A REVIEW OF STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES IN USA

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ABSTRACT

Drug shortages are a significant public health issue in the United States, and addressing shortages remains a top priority for FDA. Establishment of clear rules and guidelines for managing drug shortages is essential to overcome this issue. FDA has given this strategic plan to address drug shortages in the United States. Recently the president and congress have taken important actions which enabled FDA to learn more about possible shortages before they occur. These actions have helped FDA to prevent 78 shortages in the first three-quarters of 2014. This strategic plan is consisting of three sections. The first section is about identifying the causes of shortages, and describing current efforts by FDA’s to resolve existing shortages and disruptions in supply chain. The second section explains the actions FDA is taking to strengthen and expand its efforts to discuss shortages. The third section reviews potential actions for other stakeholders. This article reviews strategic plan for preventing and mitigating drug shortages drafted by food and drug administration in October 2013.

KEY WORDS: Drug Shortages, Strategic Plan, Food and Drug Administration (FDA).
INTRODUCTION
Drug shortage in the United States is defined as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level".¹ A term was rarely known before, until the impact of drug shortage progressed to critical levels. The shortages of drugs can create a health issue and directly affect the public health. Due to Drug Shortages prescribers can use second-line alternatives, which may be less effective or have additional risks. Drug shortages can cause harm to public health especially the case when a shortage involves a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition. Medication errors and adverse events are the main outcomes of the drug shortages; which may cause high institutional costs, and patient complaints. Number of Drug Shortages has been increased from past recent years (Figure 1). FDA has taken several actions to address drug shortages (Table 1). The agency also started referring the drug shortage list kept by the American Society of Health-System Pharmacists (ASHP)² and the University of Utah Drug Information Service³. Currently there is shortages of Metoprolol Injection, Desferal Injection, Dextrose 5% Injection Bags, Memantine Hydrochloride (Namenda) Tablet etc.⁴ To prevent these things from occurring, FDA has used a variety of methods to prevent shortages, working within the confines of the statutory and regulatory framework in place and in partnership with manufacturers and other stakeholders.⁵ On October 31, 2013, FDA issued its Strategic Plan for Preventing and Mitigating Drug Shortages. The plan has details on the origin of drug shortages, FDA’s processes and procedures for helping to prevent or mitigate shortages, and FDA’s strategy for strengthening those processes and procedures. The plan also recommends actions that other stakeholders can consider helping to prevent shortages.

Table 1: Actions taken by FDA to address Drug Shortages

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Action</th>
<th>Purpose</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Executive Order 13588 – Reducing Prescription Drug Shortages⁷</td>
<td>Purpose of this order was to know the factors causing drug shortages and use all administrative way to get notice from drug manufacturers of manufacturing discontinuances.</td>
<td>October 31, 2011</td>
</tr>
<tr>
<td>3.</td>
<td>Interim Final Rule (IFR)⁸</td>
<td>It was published in response to the Executive Order; it amended FDA’s regulations for receiving advance notification of a potential drug shortage.</td>
<td>December 19, 2011</td>
</tr>
</tbody>
</table>
4. **Draft guidance for industry on drug shortages**[^9]  
   The draft guidance was issued for public comment, and concluded that many shortages arise from quality or other issues of the manufacturing process.  
   **February 21, 2012**

5. **Food and Drug Administration Safety and Innovation Act**[^10]  
   Scope of the early notification provisions by requiring all manufacturers of certain medically important prescription drugs was explained.  
   **July 9, 2012**

6. **Strategic Plan for Preventing and Mitigating Drug Shortages**[^11]  
   The plan explains the root causes, procedures for mitigating shortages, and recommended stakeholder actions.  
   **October 31, 2013**

7. **FDA Drug Shortage Proposed Rule**[^12]  
   Rule was given to implement FDASIA’s expanded notification requirements.  
   **November 4, 2013**

8. **Drug Shortage Data System**[^13]  
   To improve system for data tracking and analysis of drug shortages.  
   **2014**

   Provide details about how FDA mitigates and prevents shortages.  
   **September 2014**

10. **FDA proposed rule to extend the notification requirements to most manufacturers of biological products**[^15]  
    Rule was given to identify such drug shortages.  
    **July 8, 2015**

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![Number of Drug Shortages Reported](image_url)

**“Fig. 1” Number of Drug Shortages reported by CDER in Year 2001-2013[^16]**

**FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages**

FDASIA specifically required the Strategic Plan to include the following.[^17]

- Strategy enhancing agency coordination, communication, and decision-making.
- Procedures to make sure drug shortages before FDA initiates a regulatory action against drug shortage.
- Strategies for doing effective communication with stakeholders.
- Procedures for knowing the effect of drug shortages on clinical trials.
An examination should be conducted to know whether Qualified Manufacturing Partner Program should be established or not.

