Strategic Plan for Preventing and Mitigating Drug Shortages

Food and Drug Administration
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Executive Summary

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA).[1] Among other things, Title X of FDASIA directs the Food and Drug Administration (FDA or the Agency) to establish a task force on drug shortages to develop and submit to Congress a Strategic Plan to enhance FDA's response to preventing and mitigating drug shortages.

Understanding and Responding to Drug Shortages

Shortages of drugs and biologics pose a significant public health threat, delaying, and in some cases even denying, critically needed care for patients. Preventing drug shortages remains a top priority for FDA.

Although FDA cannot directly affect many of the business and economic decisions that contribute to drug shortages, FDA is well positioned to play a significant role as manufacturers work to restore lost production of life-saving medications. FDA can be most effective when there is time to plan; thus, it is critical that manufacturers notify FDA as soon as possible when manufacturing disruptions are expected. Early notification about possible shortages, as requested in the President's Executive Order 13588 and then codified into law by Congress, has enabled FDA to work with manufacturers to restore production of many lifesaving therapies. There has been a 6-fold increase in notifications to FDA since the Executive Order. These increased notifications combined with allocation of additional FDA resources have resulted in real progress in addressing shortages—FDA helped prevent close to 200 drug shortages in 2011 and more than 280 in 2012. The total number of new shortages decreased from 251 in 2011 to 117 in 2012.

If notified of a potential disruption in production, FDA can take a number of steps to help prevent or mitigate a shortage, including:

- Determine if other manufacturers are willing and able to increase production
- Expedite inspections and reviews of submissions
- Exercise temporary enforcement discretion for new sources of medically necessary drugs
- Work with the manufacturer to ensure adequate investigation into the root cause of the shortage

[1] Public Law 112-144.

- Review possible risk mitigation measures for remaining inventory

When selecting specific regulatory tools, FDA works closely with manufacturers and chooses tools that are appropriate to the specific situation. FDA also makes certain that drug shortages are considered before taking an enforcement action or issuing a Warning Letter. Additionally, FDA communicates up-to-date information about a shortage to affected stakeholders and continues to monitor a shortage until it is resolved.

FDA's efforts to date demonstrate that FDA is an important part of the solution to the drug shortages problem. By working closely with manufacturers experiencing problems, as well as potential alternative manufacturers, and by exercising regulatory flexibility in appropriate cases, FDA has had a substantial positive impact on the shortage situation. However, FDA cannot address the drug shortage threat alone. An examination of FDA's response to drug shortages underscores the importance of strong collaboration and constant communication between FDA, industry, health professionals, and patients. In addition, ensuring that critical drugs are available to the patients who need them will require further action by manufacturers and other stakeholders.

FDA's Drug Shortage Strategic Plan

In its Drug Shortage Strategic Plan (Strategic Plan), FDA identifies two central goals to address drug shortages: improving our mitigation response to imminent or existing shortages, and implementing strategies for the long-term prevention of shortages by focusing on the root causes of shortages. The Strategic Plan outlines specific tasks under each goal.

Goal #1: STRENGTHEN MITIGATION RESPONSE **Improve and streamline FDA's current mitigation activities once the Agency is notified of a supply disruption or shortage**	
TASK 1.1 Develop and/or Streamline Internal FDA Processes	Revise and standardize procedures to more accurately reflect and enhance the interactions between units within FDA and maximize the efficiency of FDA's response to a notification of a disruption in supply.
TASK 1.2 Improve Data and Response Tracking	Improve Agency databases related to shortages and the tracking procedures FDA uses to manage shortages. Improved tracking will enable FDA to better assess progress on preventing and mitigating shortages.
TASK 1.3 Clarify Roles/Responsibility of Manufacturers	Clarify roles/responsibilities of manufacturers by finalizing the proposed rule explaining when and how to notify FDA of a discontinuance or interruption in manufacturing, working with manufacturers on remediation efforts, and encouraging manufacturers to engage in *best practices* to avoid or mitigate shortages.

