December 23, 2011

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

RE: Docket No. FDA-2011-N-0690

To whom it may concern:

We appreciate the opportunity to provide insight from the perspectives of our two health systems, Cleveland Clinic and Johns Hopkins, on the causes and impact of drug shortages, 76 Fed Reg. 60505 (September 29, 2011).

Cleveland Clinic (CC) is a not-for-profit, integrated healthcare system dedicated to patient care, teaching and research. Our health system is comprised of a main campus, eight community hospitals and 18 family health centers with over 2,700 salaried physicians and scientists. Last year, our system had more than four million patient visits and over 165,000 hospital admissions.

The Johns Hopkins Health System is comprised of six hospitals, which together provide an integrated healthcare system. All Children’s Hospital in St. Petersburg, Florida, recently became the first Johns Hopkins subsidiary outside of the Baltimore-Washington area. It joins Johns Hopkins’ two academic hubs, The Johns Hopkins Hospital and Bayview Medical Center, and three affiliated community hospitals, Howard County General Hospital, Suburban Hospital and Sibley Memorial Hospital in northwest Washington, D.C.

Within the past two years, both institutions have participated in numerous public forums and summits to discuss the primary factors responsible for the drug shortages and make recommendations to remedy the situation. Some of the most notable causes of drug shortages include:

**Regulatory and Legislative Factors:** The FDA lacks authority to require notification from the drug manufacturers about most anticipated drug withdrawals. The FDA does require discontinuation notification from the sole manufacturers of “medically necessary” drugs; however, it lacks statutory authority to enforce this requirement. Other factors include the cost and complexity of completing a New Drug Application (NDA) for the pre-1938 unapproved drugs, and the lengthy review time for the Abbreviated New Drug Applications (ANDA) required for changes to FDA-approved drugs. The latter limits manufacturers’ ability to develop reliable production schedules.

**Good Manufacturing Practices (GMPs).** The FDA holds manufacturers accountable to meet Good Manufacturing Practices (GMPs) for safety and quality purposes. This is important to ensure high standards for medications available to patients in the United States. However, it appears that some manufacturers are having problems meeting GMPs, therefore causing the manufacturing production...
line(s) or the entire plant to close. Can the FDA work with the manufacturers more closely to meet GMPs? A suggestion is to place an inspector at each of the manufacturing plants to ensure compliance with GMPs proactively (similar to the USDA inspectors). This would identify potential problems early and if the problem could be fixed proactively, manufacturing lines and/or plants would not have to be closed due to quality issues, thereby avoiding a drug shortage.

**Compounding versus Manufacturing:** During a time of a critical drug shortage, a hospital might “compound” a medication from raw material or manipulate the medication into a smaller dosage form (or repackage) to extend the supply. For hospitals within health-systems, one hospital cannot distribute these “compounded” or repackaged medications to other “owned-facilities” because it is considered manufacturing. A hospital needs to acquire a manufacturing license to distribute, which requires meeting GMPs. Cleveland Clinic is pursuing a “waiver” from the FDA in times of drug shortages to be able to distribute “compounded” or repackaged medications within one’s own health-system without a manufacturing license. If we cannot supply our “owned” hospitals/facilities with compounded medications, the patient will get transferred to another hospital within our system that has the medication. This increases health care costs and can impact patient care.

**Raw materials sourcing and manufacturing factors:** Secondary shortages can occur for alternative medications to those in short supply, making manufacturers unable to accommodate increased demand for these alternative therapies. Medications are not continuously manufactured. They are produced in batches, based on a pre-specified quantity, based on expected or historical demand. Therefore, if one or more manufacturers experiences problems or delays, any remaining manufacturer(s) would have little to no lead time to increase their production of the medication to supply the market. A suggestion would be to ensure 1) production line redundancies in individual manufacturers, and 2) sufficient notification to remaining manufacturers to increase production of needed medication in short supply.

**Business and market factors:** Consolidation of firms has led to fewer manufacturers of a given product, and the reallocation of production lines will increase sensitivity to supply shortages. Again, a lack of communication and transparency about possible product shortages and a lack of business incentives to enter a specific product market exacerbate the issue. Two potential solutions are: 1) to give tax incentives to domestic manufacturers of sole source or “medically necessary” medications; and 2) to give the FDA the ability to prioritize/expedite approval of another manufacturer to produce the medication in short supply.

**Distribution factors:** Inventory practices by health care facilities and supply chain entities leave little reserve volume of drug product to accommodate for a short-term drug shortage. The “grey market,” as well as price escalation and hoarding of short supply products has worsened the situation. Small ambulatory centers and rural facilities often lack the business relationships necessary to facilitate product availability and maintain adequate drug procurement.

