THE IMPACT OF DRUG SHORTAGES IN DENTISTRY

Why They Happen and What to Do if You're Affected

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Some dentists in various areas of the country may have recently experienced a nitrous oxide shortage, affecting their ability to effectively treat their patients. These types of shortages can cause drug rationing; they can also compel dentists to use alternative treatments or drugs, which can lead to medication errors. The causes and solutions to drug shortages are varied.

Recent Nitrous Oxide Shortage

An explosion at an Airgas facility in Cantonment, Florida, on Aug. 8, 2016, killed an employee and heavily damaged the plant, halting its manufacture of nitrous oxide.

In the plan of the merger dated Nov. 17, 2015, Airgas competitor, MATHESON, was mandated as part of the Federal Trade Commission (FTC) mediated consent decree to acquire two nitrous oxide plants from Airgas.[1] Several MATHESON nitrous oxide products are not labeled for human use; some of the product was being allocated for use in racing cars and unavailable for dental cases. Airgas provides the bulk of production of nitrous oxide in the United States, despite the assessment and constraints put into place to ensure competition during the FTC consent agreement.

Due to the August 2016 Airgas explosion, capacity of nitrous oxide production has diminished but was expected to reach full capacity in the third quarter of 2017, according to the U.S. Food and Drug Administration (FDA). However, the timeline of achieving full capacity has been extended several times previously.

What Causes Drug Shortages and Delays to Market?

In addition to accidents such as the one at Airgas, the United States experiences drug shortages due to a number of reasons, including inadequate competition from qualified sources to produce a drug or, for manufacturers, problems in receiving raw materials from sources. Other reasons for drug shortages and delays to market include:

- **Quality control:** Problems with the quality of drugs (such as bacterial growth or metal particulates) can lead to a shutdown of manufacturing lines or factories. If there is only one manufacturer and a factory is cited for quality control problems, there is likely to be a drug shortage.

- **Evergreening:** When a drug is about to go off-patent, a manufacturer may tweak the dosage, route, patient population (such as pediatrics) or administration to allow for government authorities to issue a new patent for the drug. This process is called evergreening, and it is legal.

- **Citizen petitions:** Filing a petition to the FDA is an often-used tactic to buy a manufacturer more time on their drug monopoly. Brand name manufacturers may file a citizen petition to prevent firms with generic drug applications from achieving a drug approval. There may be no legitimate reason behind filing the petition, but it buys the brand name manufacturer more time as the sole source of the drug, while the FDA considers the contents and claims of the citizen petition.[2]

- **Preventing access to samples:** Blocking access to samples to prevent a generic manufacturer from conducting bioequivalence studies is a relatively new tactic that some brand name manufacturers employ, according to an article in *Harvard Business Review,* "How Pharma Companies Game the System to Keep Drugs Expensive." Generic drug manufacturers must conduct studies to ensure that the generic drug meets all specifications as the brand name drug. In order to conduct those tests, generic firms need access to the brand name samples. If they are prevented access to drug samples, manufacturers are unable to complete the tests FDA requires. Hence, the manufacturer is not able to file an application for marketing, and the drug will not be allowed in the U.S. market.

- **Pay for delay:** According to the FTC, brand name drug manufacturers may work out some type of monetary compensation to delay a generic competitor's entry into the market by paying the generic company a remuneration.

- **Intentional labeling problems:** Generic manufacturers must rely on information in the brand name drug's labeling. If a brand name drug manufacturer causes confusion in the drug labeling, the generic manufacturer will be delayed to market. According to the book, "Drug Wars: How Big Pharma Raises Prices and Keeps Generics off the Market," a claim such as "medication is better absorbed when taken with food" can cause delays for generic drug manufacturers, as the claim is difficult and expensive to validate.

- **Ineffective and unnecessary capsule coating:** This is a newer strategy to delay generic development. Adding more elements to a medication to make production more complex delays entry into the market.

- **Orphan drug status:** Applying for orphan drug status for a new indication is also a fairly recent tactic for delay to keep generics out of the market, according to the FDA. An orphan drug status refers to a drug or biologic used to treat a rare disease or condition. This designation means that the sponsor of the drug qualifies for development incentives, including tax credits.

According to the 2016 U.S. Government Accountability Office (GAO) report, *Drug Shortages: Certain Factors are Strongly Associated with this Persistent Public Health Challenge,* generic sterile injectables are the most common type of drug to experience shortages. A generic drug status generally leads to lower profit margins and/or decreased economic conditions that may not add new manufacturers to the market. Chemotherapy and anti-infectives are also categories of drugs that are prone to shortages.

New drug shortages are decreasing, while ongoing shortages remain high, the GAO report says. Every shortage is different in severity and length, depending on the factors and conditions that created the shortage. Some drugs require a long lead time and a complex manufacturing process, allowing for a greater vulnerability to shortages. Many drugs require a foreign source for a material or active ingredient. Problems with trade or natural disasters may slow down the ability to access these components.

The Role of the FDA

In 2011, the medical community experienced severe shortages of sterile injectable medications. Clinical cases needed to be delayed, and clinicians were faced with difficult decisions on how to allocate chemotherapeutic drugs. Medical professionals contacted the FDA in order to find drugs for emergency cases or to treat patients with terminal illnesses. The FDA subsequently established an internal drug shortages task force to coordinate and centralize problems in the United States, yet problems persisted.[3]

The FDA cannot require a pharmaceutical company to make a drug, even if it is a medically necessary drug; increase production of a drug; or change how much and to whom the drug is distributed.

