Questions and Answers on the Propofol Shortage

The U.S. Food and Drug Administration (FDA) is aware that recent shortages of propofol injection—a quick acting sedative-hypnotic used for the induction and maintenance of anesthesia or sedation—have resulted in significant concerns for some healthcare professionals in regard to patient care. The Agency has made every effort within its legal authority to address this problem. FDA has temporarily allowed the importation of Fresenius Propoven 1% into the United States. This propofol product is comparable to the product used in the United States and is currently approved in other countries. FDA is also working with the manufacturers of propofol products to try to prevent future shortages.

Q1: When did the propofol shortage begin?

The propofol shortages began in the fall of 2009. Two U.S.-based manufacturers of propofol halted distribution and recalled several lots of propofol products because of quality problems. This action left only one company to supply propofol to the entire United States. The two companies affected by the quality problems are working to restore full production of propofol, which is anticipated to occur by fall 2010. This timeline is reflective of the complex and often long lead-time necessary to manufacture sterile injectable drug products.

Q2: How is FDA addressing this shortage in the U.S. propofol supply?

FDA is working with the manufacturers of propofol products to address these shortages. FDA has temporarily allowed the importation of Fresenius Propoven 1% (propofol 1%) into the United States. Although Fresenius Propoven 1% is an unapproved drug product in the United States, it is currently approved in other countries. FDA has determined that it is comparable to the propofol used in the United States. It is important to note that there are some key differences in the formulation and labeling between the U.S. marketed propofol products and the international Fresenius Propoven 1% (see Question 4).

Under specific circumstances, the FDA has the discretion to allow the importation, distribution, and use of unapproved drugs to address severe drug shortages and public health emergencies. FDA ensures the quality of these drugs through close inspection of the manufacturing facilities (these companies must meet current good manufacturing practices) and through evaluation of available safety and efficacy data.

Q3: Has the recent Icelandic volcanic activity disrupted shipments of Fresenius Propoven 1% to the United States because of flight cancellations?

Although the importation of Fresenius Propoven 1% has been impacted by the current flight cancellations in Europe, no significant disruption in supply is expected. FDA is in close contact with the European manufacturer of this drug, and they are taking steps to identify alternative shipping arrangements if the need arises.

Q4: Are there any differences in the formulation and labeling between the U.S. marketed propofol products and the international Fresenius Propoven 1%?

Yes. The special considerations for use of Fresenius Propoven 1% are listed below. These considerations can also be found on the FDA Drug Shortage Webpage at: Dear Healthcare Professional Letter (PDF - 490KB)[1].

- Fresenius Propoven 1% (propofol 1%) does NOT contain an anti-microbial retardant such as ethylenediaminetetraacetic acid (EDTA), sodium meta-bisulfate, or benzyl alcohol/sodium benzoate. As such, strict aseptic technique must always be maintained during handling.
- Each vial of Fresenius Propoven 1% (propofol 1%) is intended only for single administration for an individual patient. Vials are not intended for multidose use. Unused Fresenius Propoven 1% (propofol 1%) should be discarded within 6 hours after the vial has been opened. As with any propofol 1% used for IV infusion, all product and infusion therapy systems should be discarded after 12 hours.

- Fresenius Propoven 1% (propofol 1%) is contraindicated in patients who are allergic to soy or peanut.
- The barcode used on Fresenius Propoven 1% (propofol 1%) product is an international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the United States. Institutions should confirm that barcode systems do not provide incorrect information when the product is scanned.

Q5: Why are there only a few companies making propofol?

Propofol is an older drug, first approved in 1989. Other versions of this drug began appearing in the U.S. market in 1998. As more versions of a drug become available, the price of a drug can decrease. If the costs associated with making a drug begin to outweigh sales profit, companies may wish to discontinue making the drug in favor of newer, more profitable products. This business practice is not specific to pharmaceuticals, but all industries with a high-level of competition. If there is a reduction in the number of companies making an older drug, and there is a delay or problem in manufacturing, shortages can occur, as was the case with propofol.

Q6: Are there shortages of other sterile injectable drugs?

Yes. Since the FDA's Drug Shortage Program began in 2000, we have been able to more effectively identify the causes and consequences of drug shortages. Sterile injectables have experienced more severe and frequent shortages in recent years. For example, data collected by FDA showed that of 110 total shortages that occurred in 2008, 39 involved sterile injectables. In 2009 the number of total shortages rose to 157 with 73 of those involving sterile injectables.

