

Drug Shortages

CVM Perspective

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DRUG SHORTAGES

Patient care is our primary concern.
 Since 1999, FDA has worked with the pharmaceutical industry and stakeholders to address this critical issue that impacts health care delivery in the United States.

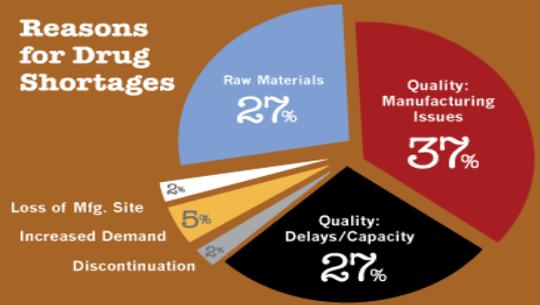


Types of Drugs FDA Considers for Drug Shortages

FDA prioritizes drugs that are medically necessary. A medically necessary drug product is a product that is used to treat or prevent a **serious disease or medical condition** for which there is no alternative drug, available in adequate supply, that medical staff has determined to be an acceptable substitute. Although the agency focuses on medically necessary drugs, all potential shortages are evaluated to help determine the possible public health impact.



Reasons for Drug Shortages



117
shortages
reported in
2012

<https://www.fda.gov/drugs/drug-shortages/drug-shortages-infographic>

FDA Works to Prevent Drug Shortages



FDA works to find ways to mitigate drug shortages. However, there are a number of factors that can cause or contribute to drug shortages that are outside of FDA's control. Sometimes manufacturers have an unforeseen breakdown in manufacturing line that affects their production. Other times, shortages are caused by longstanding quality manufacturing issues.

FDA cannot require a pharmaceutical company to:

- 1 make a drug, even if it is a medically necessary drug,
- 2 make more of a drug,
- 3 change how much and to whom the drug is distributed.



FDA issued a long-term **strategic plan** to outline the agency's priority actions, as well as actions drug manufacturers and stakeholders can take to prevent drug shortages by promoting and sustaining quality manufacturing.

<https://www.fda.gov/drugs/drug-shortages/drug-shortages-infographic>

FDA Responds to Drug Shortages

44
shortages
reported in
2014

FDA responds to potential drug shortages by taking actions to address their underlying causes and to enhance product availability. FDA determines how best to address each shortage situation based on its cause and the public health risk associated with the shortage.

FDA works to maintain availability of a drug in a variety of ways, while minimizing the risk to patients.

For manufacturing/quality problems, **FDA works with the firm** to address the issues. Problems range from very low risk, such as the wrong expiration date on package, to high risk, such as particulate in product or sterility issues.

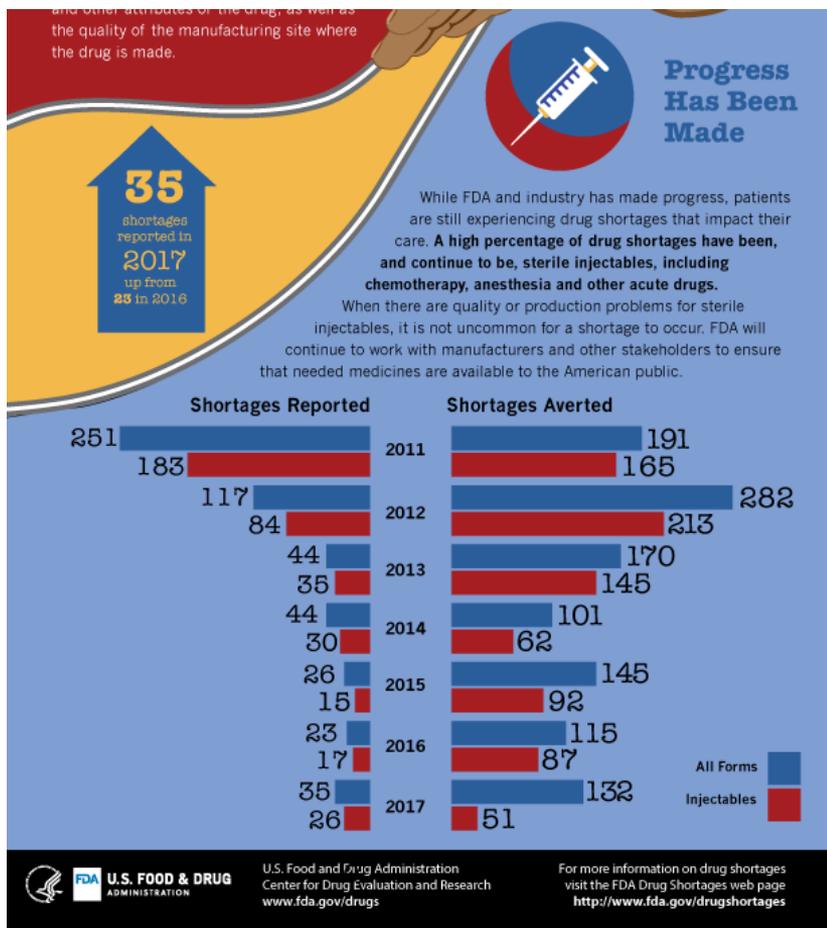
FDA also works with other pharmaceutical companies making the drugs that are in shortage to determine if they have the capacity to assist and if they are willing to do so.