TASK 1.4 Enhance Public Communications about Drug Shortages	Continue to improve FDA's public communications about drug shortages by developing a smartphone application so that individuals can instantaneously access drug shortage information, updating the website to include the therapeutic category(ies) for shortage products, and improving the functionality of the website by adding sort and search capabilities.
Goal #2: DEVELOP LONG-TERM PREVENTION STRATEGIES **Develop long-term prevention strategies to address the underlying causes of supply disruptions and prevent drug shortages**	
TASK 2.1 Develop Methods to Incentivize and Prioritize Manufacturing Quality	Identify ways FDA can implement positive incentives to promote and sustain manufacturing and product quality improvements.
TASK 2.2 Use Regulatory Science to Identify Early-Warning Signals of Shortages	Continue to develop risk-based approaches to identify early warning signals for manufacturing and quality problems to prevent supply disruptions.
TASK 2.3 Increase Knowledge to Develop New Strategies to Address Shortages	Continue to work with stakeholders to further develop our understanding of issues related to shortages, including whether a Qualified Manufacturing Partner Program would be feasible and beneficial. This additional information could help inform new strategies to address shortages.

Actions for Other Stakeholders to Consider

Stakeholders outside FDA have a significant role to play in mitigating and preventing drug shortages. Because there are limits to what FDA can do on its own to address shortages, any comprehensive drug shortages plan must also discuss other stakeholders' roles and potential contributions. FDA has identified four specific areas that merit external stakeholder attention:

- **Manufacturing incentives:** Many shortages are caused by manufacturing quality issues. FDA is exploring ways to use its existing authorities to promote and sustain quality manufacturing. However, our ability to offer financial or other economic incentives for innovation and new investments in high-quality manufacturing is limited. Given the importance of quality and its link to shortages, payers might explore financial or economic incentives to encourage high-quality manufacturing that could help reduce the occurrence and severity of shortages.

- **Use of data on manufacturing quality in purchasing decisions:** FDA makes certain information publicly available about manufacturers' historical ability to produce quality products. However, FDA cannot influence whether or how these quality data are used by buyers, such as hospitals, pharmacies, and other group purchasing organizations, when they make purchasing decisions. Better use of this information could help incentivize manufacturers to focus on quality and, ultimately, prevent shortages.

- **Redundancy, capability, and capacity:** A disruption in supply is exacerbated if there is limited manufacturing capacity and capability, market concentration, or just-in-time inventory practices that result in minimal product inventory being on hand at any given time. However, FDA cannot prevent manufacturing concentration or require redundancy of manufacturing capability and capacity. Nor can FDA require a company to manufacture a drug, maintain a certain level of inventory of drug product, or reverse a business decision to cease manufacturing. Manufacturers could consider opportunities for building redundant manufacturing capacity, holding spare capacity, or increasing inventory levels to lower the risks of shortages; and other stakeholders might explore how to incentivize such practices.

- ***Gray market*:** In the context of drug shortages, the term *gray market* is used to reference the downstream distribution of approved drug products at significantly marked-up prices. FDA has limited data on the *gray market* and limited influence on its workings (for example, we have no authority regarding product pricing). However, there is evidence that *gray market* activities can worsen the impact of drug shortages. Actions on the part of other stakeholders to minimize *gray market* activities when such activities exacerbate the impact of drug shortages could play a role in mitigating the impact of shortages and reducing risks to patients.

