Mitigating Shortages of Injectable Drugs in the United States

Sep 20, 2017 4:47:40 PM PAO-M09-17-CI-001

Tags: CDMO Drug Development Drug Delivery Injectables Grifols

The quantity of drugs in short supply in the US remains fairly high, with some shortages continuing for multiple years. The majority of these drugs are generic sterile injectable products most commonly in short supply due to manufacturing, i.e. quality, issues. Shortages can have significant consequences for patients and hospitals. CDMOs like Grifols Partnership, with excellent quality systems and the ability to rapidly transfer in sterile injectable manufacturing processes, can play a crucial role in the mitigation of drug shortages.

Drug Shortages Lead to Real Consequences

Drug shortages continue to pose a real challenge to public health in the US, despite a decline since 2010 in the number of new shortages occurring each year.[1] According to a recent article in the Journal of Emergency Medicine, on June 26, 2017, there were 69 preparations of 28 emergency care preparations in short supply, including most forms of adenosine, atropine, bicarbonate, calcium, dextrose, dopamine, epinephrine, fentanyl, labetalol, magnesium, and lorazepam, and an additional 50 large volume intravenous fluid preparations that were unavailable.[2]

The majority of these drugs (72%) are sterile injectable products in a variety of disease indications, including anti-infective and anesthetic drugs to cardiovascular and oncology treatments.[3] They are most commonly in short supply due to manufacturing issues, which is apt to continue for multiple years.[1] According to the US Government Accounting Office, since 2013, the majority of ongoing shortages in a given year were first reported at least two years earlier.[1] Shortages of critical cancer therapies, drugs that provide parenteral nutrition and even basic drugs, such as intravenous saline solution, can delay or deny patients the crucial treatments they require, potentially leading to further medical complications and possibly death.[4] For instance, at least one drug shortage (of norepinephrine) has been directly linked to increased patient deaths.[5] In some cases when facing drug shortages, prescribers turn to second-line alternatives, which may be less effective or pose additional risks and typically carry higher costs.[1,4]

Quality Is the Leading Problem

Previously, as mentioned in the 2016 GAO report, the agency noted that many shortages of sterile injectable drugs were generally due to supply disruptions triggered by the slowing or halting of production by manufacturers in order to address quality problems.[1] Quality issues were magnified by other features of the sterile injectables sector, including generally limited inventories, the need for regulatory approval, production complexity and constrained manufacturing capacities. In its 2016 study, GAO investigated more fully potential factors causing shortages of sterile anti-infective and cardiovascular injectable drugs.[1]

Notably, both the number of warning letters issued to sterile injectable drug manufacturers by FDA and shortages of drugs manufactured by the facilities receiving these warning letters increased from the 2007 fiscal year through the 2013 fiscal year.[1] Overall, however, it was concluded that the issuance of warning letters was not a direct cause of drug shortages, because the facilities receiving the warning letters had histories of poor compliance and thus were facing ongoing quality issues. These issues persisted despite investments by the manufacturers to address the noted insufficiencies. Consequently, shortages of sterile injectable drugs will likely continue for some time.

The study, conducted by the Pew Charitable Trusts and ISPE, also found that quality is a driver of drug shortages.[3] Quality issues, in this case, were defined as "a combination of cGMP compliance violations and matters related to product development or manufacturing that led to lower-than expected product yields." The researchers found that 45% of the reference products reviewed in the report suffered shortages due to quality issues. Problems with quality led to delays in regulatory approvals as well as delays in production and transfer from development to production, leading to reduced yields/quantities produced and withdrawal of products from the market.

When there are quality or production problems for sterile injectables, the result is almost always a drug shortage. To minimize such shortages, an industry commitment to a culture of quality manufacturing is required.

Raw Material Sourcing, Low Pricing and Other Factors Important Too

In addition to quality problems, there are a number of other factors that have been identified as contributing to shortages of sterile injectable drugs. GAO found the decreasing numbers of suppliers and the fierce competition and low pricing in the generic injectables market to be important issues.[1] Manufacturers have temporarily halted production of sterile injectables due to raw material unavailability and to address manufacturing/quality issues. Others have elected to exit the market due to the poor profitability of a product or because of the high cost of addressing manufacturing issues at the low level of profitability of many generic injectables. Inventory is often limited because there are only a few pharmaceutical companies producing generic sterile injectables, and manufacturers typically schedule production of specific drugs only at certain times. Any decrease in supply can thus have a significant impact on product availability.

