

Shortage of Peritoneal Dialysis Solution and the Food and Drug Administration's Response

Valerie Jensen and Douglas C. Throckmorton

Abstract

Although the number of new drug shortages has been lower in recent years than in the past, severe shortages have occurred that have affected large numbers of patients. A new law entitled the Food and Drug Administration Safety and Innovation Act was enacted in July of 2012, which requires companies to notify the Food and Drug Administration of anticipated shortages. This notification requirement has allowed the Food and Drug Administration to work closely with manufacturers earlier to mitigate and, often, prevent shortages. However, not all shortages are able to be prevented, and the shortage of peritoneal dialysis solution is one that has had a significant effect on patients. The Food and Drug Administration continues to use all available tools to address this shortage with manufacturers, including temporary availability of imported peritoneal dialysis solution from Ireland. Mitigating shortages is a top priority for the Food and Drug Administration, and communication with all stakeholders is essential.

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Introduction

Over the past several years, drug shortages have had significant detrimental effects on medical practice in the United States, which in some cases, have kept patients from receiving the level of care that they deserve and have come to expect. The number of new drug shortages quadrupled from approximately 60 shortages in 2005 to >250 in 2011. This number decreased in 2012—117 new shortages—and further decreased to 44 new shortages in 2013. The number of new shortages flatlined in 2014, with 44 new shortages reported to the Food and Drug Administration (FDA). This overall decreasing trend in the number of new shortages has been aided by new legislation enacted in 2012 entitled the FDA Safety and Innovation Act (1). This law requires manufacturers to notify the FDA of potential disruptions in supply. These notifications give the FDA time, in many cases, to coordinate with manufacturers to prevent or mitigate shortages. To do this, the FDA determines how best to address each shortage situation on the basis of its cause and the public health risk associated with the shortage. For manufacturing or quality problems, the FDA works with the firm to address the issues and works with other firms making the drugs that are in shortage to help them ramp up production if they are willing and able to do so. For example, in 2012, a large manufacturer of multiple intravenous nutrition drugs, which are needed for adults, children, and babies unable to take food by mouth, shut down manufacturing because of quality problems, including particulate matter in injectable drugs (2). The FDA worked with the company to address its quality issues, including requiring the use of filters temporarily for some products to mitigate risk to patients. Numerous critical drugs made by the manufacturer were no longer

available when the company halted production, and it is important to note that the FDA cannot force a firm to manufacture a drug or require any particular amount to be made. It was challenging in this case to find manufacturers to address these shortages in a timely manner because of the lead times required to manufacture the drugs as well as the ability of manufacturers to help meet the needs of the United States while not causing shortages in other countries in which the drugs were marketed. After manufacturers were identified that could help, the FDA evaluated their manufacturing facilities and products to ensure that there was no undue risks for patients, and it took several months for the drugs to be manufactured and shipped in the amounts required to meet United States patients' needs.

The FDA can and does expedite the work needed to start up new production lines or get new raw material sources approved to help resolve shortages of medically necessary drugs. Despite these efforts, however, not all shortages can be prevented, and although new shortage numbers continue to trend lower in 2014, some of the recent shortages, like the peritoneal dialysis (PD) fluid shortage, have had dramatic patient effect.

PD Solution Shortage

One of the most critical shortages of 2014 has been the ongoing PD solution shortage. The two FDA-approved manufacturers of PD solution for the United States market are Baxter Healthcare Corporation, with headquarters in Deerfield, Illinois, and Fresenius Medical Care, with headquarters in Waltham, Massachusetts. These solutions are distributed directly to patients' homes to be used and administered by the patients themselves; each firm has its

Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland

Correspondence: Valerie Jensen, Room 6204, Building 22, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Email: Valerie.Jensen@fda.hhs.gov

own customer network, distribution, and delivery system, and the equipment is not always interchangeable for the two manufacturers' products. In late July of 2014, Baxter Healthcare Corporation notified the FDA of an anticipated shortage of PD solution. Unlike the majority of shortages that have been reported during recent years (3), there was not a manufacturing or quality problem associated with this shortage. Baxter Healthcare Corporation reported that there had been an ongoing increase in demand because of more patients requiring PD at a time when the company was not able to immediately expand manufacturing efforts and meet the growing demand. Manufacturing a sterile fluid like PD solution is highly specialized and complex, and there are limited numbers of manufacturing lines at each company that are capable of making these solutions. Additionally, the manufacturing takes several weeks because of processes required to ensure sterility, and the lines are often operating continuously. As a result, even when a manufacturer is willing and able to add capacity to address a shortage of a drug, it can take months to years for a firm to complete necessary planning and development to initiate the new production lines successfully. The time needed for these changes will have real effect on patients. In the case of PD solution, although Baxter Healthcare Corporation plans to add new capacity in 2015, patients who depend on PD will be critically affected if they lose this option and have to switch to hemodialysis. Additionally, new patients requiring dialysis who are good candidates for PD are also affected, because they do not have the option of PD available to them. Finally, although the small-volume bags continued to be available, any shortage that included the large-volume bags (5 and 6 L) was problematic, because these products are not interchangeable by current patients using Baxter Healthcare Corporation or Fresenius Medical Care products and are needed for patients to do exchanges with an automatedycler. Switching from an automatedycler to manual exchanges with smaller bags poses a severe inconvenience for patients currently using larger-volume bags, because it means manual exchanges that are more frequent throughout the day. Another concern is that some patients using an automatedycler would not have previous experience or training with manual exchanges. The FDA understood the need to work hard to address this critical shortage of dialysis fluids as quickly as possible.