FDA began tracking prevented shortages in 2010. Drug Shortages predominantly affect sterile injectable products (Figure 2).

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Number of New and Prevented Shortages by Dosage Form, 2005-2012
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The Strategic Plan consists of three sections.
1. Understanding and Responding to Drug Shortages
2. Continuing Progress: FDA’s Strategic Plan
3. Actions Other Stakeholders could perform

I. Understanding and Responding to Drug Shortages
For understanding and responding to drug shortages FDA has taken following actions.

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Identifying root cause of drug shortages
Notifying FDA of a Disruption in Supply
Assessing the Risk of Shortage
Mitigating an Actual or Imminent Shortage
Internal and External Communication During Shortage Management
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“Fig3”Understanding and Responding to Drug Shortages
Mainly drug shortages are caused by

“Fig.4” Drug Shortages by Primary Reason for Disruption in Supply in 2012 [19]

Notifying FDA of a Disruption in Supply: Notification of a disruption in production can come from a drug manufacturer, a professional organization, patients, and health care professionals, or through internal channels at FDA. As soon as FDA is notified about disruption in production, FDA got more time to prevent potential drug shortages.

Assessing the Risk of Shortage: Once FDA is notified about shortage first they verify the shortage exists or not. The FDA staff may take following actions: 1) Use a market research database to collect initial information to determine whether or not the current supply of product across manufacturers is stable 2) Contact product manufacturer(s) to collect up-to-date inventory information, rate of demand (units/month), manufacturing schedules, and any changes in ordering patterns. 3) Evaluate product inventory in the distribution chain to the extent possible.

Mitigating an Actual or Imminent Shortage: Once FDA confirmed that there is a shortage or shortage could occur of a medicinally necessary drug.FDA start taking following actions to mitigate a shortage: 1) Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap 2) Expedite FDA inspections and reviews of submissions from manufacturers attempting to restore production 3) Expedite FDA inspections and reviews of submissions from competing manufacturers who are interested in starting new production or increasing existing production
of products in shortage  4) Exercise temporary enforcement discretion for new sources of medically necessary drugs 5) Work with the manufacturer to ensure adequate investigation into the root cause of the shortage 6) Develop risk mitigation measures for a batch(es) of product initially not meeting established standards.

**Internal and External Communication during Shortage Management:** FDA communication and collaboration processes are essential to prevent and manage drug shortages. These types of interactions occur in a variety of ways.

**II. Continuing Progress: FDA’s Strategic Plan**

The Task Force has identified two central goals and related tasks for FDA to address drug shortages, stated below.

**Table 2: Two central goals by FDA to address drug shortages**[21]

<table>
<thead>
<tr>
<th>Goal #1</th>
<th>STRENGTHEN MITIGATION RESPONSE. Improve and streamline FDA’s current mitigation activities once the Agency is notified of a supply disruption or shortage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal #2</td>
<td>DEVELOP LONGTERM PREVENTION STRATEGIES. Develop prevention strategies to address the underlying causes of production disruptions to prevent drug shortages.</td>
</tr>
</tbody>
</table>

“Fig.5” Internal and External Communication during Shortage Management[20]

**A. Strengthen Mitigation Response**

The Task Force identified the following tasks to strengthen FDA’s ability to respond to a notification of a production disruption.
Develop and/or Streamline Internal FDA Processes: As a part of this work, the Centre for Biologics Evaluation and Research (CBER) is undertaking a review of its internal procedures to address shortages, including revising its standard operating policy and procedure on CBER-regulated product shortages. CDER has also revised its Manual of Policies and Procedures (MAPP) on Drug Shortage Management.

Improve Data and Response Tracking: CDER has created a database that focuses on collecting data related to shortages. This will enable FDA to better assess progress on preventing and mitigating shortages and will enhance FDA’s ability to compile the information necessary for the required annual report to Congress on drug shortages.

Clarify Roles/Responsibility of Manufacturers

Table 3 Practices to avoid or mitigate shortages

<table>
<thead>
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<th>Sr. No.</th>
<th>Practices</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Creating Allocation Plans</td>
<td>Allocation plan should be designed in advance, for a product shortage that could be occur</td>
</tr>
<tr>
<td>2.</td>
<td>Enhance Communications with Contract Manufacturing Organizations</td>
<td>Knowledge of manufacturing processes and facilities and anticipation of problems that might lead to a shortage should be regulatory updated</td>
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<tr>
<td>3.</td>
<td>Manage Inventory</td>
<td>Robust inventories should be established before major manufacturing changes</td>
</tr>
<tr>
<td>4.</td>
<td>Develop Short- and Long-Term Proposals</td>
<td>Provide short- and long-term proposals to address issues that could cause a shortage</td>
</tr>
<tr>
<td>5.</td>
<td>Communicate with FDA</td>
<td>Engage in dialogue with FDA to work on a long-term solution to a shortage</td>
</tr>
<tr>
<td>6.</td>
<td>Investigate Root Causes</td>
<td>Provide a realistic timeline for investigation of product defects and scheduled restart after shutdowns</td>
</tr>
<tr>
<td>7.</td>
<td>Consider Clinical Trials</td>
<td>Consider the possibility of shortages during initial clinical trial design and developing and implementing contingency plans for handling a shortage during the clinical trial</td>
</tr>
</tbody>
</table>