Conclusion

Drug shortages remain a significant public health issue in the United States, and addressing shortages remains a top priority for FDA. Early and open dialogue between FDA and manufacturers is critical to successfully mitigating and preventing shortages. Recent important actions by the President and Congress have enabled FDA to learn more about possible shortages before they occur. These actions, combined with an increase in the resources FDA is devoting to drug shortages, have helped prevent numerous recent shortages—more than 280 in 2012. Nevertheless, substantial challenges remain, and more work by all relevant stakeholders is needed. This Strategic Plan identifies a number of activities to improve the Agency's ability to address drug shortages, focusing on two goals:

- Strengthening FDA's ability to respond to notices of a disruption in supply, including improving our mitigation tools
- Developing long-term prevention strategies to address the underlying causes of supply disruptions and prevent drug shortages

Recognizing that manufacturers and other stakeholders have important roles to play in ensuring that drugs are available to the patients who need them, the Strategic Plan also identifies actions others can consider that show promise in helping to prevent shortages.

FDA looks forward to implementing this Strategic Plan as part of a collaborative and sustained effort to address drug shortages in the United States.

FDA's Strategic Plan for Preventing and Mitigating Drug Shortages

Introduction

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA). Title X of FDASIA pertains to drug shortages and defines a *shortage* or *drug shortage* as a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug.[2] Among other things, FDASIA directed FDA to establish a task force on drug shortages to develop and submit to Congress a Strategic Plan to enhance FDA's response to preventing and mitigating drug shortages. FDASIA specifically required the Drug Shortages Strategic Plan (Strategic Plan) to include the following:

- Plans for enhanced inter- and intra-agency coordination, communication, and decision-making
- Plans to ensure drug shortages are considered when FDA initiates a regulatory action that could precipitate or exacerbate a drug shortage
- Plans for effective communication with external stakeholders
- Plans for considering the impact of drug shortages on clinical trials
- An examination of whether to establish a "qualified manufacturing partner program" as further described in FDASIA

Appendix B includes a table indicating where each statutory element is discussed in this document.

Since the passage of FDASIA, FDA has convened a Drug Shortages Task Force (Task Force), representing multiple disciplines, centers, and offices within FDA.[3] This Strategic Plan[4] is the culmination of the efforts of the Task Force over the last several months. The Plan also reflects input received from a wide variety of sources, including discussions with outside stakeholders

[2] Section 506C(h)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 356c(h)(2), as amended by Title X of FDASIA.

[3] Information on drug shortages, including the members of the Task Force can be found at http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm (drug shortages). Information about biologics shortages can be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm (biologics shortages).

[4] The Strategic Plan encompasses both drugs and biologics—although shortages of drugs outnumber shortages of biologics, both can have a similar and equally troubling impact on patient care. Unless otherwise indicated, we use the term *drug* to refer to both drugs and biologics.

and comments responding to a *Federal Register* notice FDA published on February 12, 2013 (Appendix A).[5] FDA also recognizes that numerous other groups are examining drug shortages, including the Government Accountability Office (GAO) and several private organizations.

Following this Introduction, the Strategic Plan consists of three sections. The *first section* explains FDA's oversight of drug shortages, examines what is known about the causes of shortages, and describes FDA's current efforts to resolve existing shortages and respond to disruptions in supply. The *second section* is the Strategic Plan: it explains the actions FDA is, or will be, taking to strengthen and expand its efforts to address shortages. Recognizing that FDA cannot address this problem alone, the *third section* outlines potential actions for other stakeholders to consider.

I. Understanding and Responding to Drug Shortages

Drug shortages pose a significant public health threat, affecting critically important drugs including those intended for intravenous administration (e.g., chemotherapy, nutritional support, and antibiotics). A shortage can result in delaying or denying needed care to patients and may cause practitioners to prescribe an alternative therapy that may be less effective for the patient or that poses greater risk.[6] Drug shortages have even disrupted clinical trials, potentially delaying research on important new therapies.

The number of new drug shortages quadrupled from approximately 60 in 2005 to more than 250 in 2011. These statistics reflect the number of new shortages reported in a given year, but because shortages typically continue for extended amounts of time, the actual number of shortages at a given point in time is likely to be higher. As a result, although the number of new shortages significantly decreased in 2012 to 117 (from 251 in 2011), more than 300 shortages remained active at the end of 2012.[7]

Behind these statistics are individual patients from across the United States who are in need of drugs to treat life-threatening diseases, including cancer and serious infections. Preventing drug shortages has been, and continues to be, a top priority for FDA. Working within the confines of the current statutory and regulatory framework and in partnership with manufacturers and other stakeholders, FDA helped prevent close to 200 drug shortages in 2011 and more than 280 shortages in 2012.