When the U.S. manufacturers are not able to resolve a shortage immediately and the shortage involves a critical drug needed for patients, **FDA may look for a pharmaceutical company that is able to redirect product into the U.S. market to address a shortage.** FDA considers a list of criteria to evaluate the product to ensure efficacy and safety, including the formulation and other attributes of the drug, as well as the quality of the manufacturing site where the drug is made.

The Pharmaceutical Industry Can Help Prevent Drug Shortages

Notifying FDA early is critical to helping prevent or mitigate a drug shortage. Through the Food and Drug Administration Safety and Innovation Act (FDASIA), pharmaceutical companies are required to notify FDA, when manufacturing interruptions or production changes could lead to a supply disruption or discontinuation.

<https://www.fda.gov/drugs/drug-shortages/drug-shortages-infographic>



<https://www.fda.gov/drugs/drug-shortages/drug-shortages-infographic>

FDA Drug Shortages Task Force

The FDA Drug Shortages Task Force was formed in July 2018 to identify the root causes of drug shortages and provide long-term solutions in a report to Congress. The task force published an [FR notice](#) in September 2018 to solicit comments, and then hosted six stakeholder listening sessions:

1. Experts and Think Tanks
2. Adverse Consequences
3. Pharmacies and Hospitals
4. Manufacturing Groups
5. Medical Groups
6. GPOs and Distributors

In November 2018, the task force held a public meeting to get additional input.

The task force has continued to work since the public meeting and plans to submit their report to Congress this year.

***This task force mainly focused on human drugs, but it's important to look at root causes and solutions from human drugs since they often inform the policy on the veterinary side as well.**

Problem Defined

Drug shortages do not resolve according to the “textbook” pattern of market response. “Textbook” is defined as prices rising after a supply disruption and providing an incentive for existing and new suppliers to increase production until there is enough supply of a product to meet demand. The Task Force sought to understand why the drug market differs and to propose solutions to avoid future shortages.

Potential Problem: Drug Pricing

“We have drug prices that are too high. But we also have markets where the prices may be too low to sustain reliable supply and the high-quality investments in manufacturing that patients deserve.”

Scott Gottlieb, M.D. November 27, 2018, Public Meeting on Identifying the Root Causes of Drug

Shortages and Finding Enduring Solutions

Potential Problem: Drug Pricing

- Production costs high:
 - If product is not sufficiently profitable, less interest in manufacturing drug, even if it is medically necessary.
 - This is especially true for older, sterile injectables where production costs are high, but prices are low.
- Human drug prices: perception that there is a race to the bottom
 - Price competition from competitors to obtain long term contracts.
 - Drug prices are reduced, leaving manufacturers with fewer resources to invest in manufacturing or redundant capacity for drugs.
 - If sufficient investment is not made into quality, higher risk for shortages.

Potential Problem: Quality Systems

- The market does not differentiate the various levels of quality management systems maturity.
 - In the current state, many manufacturers only focus on meeting cGMP requirements.
 - If a manufacture only focuses on meeting a minimum standard, they lose the opportunity to have robustly controlled processes that are predictive and addresses problems (including drug shortage) before they occur.



Quality Maturity in Manufacturing Facilities

- St. Gallen top 10 quality maturity attributes*
 1. Optimized set-up and cleaning procedures are documented as best practice process and rolled out throughout the whole plant.
 2. A large percentage of equipment on the shop floor is currently under statistical process control.
 3. For root cause analysis, the firm has standardized tools to get a deeper understanding of the influencing factors for problems.
 4. Goals and objectives of the manufacturing unit are closely linked and consistent with corporate objectives and the site has a clear focus.
 5. Manufacturers have joint improvement programs with suppliers to increase performance.
 6. All potential bottleneck machines are identified and supplied with additional spare parts.
 7. For product and process transfers between different units or sites, standardized procedures exist that ensure a fast, stable and complied knowledge transfer.
 8. Charts showing the current performance status such as current scrap rates and current up times are posted on the shop floor and visible for everyone.
 9. The firm regularly surveys customers' requirements.
 10. The firm ranks its suppliers and conducts supplier qualifications and audits.