**Recommendations:**
- Expand the FDA authority to require manufacturer notification of market withdrawals.
- Establish evidence-based criteria for identifying critical drugs that are vulnerable to shortages.
- Provide incentives to manufacturers that produce critical drug products.
- Require notification to the FDA when there is only a single Active Pharmaceutical Ingredient (API) source.
• Establish an expedited approval process for those unapproved drugs deemed as "critical therapies", as well as for Abbreviated New Drug Applications (ANDAs) and supplemental applications.
• Require manufacturing redundancies as part of the FDA approval process.
• Promote notification to the FDA when there is a single API or manufacturing source.
• Improve mechanisms to communicate anticipated or actual manufacturing and inventory problems, with detailed information on the reason and estimated duration of the shortage.
• Decrease barriers and disincentives to market entry.
• Enhance communication among manufacturers, health professional associations, and the FDA to support adequate product distribution.

Also, we support the Preserving Access to Life Saving Medications Act (Senate Bill 296 and House Bill 2245) which would require 6-month advance notification to the FDA of any discontinuance, interruption, or adjustment in the manufacture of a drug that may result in a shortage. The bill would impose a monetary penalty for noncompliance with the new requirement, while encouraging the creation of evidence-based criteria to identify drugs vulnerable to a shortage.

The following are recent examples (there are many more) of how drug shortages have impacted Cleveland Clinic and Johns Hopkins hospitals:

**Norepinephrine:** This agent is the drug of choice to support a patient’s blood pressure that is in septic shock. We temporarily ran out of Norepinephrine and were forced to utilize other, less desirable alternatives such as dopamine (which can cause arrhythmias) and phenylephrine (less effective) for a prolonged period of time until we were able to obtain more supply.

**Protamine:** Our institution nearly ran out of Protamine. In order to perform many cardiac surgeries, surgeons require patients to be placed on a bypass machine. In order to “go on bypass”, the patient’s blood needs to be “thinned” with an anticoagulant (Heparin). When the procedure is completed, the effects of Heparin need to be reversed with the use of Protamine to prevent the patient from bleeding to death. Running out of Protamine would be catastrophic to patients as the vast majority of cardiac surgeries would not be possible. Alternative methods to “thin the blood” for bypass are extremely expensive and the bleeding rates are much higher. With extensive time and effort we were able to obtain an allotment of Protamine just prior to running out. Another option to deal with this shortage would have been to compound the Protamine from “raw material” (Protamine powder) in our USP 797 Clean Room. However, this would have been time consuming and would have increased the workload of our Clean Room Pharmacists and Technicians.

**Anesthesia drugs:** Drugs used in the intra-operative setting, such as paralytics, agents that reverse the effects of paralytics (such as Neostigmine), and sedatives such as Propofol have intermittently been in short supply. Loss of availability of any of these agents is potentially extremely hazardous and can result in sub-standard peri-operative and intra-operative care. To deal with the Neostigmine shortage, we took the vials of Neostigmine and divided them into smaller vials (repackaged) to extend our supply. To do this, we worked with our physicians to determine what the most common doses of Neostigmine were being used in the operating rooms. As described in a previous section (Compounding versus Manufacturing), if hospitals could have a “waiver” from being licensed as a manufacturer during drug shortages, we could have repackaged the Neostigmine into smaller vials for our entire health system.
**Antibiotics:** Drugs such as Amikacin and injectable Trimethoprim/Sulfamethoxazole have intermittently been on shortage. We’ve been able to take extreme steps to conserve and extend supply for critical indications so far. For certain (usually highly resistant) infections, these may be the only effective drugs, and the absence of availability of these agents for a given patient with these infections, when oftentimes curable, could result in death.

**Chemotherapy / oncology:** Shortage of multiple chemotherapy agents has resulted in a number of complications. For patients with curable cancers, providers have had to switch to second line treatments due to shortage of the first-line agent. These second line agents can potentially be less effective, and/or more toxic, as well as more costly. In general, shortages of chemotherapy agents can force providers to alter the prescribed chemotherapy treatment cycle by delaying doses. In addition, patients responding well to a particular therapy that goes on shortage may need to be switched to another agent, a change that can be very distressing for the patient. Two examples of these shortages would be the Cytarabine and Doxorubicin chemotherapy shortages. In addition, Leucovorin is not available from any manufacturer in the United States. The FDA has permitted the importation of a European Leucovorin product during this shortage. Although this is an alternative, it takes time to convert electronic drug records and to coordinate a conversion to a different product.

As a final note, both Cleveland Clinic and Johns Hopkins expend tremendous resources tracking over 100 ongoing shortages. In addition, each shortage action plan that gets put into place (i.e., “use of an alternative agent”) requires extensive time and effort to re-engineer electronic systems in order to make the switch. Switching products due to a shortage presents numerous medication safety hazards, including unfamiliarity with the product/dosing and inappropriate dosing conversions, and often necessitates changes in clinical practice that can cause safety-related problems. Cleveland Clinic has a full-time Drug Shortage Pharmacist. This pharmacist is responsible for monitoring, tracking, and managing drug shortages for the health-system. This is a needed position within our health-system; however, it diverts this pharmacist’s time away from direct patient care.

We would be happy to make ourselves available to speak with you in person about any of the information provided above and to answer any questions you may have.

Sincerely,

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