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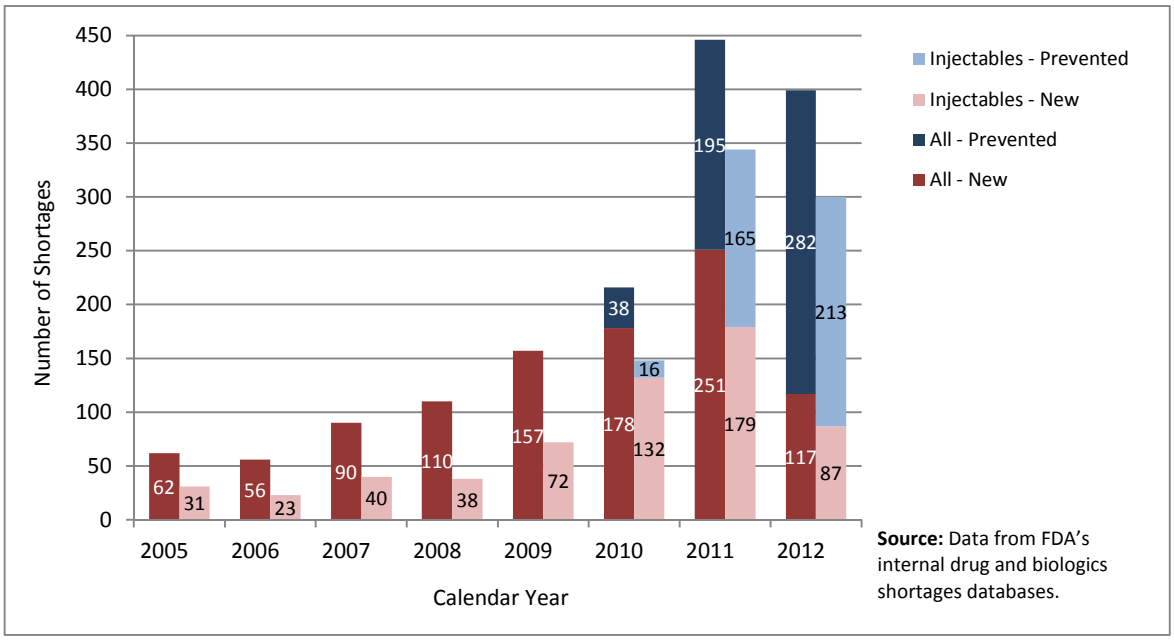
[5] The *Federal Register* notice and the submitted comments can be found online at http://www.regulations.gov, Docket No. FDA-2013-N-0124.

[6] Berg N, Kos K, et al. Report on the ISPE 2013 Drug Shortages Survey. June 2013. Tampa, FL: International Society for Pharmaceutical Engineering. Available at www.ispe.org/drugshortages/2013JuneReport.

[7] FDA drug shortage statistics can be found at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm.

Figure 1 illustrates the number of new drug shortages by year from 2005-2012 and the number of prevented shortages by year from 2010-2012 (FDA began tracking prevented shortages in 2010). Figure 1 also shows that shortages predominantly affect sterile injectable products and reflects FDA's focus on preventing nationwide shortages of these critical drugs[8].