Stakeholders began meeting with each other to determine if there were any possible legislative solutions to drug shortage problems. Certain provisions were included in a bill later attached to the 2012 FDA user fee act (UFA) bill. Notification of drug shortages are required at least six months prior to discontinuance or disruption of a life-supporting or life-sustaining drug. A report from the FDA to Congress is due each year to assess the trend analysis of shortages. The FDA must establish a drug shortage list to include the reason for the shortage, and the U.S. attorney general must coordinate issues with the FDA in cases where there is a quota on controlled substances.[4]

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) became Public Law 112-144 and included the above provisions.[4] The law allows the FDA to deliver more oversight in coordinating aspects of drug shortages and provide assistance to prevent them. While the law allows for centralized management of drug shortages, it has not abated the shortages themselves.

Current Government Oversight

The 2016 GAO report contends that the FDA has been instrumental in preventing at least 100 drug shortages annually since 2012. The Department of Health and Human Services (DHHS) acknowledges that there is a correlation between a manufacturer receiving a warning letter from the FDA and subsequent drug shortages. Warning letters are commonly issued due to a manufacturing quality control problem.

If one manufacturer identifies a shortage, the FDA contacts all manufacturers of the particular drug. If the market demand can be met by other suppliers, it would not be classified as a shortage. The FDA prioritizes reviews of drug applications and inspections in order to restore and increase the production of

Report a Drug Shortage to the FDA

Manufacturers, health care professionals and members of the public can report drug shortages to the agency. To report a drug shortage to the FDA, email *drugshortages@fda.hhs.gov.*

the drug. Additionally, the agency can use its regulatory discretion to refrain from taking action on a manufacturer, even if there is a labeling or quality control issue.

The FDA can also solicit foreign manufacturers for help in producing a needed supply, though some health policy experts say that foreign importation is a gateway to ruining the quality and integrity of the U.S. drug supply chain. Other health policy experts are advocating for foreign drug importation, as are some legislators. However, it is notable that four previous FDA commissioners have come out vociferously against foreign drug importation. Nonetheless, the United States is already the No. 1 importer of pharmaceutical drugs in the world, with $86 billion in imports in 2015.[5]

Potential Solutions

The Generic Drug User Fee Act was reauthorized in August 2017, as part of FDA user fee acts.[6] Funding provided by drug application fees will add resources for FDA staff to address the generic drug application backlog. Additionally, there are calls for the FDA to prioritize applications for generic drugs in which three or fewer manufacturers are active in the U.S. market.

Brookings Center for Health Policy produced a working paper wherein the authors proposed that the FDA should establish a single electronic window for generic medications from multiple countries whose national regulatory schemes are stringent.[7] Proposed countries could include the United States, Canada and those part of the European Union. Expansion could add the United Kingdom, Australia, New Zealand, Japan and potentially other well-established regulatory authorities. Manufacturers could file one application that would be recognized by all participating countries, reducing generic application filing costs and allowing makers to reach larger markets. Efforts to harmonize technical requirements in regulatory submissions have been ongoing for decades.

The FDA could also consider a reciprocal approval for generic drugs with countries with stringent regulatory authorities. This potential agreement could be established with a memorandum of understanding between countries.[6] Eighty percent of active pharmaceutical ingredients and 40 percent of drugs used in the United States are imported from other countries.[8] Long-term economic and safety consequences of these potential solutions are unknown. ✦

Taking Care of Patients during a Drug Shortage

Dentists may want to take note of potential drug shortages at a very early stage. Communication with vendors is critical to ensure that your practice is pursuing all available options to acquire necessary drug stock to treat your patients.

When all efforts to obtain necessary drugs have been exhausted, dentists may need to cancel or reschedule some cases if the drugs are needed for those patients, unless the needs of ongoing care require that the cases not be rescheduled. Dentists are reporting increased costs of nitrous oxide, delivery fees and cylinder rentals due to the recent nitrous oxide shortage.

Every drug shortage is different and lasts a varied duration. Some suggestions to mitigate your next drug shortage include:

- Be aware of what is occurring in your local dental community. Communicate with providers in your area who are likely to know about a drug shortage you are experiencing. Find out how other dentists are managing their drug shortage(s).
- Call the affected company/companies, and inquire about how long the shortage is expected to last.
- Be aware of all of the options in your local drug supply chain distribution.
- Stay involved in organized dentistry. Advocacy efforts to bring an end to the nitrous oxide shortage and avoid the potential down time due to a lack of drugs can justify annual dues payments for years.
- Communicate with all of the pertinent national and local dental advocacy organizations that you are affiliated with about drug shortages you are experiencing.
- Contact your AGD advocacy staff on how to best communicate with state and federal legislators, including those members serving in the U.S. Congress who are dentists.

For more information on drug shortages, visit *www.fda.gov/drugs/drugsafety/drugshortages/default.htm.* To access the FDA Drug Shortage Database, visit *www.accessdata.fda.gov/scripts/drugshortages/default.cfm.*

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