Potential Problem: Quality Systems

- In the current system, purchasers have limited information that can be used to assess the state of quality management of a manufacturer. Purchasers rarely have information to link the drug products they purchase to the facilities where they are manufactured.
 - No positive impact (e.g. price premiums) for drug manufacturers that have mature quality management, back-up manufacturing capabilities and risk-management plans.
 - No negative impact for drug manufacturers that do not invest in modernization of manufacturing equipment and facilities to ensure a reliable supply.
 - Result: manufacturers more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to quality problems, triggering supply disruptions and shortages.

Potential Problem: Regulatory Challenges

- Drug supply chain is longer, more complex and fragmented as companies have located more production overseas and increased the use of contract manufacturers. Difficult to find new sources of active ingredients.
- Manufacturers and distributors have moved toward “just in time” inventory management, so there is little redundancy in the supply chain when a disruption occurs.
- Not always feasible for new manufactures to enter market or for sponsors with existing approvals to increase capacity in a timely enough fashion to address shortage.
 - The shortage may be over by the time manufacturer gains approval, so few sponsors want to take the risk and end up in a situation where they have no market.
- Even if a company has an existing approval, the changes that may need to be implemented in order to meet market demand may require approvals from many different national regulatory bodies, and/or find a new source of active pharmaceutical ingredients (APIs), both of which can be challenging.

Solutions? Embrace the concepts described in ICH Q8, 9, 10 (and soon Q12)



Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: <ul style="list-style-type: none">•facilitate science based pharmaceutical quality assessment;•enable innovative approaches to process validation;•establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: <ul style="list-style-type: none">•increase use of risk based approaches for regulatory inspections;•facilitate science based pharmaceutical quality assessment;•optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement;•enable innovative approaches to process validation;•establish real-time release mechanisms.

Solutions?

- Develop a system for measuring quality management maturity (e.g. quality metrics):
 - Provide transparency to customers on the status of a facilities' quality management system maturity.
 - Promote continuous improvement and the use of tools to measure manufacturing performance to allow earlier detection of potential problems that could lead to shortage.
 - FDA can exercise a more flexible regulatory approach, ensuring that high quality drug products are on the market.

Solutions?

- New drug inspection paradigm?
 - If drug inspections are focused only on compliance with cGMPs, they are not likely to shift the drug industry's focus to achieving mature quality management systems.



Better Assessment of Quality System Maturity During cGMP Inspections

New Inspection Protocol Project (NIPP)

The NIPP is intended to develop standardized electronic inspection protocols to collect data in a structured manner; to reduce the variability in inspectional findings among investigators; and facilitate more efficient analysis of findings. The NIPP is aimed at expanding the investigator's focus beyond identifying specific current good manufacturing practice (CGMP) violations towards assessing the overall state of a facility's quality systems and operations.

Currently just being used for aseptic processing.

Questions

- Are the drivers for the veterinary industry similar to those of the human drug industry?
- Where the drivers are different, how should our solutions be different?
- How can we improve the quality and reliability of manufacturing facilities?

Current Process and Communication

- Identifying/Communicating the Root Causes and Drivers of Drug Shortages
- Identifying Strategies for Preventing and Mitigating Drug Shortages

Communication

- Identifying/Communicating the Root Causes and Drivers of Drug Shortages
 - Early communication of common factors that cause shortages:
 - Quality e.g. manufacturing issues, delays/capacity
 - Unavailable raw materials/packaging materials
 - Increased demands
 - Marketing decisions by manufacturers

Identifying Strategies for Preventing and Mitigating Drug Shortages

- Encourage manufacturers and sponsors to report anticipated animal drug product shortages, including an assessment of the cause(s) and potential solutions.
- Be proactive – Determine the medical necessity of the drug shortage

Mitigating Drug Shortages

- When the shortage is not resolved immediately, then the process is determined for Medically Necessary Veterinary Product (MNVP) status
- Each shortage situation is addressed
 - Priority
 - Evaluating risk/benefits of the situation

What Is a Medically Necessary Veterinary Product?

- Used to treat or prevent a serious animal disease or condition
 - Is needed to assure the availability of safe food products of animal origin, and
 - No other available source of that product or adequate alternative drug substitute exists.
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- **Owner inconvenience and non-therapeutic uses are inappropriate reasons for classifying a product as an MNVP**
 - **MNVP status is not the resolution or short cut to the approval process**

Conclusion

- Mature quality management systems combined with regulatory solutions are critical for preventing supply chain interruptions and avoiding drug shortages.
- Communicate anticipated animal drug product shortages early, including an assessment of the cause(s) and potential solutions.



Thank you



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