Figure 1. Number of New and Prevented Shortages by Dosage Form, 2005-2012



A. Recent Changes to FDA Oversight of Drug Shortages

Authorities granted by Congress as part of the Federal Food, Drug, and Cosmetic Act (FD&C Act) have enabled FDA to coordinate with manufacturers to help prevent or mitigate drug shortages. However, FDA's ability to take effective action depends on the relevant manufacturer notifying FDA in a timely fashion of a disruption or possible disruption in supply. FDA has at its disposal a variety of mitigation tools (more fully described in section C.3) that the Agency can use when working with a manufacturer (or manufacturers) to prevent a possible shortage or to take appropriate remedial actions once a shortage has occurred; but these tools are only useful to the extent that FDA receives early notification about the supply disruption. Lack of, or late, notification severely limits FDA's ability to coordinate a timely response with manufacturers.

[8] There are regional or local shortages of certain products. However, these are often the result of distribution issues that can be resolved locally and are not indicative of a national supply and demand imbalance. In general, FDA focuses its resources on nationwide drug shortages of medically necessary products that have the most significant impact on public health across the country.

Recently, the White House and Congress have taken important and welcome steps to expand early notification of interruptions and discontinuations, enhancing FDA's ability to address drug shortages. Before FDASIA, notification under section 506C of the FD&C Act was limited in scope, applying only to sole manufacturers; only to a discontinuance (which could be read to imply a permanent shutdown); and only to certain approved drugs (e.g., unapproved drugs and biologics were excluded).[9] The following actions have expanded the scope of early notification requirements and the rate of early reporting:

- **October 31, 2011, Executive Order 13588 – Reducing Prescription Drug Shortages**[10]: acknowledged the need for a "multifaceted approach" to address the many different factors that contribute to drug shortages, and, among other things, directed FDA to "[u]se all appropriate administrative tools" to require drug manufacturers to provide advance notice of manufacturing discontinuances that could lead to shortages.[11]

- **December 19, 2011, Interim Final Rule (IFR)**[12]: published in response to the Executive Order, the IFR amended FDA's regulations related to early notification to improve the likelihood of FDA receiving advance notification of a potential drug shortage.[13]

- **July 9, 2012, FDASIA**: broadens the scope of the early notification provisions by requiring all manufacturers of certain medically important prescription drugs[14] (approved

[9] See 21 CFR 314.80(b)(3)(iii) (as amended by the Interim Final Rule of December 19, 2011).

[10] Executive Order 13588, available at http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages.

[11] On October 31, 2011, FDA also released a review of the Agency's approach to drug shortages, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm277749.htm and sent a letter to drug and biologic manufacturers, encouraging them to voluntarily report potential shortages to FDA, beyond what was required under the FD&C Act.

[12] 76 FR 78530 (December 19, 2011). The IFR is a final rule implementing the pre-FDASIA section 506C. FDASIA significantly amended section 506C and requires FDA to initiate a new rulemaking process to implement the amended section 506C. FDA is in the process of developing a proposed rule for public comment implementing the new drug shortages provisions of FDASIA. Once final, the rule will supersede the IFR.

[13] As a complement to the IFR, the Agency also published a draft guidance for industry on drug shortages on February 21, 2012, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292426.pdf. The draft guidance was issued for public comment, and: (1) further discussed the Agency's interpretation of the mandatory early notification requirements in the IFR; (2) explained a policy of encouraging additional voluntary reporting; and (3) discussed the role that manufacturers play in preventing or responding to drug shortages, including that many shortages arise from quality or other issues experienced during the manufacturing process.

[14] Specifically, the requirement currently applies to prescription drugs that are not biologics, and that are: (1) life-supporting; life-sustaining; or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and "(2) … not a radio pharmaceutical drug product…." FD&C Act § 506C(a).

or unapproved) to notify FDA of a permanent discontinuance or (temporary) interruption in manufacturing. FDASIA also allows FDA to require, by regulation, early notification of discontinuances or interruptions in the manufacturing of biologics, and requires FDA to send a noncompliance letter to firms that fail to notify the Agency in accordance with FDASIA.[15]

