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December 23, 2011

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

Re: Docket No. FDA-2011-N-0690: Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage; Public Workshop; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Center for Drug Evaluation and Research (CDER), Approach to Addressing Drug Shortage; Public Workshop; Request for Comments," published in the Federal Register on September 29, 2011. BIO appreciates that FDA opened this comment period following the September 26, 2011 CDER Drug Shortage Public Workshop in an effort to gain additional insight into the causes and impact of drug shortages, and possible prevention and mitigation strategies.

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.

In recent years, the FDA has documented a significant increase in the prevalence of prescription drug shortages, reporting 178 shortages in 2010 and 200 shortages to date in 2011.[1,2] These shortages can create significant concerns for patients seeking to maintain a treatment regime for their disease or condition and can even delay or halt clinical trials necessary to bring new therapies to market. 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 stands counter to our driving mission to extend and enhance the lives of patients.

BIO welcomed the Administration's October 31, 2011 Executive Order and FDA's and the Department of Health and Human Services' (HHS') associated activities regarding drug shortages. The Executive Order correctly observes that many different factors contribute to drug shortages, and that preventing and mitigating drug shortages requires a "multi-faceted approach." These comments discuss the differing causes of drug shortages, the challenges of biotechnology manufacturing, and approaches to resolving drug shortages.

I. The Differing Factors Contributing to Drug Shortages:

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 each individual contributing factor must be critically evaluated. Recent studies and public workshops have cited a number of contributing factors to drug shortages, including:[3,4,5]

- Unanticipated shifts in market demand, clinical guidelines, or the practice of medicine
- Manufacturing production and quality problems
- Limited manufacturing capacity
- Delays in site consolidation and facility modernization
- Disruptions in ingredient supplies

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[1] Food and Drug Administration, "Webinar on Prescription Drug Shortages", September 30, 2011, http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM273360.pdf.

[2] Center for Drug Evaluation and Research, *Current Drug Shortages*, http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm (accessed on November 11, 2011).

[3] Hill and Reilly, American Society of Health System Pharmacists, *Can the United States Ensure an Adequate Supply of Critical Medications?*, Food and Drug Law Institute Policy Forum, Volume 1, Issue 16, August 24, 2011, http://www.fdli.org/pubs/policyforum/.

[4] Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), *Approach to Addressing Drug Shortage; Public Workshop*, September 26, 2011, http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm.

[5] U.S. Government Accountability Office. (2011, September). *Manufacturer Discounts in the 340B Program Offer Benefits, but Federal Oversight Needs Improvement.* Publication No. GAO-11-836. http://www.gao.gov/new.items/d11836.pdf.

- Regulatory actions, including recalls, inspections and changes in compliance requirements, delayed new drug approvals, and delays in approval of facility upgrades
- Industry consolidation, product discontinuations, and economic factors
- Just-in time supply chain with short inventory management

Currently, critical shortages are most acute for off-patent sterile injectable products, including certain chemotherapy agents, total parenteral nutrition (TPN) electrolytes, and anesthetics. FDA's recent report "A Review of FDA's Approach to Medical Product Shortages" (the "Report") studied 127 drugs in shortage in 2010-11 and found sterile injectables accounted for the majority (80%) of drugs in short supply. The Report also found that the major therapeutic classes of drugs in short supply included oncology drugs (28%), antibiotics (13%), and electrolyte/nutrition drugs (11%). The leading primary reasons for the shortages reported to FDA were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active pharmaceutical ingredient (API) shortages (10%).[6]

The Report confirms that different and sometimes multiple factors contribute to the drug shortage problem and that no one solution will resolve the problem. The Report rightly finds that only a sustained multi-faceted approach that engages all stakeholders will advance the goal of preventing and mitigating shortages.

II. Potential Shortages Related to Biotechnology Product Manufacturing

Companies invest, on average, more than $1 billion over a decade or longer to produce a new biologic.[7] Moreover, these products have a limited patent life to recoup this investment, and 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.