Researchers at the Pew Charitable Trusts and ISPE found that the inability of manufacturers to rapidly increase production when another producer exits the market is a notable contributor to drug shortages.[3] Lack of any incentives for manufacturers to produce drugs in order to prevent shortages is another factor. Manufacturers are also challenged to establish flexible supply chains that enable rapid response to changing market demand.

Focusing on Technologies, Materials and Robust Manufacturing Process

Solutions to parenteral manufacturing challenges are focused on technology, new materials and robust manufacturing processes. Contract development and manufacturing organizations (CDMOs) can help address these problems and thus assist in the mitigation of drug shortages. To do so, they must be committed to a holistic approach to quality across the entire organization and have the capability to adopt new technologies and rapidly transfer in sterile injectable manufacturing processes.

Prior to advancing a strategic initiative aimed at reducing a drug shortage, an effective CDMO knows to both evaluate competitor responses and identify any new technologies that might be intended to target the same indication. In addition, the CDMO should have the ability to evaluate seemingly unrelated new technologies for the potential use in novel solutions for addressing drug shortages.

Because many drug shortages for sterile injectable drugs are related to quality issues, and most notably particulate contaminants, it is essential that CDMOs providing sterile injectable manufacturing services understand the potential causes of particulate contamination and have the knowledge, experience and systems to prevent this issue from occurring.

Taking Action to Address Shortages of Larger-Volume Parenterals (LVPs)

In recent years, there have been a number of shortages of LVP due to problems with contamination; manufacturing issues or product discontinuationLVP products must typically be terminally sterilized, and the main issue leading to drug recalls is the presence of particulates in the final, packaged products.

In many cases, particulates arise due to incompatibilities between the parenteral drug formulation and packaging. To ensure the perfect match between these, it is essential to have long-term experience managing both aspects of the drug manufacturing process. Close collaboration between the sponsor firm and CDMO can further minimize risks. Unlike most other CDMOs, Grifols avoids risks and guarantees high-quality products by manufacturing its own flexible containers.

In addition, Grifols has decades of experience in the plasma-derived proteins market and, unlike most other players in this market, has never experienced any quality problems due to virus contamination. The same level of commitment to quality applies across all of Grifols' activities, including its parenteral fill/finish services.

Furthermore, beyond adopting a vertical integration model for control of the entire manufacturing process, Grifols has introduced automation technologies (robotics) and implemented advanced process controls to reduce human interactions with injectable products and thus further minimize the potential for contamination. This approach allows Grifols to maintain complete control of the production process.

Grifols is currently working with several pharmaceutical companies seeking to mitigate drug shortages and their significant impacts on patients. We are prioritizing such products above other requests. As a reliable CDMO with a long track record of excellent quality performance, extensive expertise and knowledge in parenteral manufacturing and the ability to rapidly implement manufacturing processes, Grifols can help customers address drug shortage situations by accelerating their time to market for these important products.

References

1. US Government Accounting Office, "Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public-Health Challenge" (Report # GAO-16-595), July 7, 2016, https://www.gao.gov/products/GAO-16-595.
2. James J, Augustine, "Shortages and Rapid Price Escalation: The Latest on the Crisis," Journal of Emergency Medical Services, July 6, 2017, http://www.jems.com/articles/2017/07/drug-shortages-and-rapid-price-escalation.html.
3. The Pew Charitable Trusts and the International Society for Pharmaceutical Engineering, "Drug Shortages: An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies," January 2017, http://www.pewtrusts.org/~/media/assets/2017/01/drug_shortages.pdf.
4. FDA, "Report on Drug Shortages for Calendar Year 2016," 5/19/17, https://www.fda.gov/downloads/Drugs/DrugSafety/UCM561290.pdf.
5. Journal of the American Medical Association, "Shortage of Drug to Treat Low Blood Pressure from Septic Shock Associated With Increased Deaths," Press release, http://jamanetwork.com/journals/jama/fullarticle/10.1001/jama.2017.2841.

Tags: CDMO Drug Development Drug Delivery Injectables Grifols

RELATED CONTENT

CDMO
World's Largest Biologics Plant Gets EMA Nod
PAO-M12-17-NI-029

CDMO
Renova Therapeutics' Gene Transfer Tech Enters the Fast Lane
PAO-M12-17-NI-028

CDMO
Novo Nordisk Bags FDA Approval for New Diabetes Treatment
PAO-M12-17-NI-024

NICE INSIGHT / THAT'S NICE
89 Fifth Avenue
Fifth Floor
New York
NY 10003-3020

New York – Raleigh – Chicago
San Diego – San Francisco – Dallas
Frankfurt – Shanghai – Shenzhen