B. Root Causes of Drug Shortages

In addition to understanding the legal and regulatory authorities related to drug shortages, it is important to explain why drug shortages occur. In most cases, a shortage is preceded by a production disruption (i.e., a discontinuance or interruption in manufacturing). Once a manufacturer experiences a discontinuance or interruption in manufacturing, a shortage will occur if there is no other manufacturer to step in to fill the gap in supply, or if other manufacturers cannot increase production quickly enough to make up the loss.[16]

A production disruption can be triggered by several factors, including a natural disaster or other unexpected event not within a manufacturer's control, or a business decision to permanently discontinue production of a drug (e.g., because the product is no longer profitable or is less profitable than other products that could be produced with the limited production capacity available to the firm) (Figure 2).

More often, however, failures in product or facility quality are the primary factor leading to disruptions in manufacturing (Figure 2). In 2012, for example, based on information collected from manufacturers, FDA determined that the majority of production disruptions (66%) resulted from either (1) efforts to address product-specific quality failures (31%, labeled Quality: Manufacturing Issues in Figure 2) or (2) broader efforts to remediate or improve a problematic manufacturing facility (35%, labeled Quality: Remediation Efforts in Figure 2). Quality or manufacturing concerns can involve compromised sterility, such as roof leakage; mold in manufacturing areas; or unsterilized vials or containers to hold the product—issues that could pose extreme safety risks to patients.

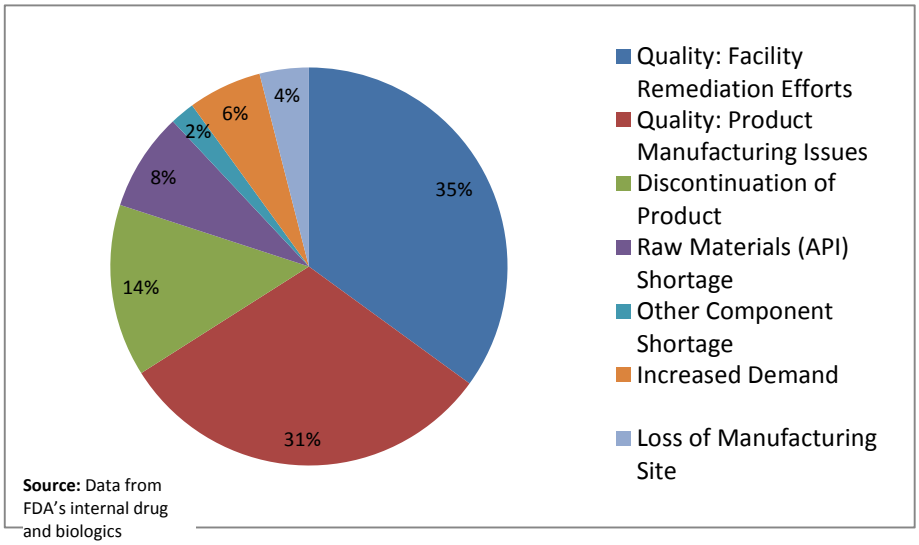
Since 2011, the number of shortages associated with shutdowns or slowdowns in manufacturing to address overall facility quality (remediation) has not changed significantly, although there has been a decline in the number of shortages due to quality concerns related to a specific product (e.g., particulates, contamination). Remediation efforts can lead to a short-term risk of a shortage for specific products while facility upgrades are made, but this risk is balanced by the

[15] Under FDASIA, FDA must issue a final rule implementing certain of the FDASIA shortages provisions by January 9, 2014.

[16] *See* Woodcock J, Wosinska, M. Economic and technological drivers of generic sterile injectable drug shortages. *Clin Pharmacol Ther*. 93:170-176 (2013), pp. 174-75 (discussing why one manufacturer's disruption in supply may result in a market-wide shortage).

expectation that improvements will lead to long-term, stable, high-quality manufacturing capacity, thus reducing the long-term risk of shortages.[17]

Figure 2. Drug Shortages by Primary Reason for Disruption in Supply in 2012



Source: Data from FDA's internal drug and biologics shortages databases.