However, BIO recognizes there have been shortages of a handful of biotechnology products in recent years due in part to the challenges associated with the manufacturing these products. These products represent only a small minority of overall drug shortages. A review of FDA's drug shortage databases indicates that 83 drugs are currently in short supply, but only 4 of those products (5%) are therapeutic biologics and another 7 are vaccines or CBER-regulated products (8%). Further, of the 184 brand and generic companies individually associated with distinct drug shortages, only 27 (14%) are brand-name BIO member companies.[8,9]

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[6] Food and Drug Administration, *A Review of FDA's Approach to Medical Product Shortages*, October 31, 2011.

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

[8] FDA Center for Drug Evaluation and Research, *Current Drug Shortages*, http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm, (accessed October 17, 2011).

[9] FDA Center for Biologics Evaluation and Research, *Biologic Drug Shortages*, http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm, (accessed October 17, 2011).

Most of the current biologic drug 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 product manufacturing processes, addressing either of these causes takes time. When a manufacturer has difficulty ramping up the process or encounters unexpected difficulties producing a pure and potent final product, it works overtime to address the issue and restore manufacturing capability. In these instances, it is essential to plan ahead and have a timely and efficient interaction between the manufacturer and regulatory authorities to resolve issues and restore patient access to these important products.

III. Multi-Faceted Approaches to Resolve Drug Shortages

BIO agrees that there is no "single or simple solution" that can resolve the drug shortage problem and that efforts to address the problem will need to be "multifaceted, sustained over the long term, and will require the engagement of all parties involved in the manufacture and distribution of medical products."[10] BIO welcomes the Agency's recent identification of immediate and long-term actions that the Agency can take to improve internal processes in order to maximize the Agency's contribution to the prevention and mitigation of shortages.[11] 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. However, we believe that there are several additional steps that the Agency can take to help further bolster the ability of both FDA and manufacturers to prevent and respond to drug shortages.

Additional recommendations to minimize the potential for and impact of shortages include:

- **Expedited Review of Manufacturing Supplements:** Some shortages may be caused when manufacturers are upgrading facilities, use new or alternate API or drug product manufactures or analytic methods, but the supplement requesting approval for such changes has not been approved in a timely manner or has undergone multiple review cycles. Expedited review of these regulatory submissions may contribute to resolving the shortage.

- **Review of New Drugs:** Occasionally, a new drug or efficacy supplement can help to resolve a shortage, and passage and implementation of PDUFA V will reinforce FDA's capacity to take timely action on these submissions, particularly for New Molecular Entities (NMEs).

- **Prioritized Reinspections of Facilities:** To the extent that a reinspection can help to resolve a prior adverse inspectional finding and bring a facility back online, the Agency should strive to prioritize reinspections for facilities related to a shortage.

[10] Food and Drug Administration, *A Review of FDA's Approach to Medical Product Shortages*, October 31, 2011.
[11] See id. The Report identifies five immediate actions and nine longer-term options.

- **Joint and Harmonized Inspections:** Leveraging resources among established regulatory authorities to conduct joint inspections may also help to expedite inspections. We also encourage international harmonization of standards for compliance inspections to minimize inconsistency between inspectorates, and between individual inspectors.

- **Guidance on Continuity of Supply Chains and Risk Mitigation:** To help ensure that all manufacturers have firm knowledge of suppliers and adopt best practices to help mitigate risk in the upstream supply chain and manufacturing processes, we suggest that the Agency issue guidance for industry. Voluntary and coordinated information sharing between stakeholders regarding the quality and authenticity of supply and suppliers and information on potential vulnerabilities in the supply chain can help to identify and mitigate potential disruptions before they manifest into a drug shortage.

- **Publication of Periodic Metrics on Drug Shortages:** The identification and public availability of metrics and measures on the Agency's website related to drug shortage trends, including metrics on the effectiveness of mitigation strategies such as expedited review, would allow industry and stakeholders to better prevent and prepare for shortages and increase public accountability.

IV. Conclusion

BIO appreciates this opportunity to comment on the "Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage; Public Workshop; Request for Comments." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)