Actions Taken

Recognizing the potential effect of a dialysate shortage, the FDA prioritized this shortage, which we do with all medically necessary drugs, using all tools available to work with manufacturers to resolve the shortage as quickly as possible. Because the Baxter Healthcare Corporation shortfall in manufacturing capacity was not able to be immediately addressed by the manufacturer, the FDA notified the other manufacturer, Fresenius Medical Care, of the anticipated supply gap to see if the company was able to increase production to alleviate the shortage. Fresenius Medical Care reported that they had additional availability of smaller-volume PD bags. The company agreed to work with Baxter Healthcare Corporation to allow Baxter Healthcare Corporation to distribute Fresenius Medical Care bags to help meet patient needs during the shortage. However, there was still a shortage, especially of the larger PD bags.

In cases such as the PD solution shortage, where there is an ongoing shortage affecting patients in the United States and the other tools that we use are not able to address the shortage, the FDA can look for manufacturers already making the drug for other markets, such as Europe, Australia, and Canada. Because of ongoing shortage of the larger-sized PD bags and the need for bags that are compatible with the equipment used by patients using Baxter Healthcare Corporation products, the FDA worked with Baxter Healthcare Corporation on possible solutions to the immediate supply needs. Baxter Healthcare Corporation was able to find excess larger-sized PD bags that could be used by patients in the United States at one of their manufacturing sites in Ireland and proposed temporary availability from that site until the shortage is resolved. To consider temporary availability from Baxter Healthcare Corporation's manufacturing establishment in Ireland, the FDA evaluated inspectional findings and compliance histories and ensured that the facility meets the United States standards. The formulation, labeling, and other product information were also evaluated to ensure there were no undue risks for patients in the United States. There were no clinically relevant differences found between the overseas PD solution and the United States–approved version, and the differences observed were highlighted in a "Dear Healthcare Professional" letter as well as a "Dear Consumer" letter, both dated October of 2014, which are posted on the FDA website and shipped by the manufacturer with the imported product. It was the priority of the FDA and Baxter Healthcare Corporation to have the imported PD solution from Ireland available for patients as soon as possible. However, it took over 3 months to have the imported product available, including the time for the FDA's evaluation of the facility and product to ensure that there are not significant risks for patients and the initial lead times involved with manufacturing, shipping, and distributing large volumes of product from overseas. The additional supply being imported is expected to be ongoing and will help meet patient needs until the shortage is resolved. As with all shortages, the FDA continues to monitor the situation closely. The FDA will look at the long-term use trends and understand when the manufacturing is once again meeting the public health need before we consider a shortage to be resolved.

Communications and Outreach

To help patients and caregivers, the FDA manages a Drug Shortage website (4), which includes information about shortages, discontinuations, and availability information. Updates to the website are received daily from manufacturers, and the FDA encourages manufacturers to supply as much detail as possible about the reasons for shortages, the anticipated duration, and the projected timeline for resolution. Information about the PD solution shortage continues to be updated as new information becomes available. In addition to keeping the website updated, the FDA regularly participates in outreach calls and meetings with industry, outside stakeholders, and patient groups to hear about the effects that shortages are having and work with manufacturers to mitigate shortages. The FDA participated in multiple stakeholder calls during the PD solution shortage and received feedback from health

care professional organizations, patient groups, and others regarding the situation.

Conclusion

Preventing and mitigating shortages of medically necessary drugs, like PD fluid, are top priorities for the FDA. After we learn of a potential shortage, the FDA has a number of tools available to help with shortages, including assisting firms with manufacturing or quality problems, expediting review of manufacturing changes to increase supplies, and allowing temporary availability from alternate manufacturers. Although the FDA cannot require firms to increase production or cover shortfall when a shortage occurs, with these tools, progress is being made in reducing the number of new shortages that occur. In the case of PD fluids, temporary importation is being used, and increases in manufacturing capacity are being worked on by the manufacturers. With the public health in mind, future work by the FDA is focused on preventing drug shortages through the

continued support of the FDA wherever possible to improve manufacturing quality and capacity and decrease the potential for shortages.

Disclosures

None.

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