The propofol injection shortage, as well as shortages of other commonly used anesthetics including etomidate, ketamine and thiopental injectables, occurred during the fall of 2009. Other anesthesia-related shortages that have occurred in recent months include the neuromuscular blocking agents (vecuronium injection, succinylcholine injection, atracurium injection, and cis-atracurium injection), metoclopramide injection, prochlorperazine injection and ephedrine injection. Shortages that have occurred so far in 2010 have involved several medically necessary sterile injectables.

These shortages have occurred for a number of reasons and the major factors that have contributed to these shortages include:

- The limited number of companies making sterile injectable products. The process for manufacturing sterile injectables is complex and involves a long lead-time relative to other drug dosage forms.
- When a product goes off-patent, other versions of this drug may begin to appear in the U.S. market. As more versions of a drug become available, the price of a drug can decrease. If the costs associated with making a drug begin to outweigh sales profit, companies may wish to discontinue making the drug in favor of newer, more profitable

products. A decrease in the number of companies making a drug can lead to shortages if there is a manufacturing problem at one of the remaining companies making that drug.

- Capacity constraints for making older sterile injectable drugs can exist at the level of manufacturer. Often, production lines for these drugs are dedicated to multiple products. If there is a disruption in production with any drug made on the same line, it can affect all drugs made on that line. If this were to occur, shortages in drug supply can result. These shortages become severe if the other companies making the same drug lack the capacity to ramp up production to compensate for the shortage.
- The pharmaceutical supply chain does not typically have much excess inventory in the system. The inventory for most products maintained at the manufacturer, wholesaler, and pharmacy level is less than 1 month of supply. A sudden halt in manufacturing evolves quickly into a shortage at the pharmacy level.
- Drug product shortages have been caused by manufacturers not following quality standards, such as the Current Good Manufacturing Practices (CGMP). Poorly maintained facilities and equipment, and inadequately trained personnel are some of the reasons leading to manufacturing problems, recalls, halt in production, and ultimately the shortage of drug products.

Q7: What can FDA do to address shortages?

When FDA is notified of a shortage, there are multiple mechanisms that can be utilized to resolve the shortage, depending on the reasons for the shortage. The most common means of addressing shortages are as follows:

- When manufacturing problems occur, FDA works closely with the company to resolve the issues and ensure that safe, effective product is returned to the market as quickly as possible.
- If a product is made by multiple companies and one company has manufacturing issues or delays, FDA encourages the remaining companies to ramp up production. The FDA also offers assistance to all companies on issues related to increasing supplies.
- When a company needs a new manufacturing site or new raw material supplier, FDA can expedite the review of these changes.
- For products in shortage or at risk for shortage, FDA can expedite the review of new manufacturers interested in producing the product.
- When a product is deemed medically necessary and in short supply, but deviates from the manufacturing specifications and quality standards, FDA can work with the company to assess the potential health impact. This impact determines whether FDA can give regulatory discretion to allow products that do not meet all specifications in the approved application to be distributed or to stay on the market. FDA can sometimes allow a firm to implement corrective measures so that drug product may be released or remain on the market, to avoid a shortage.
- FDA works to identify alternative sources of the product in circumstances where no product is available or substantial risks preclude continued use of the product. In rare cases, importation of drug from unapproved sources may be allowed on a temporary basis until the shortage is resolved.

Q8: What are the things that FDA cannot do to address shortages?

FDA does not have the authority to require a company to continue manufacturing a product if it wishes to discontinue production. In addition, FDA cannot require a company to increase production of a drug.

FDA cannot require that companies report shortages, nor are they required by current regulations to report decisions to discontinue products to FDA—the exception is when a company is the sole source of a medically necessary drug. There is no penalty if companies do not comply.

Q9: How can healthcare professionals help FDA address drug shortages?

FDA encourages manufacturers as well as healthcare professionals and patients to report all shortages to our FDA Drug Shortage Program at drugshortages@fda.hhs.gov.

Early notification of potential or actual shortage issues allows the shortage to be addressed more quickly and may even prevent the shortage from worsening or occurring in the first place.

FDA posts shortages of medically necessary drug products on our Web site: Drug Shortages[2] and the Web site is updated with information provided by the manufacturers regarding timelines for availability and other information.

All inquiries or questions about shortages are welcome and may be directed to FDA's Drug Shortage Program at drugshortages@fda.hhs.gov.