that perform services for a number of companies, FDA may want to consider setting up an early warning system to proactively alert companies when an CMO is cited for a GMP issue that could negatively impact multiple products.

CONCLUSION:

BIO appreciates this opportunity to comment on the *Food and Drug Administration Drug Shortages Task Force and Strategic Plan*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Ruth DeLuca
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)