Enhance Public Communications about Drug Shortages: Public communications about drug shortages can be improved by 1) by developing a smartphone application individuals can access the drug shortage information posted online from their mobile phones or tablets. 2) Updating the website to include the therapeutic category (or categories) for the products listed in shortage. 3) Improving the functionality of the drug shortages website so that users will be able to sort by therapeutic or other categories and view the relevant products confirmed to be in shortage nationally.
B. Develop Long-Term Prevention Strategies: By developing long-term strategies focused on the underlying causes of production disruptions can prevent drug shortages.

Develop Methods to Incentivize and Prioritize Manufacturing Quality: FDA is exploring what it can do to improve quality improvements, with the responses received to the Federal Register notice.

Using Regulatory Science to Identify Warning Signals of Shortages: FDA is working with stakeholders to identify vulnerabilities that could put the production of quality drugs at risk, and thereby contribute to shortages.

Increase Knowledge to Develop New Strategies to Address Shortages: FDA intends to: 1) Work with the International Society for Pharmaceutical Engineering (ISPE) to analyse data from a recent global survey 2) Join with other stakeholder groups, such as groups convened by the American Society of Anaesthesiologists and ASHP, and with individual companies, patient groups, and group purchasing organizations to discuss shortages 3) Work with manufacturers to identify best practices for avoiding disruptions in production 4) Continue to explore the potential benefit, and assess the identified challenges, of establishing a Qualified Manufacturing Partner Program (QMPP).

III. Actions Other Stakeholders Should Consider
FDA has identified four key areas that are consideration to reduce drug shortages.

Table - 4 Main four areas considered for reduction in drug shortages by other stakeholders

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>AREA</th>
<th>FDA Limitation</th>
<th>Opportunities for Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Manufacturing Incentives</td>
<td>financial or other economic needs to explore innovation in quality manufacturing</td>
<td>Other stakeholders can help to explore economic, financial, or other means to encourage innovation and new investments in manufacturing quality drugs</td>
</tr>
<tr>
<td>2.</td>
<td>Use of Data on Manufacturing Quality</td>
<td>FDA’s Publicly available quality information is not strictly implemented for buyers by FDA.</td>
<td>Buyers should use publicly available information to improve quality when making drug purchasing decisions</td>
</tr>
<tr>
<td>3.</td>
<td>Redundancy, Capability, and Capacity</td>
<td>Manufacturing concentration, capability or capacity is not regulated by FDA.</td>
<td>Manufacturers could explore building redundant manufacturing capacity, holding spare capacity.</td>
</tr>
<tr>
<td>4.</td>
<td>The Gray Market</td>
<td>Influence on the gray market, its data and activities is limited.</td>
<td>Stakeholder’s can take actions to minimize gray market activities.</td>
</tr>
</tbody>
</table>
IMPACT OF THIS PLAN
This plan describes strategies to improve communication with stakeholders. Launching of a new searchable format for the FDA Drug Shortage website can be considered as an example of enhanced communications. This enhanced feature can help health care professionals to quickly identify drugs in shortage and find information on availability. The plan also identified the limitations of confronting other issues in the drug marketplace and indicated steps other stakeholders could take in the market to prevent shortages. Food and Drug Administration (FDA) officials are working closely with all the resources of health care system to prevent and mitigate shortages of “medically necessary” medicines.[27] The decrease in shortages has definitely been a combination of efforts and the work of partners – particularly the increased numbers of notifications from manufacturers and health care providers. As a result of successes, 5 fewer new drug shortages was reported in the first three quarters of 2014, compared to the same period in 2013.[28]

CONCLUSION
In conclusion, FDA and industry has made progress, but patients are still experiencing drug shortages that impact their care. FDA does not have any examples of shortages that would have been prevented or improved by its Strategic Plan. Although last year less shortages were reported, the United States experienced several critical shortages but they have not achieved their goal to prevent all shortages. After this strategic plan new bills have also been proposed to prevent or mitigate supply issues, but it will take efforts in lobbying for their incorporation into law, and their ultimate effect is unclear. The decrease in shortages, the increase in notifications, and uptick in focus on manufacturing quality are all things we are hoping to see. However, the battle against drug shortage is likely to be long-term and more work needs to be done.

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REFERENCES