C. Current FDA Efforts to Prevent and Mitigate Drug Shortages

Preventing or mitigating drug shortages requires a careful and coordinated response by FDA, which begins with a notification to FDA of a potential disruption in supply. This notification allows FDA to assess the risk of a shortage developing and subsequently deploy one or more regulatory tools, as appropriate, to prevent or mitigate the shortage. FDA largely focuses its efforts on ensuring that a disruption in production does not result in a shortage, or on mitigating the impact of the shortage should it become unavoidable.

1. Notifying FDA of a Disruption in Supply

The most important way to prevent or mitigate a drug shortage is for FDA to learn about a disruption in production as soon as possible. The sooner FDA is notified of a discontinuance or interruption in manufacturing, the more time FDA has between the disruption and the potential shortage to help coordinate the manufacturers' response. Notification of a disruption in production can come from a variety of sources outside the agency, including a drug manufacturer, a professional organization, interest groups, patients, and health care professionals, or through internal channels at FDA. Since the Executive Order was issued in

[17] Berg N, Kos K, et al. Report on the ISPE 2013 Drug Shortages Survey. June 2013. Tampa, FL: International Society for Pharmaceutical Engineering. Available at http://www.ispe.org/drugshortages/2013JuneReport.

October 2011, FDA has seen a six-fold increase in the number of notifications from manufacturers (from 10 notifications per month prior to the Executive Order to an average of 60 per month since the Executive Order). These early notifications have had a direct impact on the number of shortages FDA has been able to prevent.

2. Assessing the Risk of Shortage

Once FDA's shortage staff has been alerted to a discontinuance or disruption in production, they first verify if an actual shortage exists or may occur. The shortage staff may take the following actions to do this:

- Use a market research database to collect initial information to determine whether or not the current supply of product across manufacturers is stable
- Contact product manufacturer(s) to collect up-to-date inventory information, rate of demand (units/month), manufacturing schedules, and any changes in ordering patterns. Although manufacturers are not required to provide this information to FDA, voluntarily sharing this information greatly facilitates the management of shortages
- Evaluate product inventory in the distribution chain to the extent possible. This information can help predict how quickly a shortage may develop (if at all)

Additional information on how FDA collects and uses data to assess the risk of a shortage can be found in Appendix C.

When the shortage staff determines that a shortage either exists or is likely to occur imminently, shortage staff members lead and coordinate the mitigation efforts with multiple other offices within FDA. Working with FDA's drug review division and/or professional organizations, they determine if the drug is medically necessary.[18] FDA uses the information about whether or not a drug is medically necessary to prioritize its response to a shortage overall and to inform the risk-benefit assessment for the specific product in question.

3. Mitigating an Actual or Imminent Shortage

Mitigation efforts begin once FDA has confirmed that a shortage exists or could occur and that the drug is medically necessary. The actions FDA can take to mitigate a shortage include, as appropriate:

- Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap

[18] 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 in adequate supply that is judged by medical staff to be an appropriate substitute. Off-label uses are taken into account when making medical necessity determinations. CDER MAPP 6003.1, Drug Shortage Management at 2, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf.

- Expedite FDA inspections and reviews of submissions from manufacturers attempting to restore production
- 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
- Exercise temporary enforcement discretion for new sources of medically necessary drugs
- Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
- Develop risk mitigation measures for a batch(es) of product initially not meeting established standards

FDA may use one or more of these mitigation tools, or may seek to develop other options, depending on the severity of the shortage and the circumstances surrounding the shortage. When selecting specific tools, FDA continues to work with the manufacturer to tailor its response to the specific situation. FDA also frequently communicates available information about a shortage to affected stakeholders and monitors a shortage until it is resolved. Additional information on how FDA collects and uses data to manage a shortage can be found in Appendix C.

It is important to note that FDA's standards of safety, efficacy, and quality do not change in a shortage situation. FDA's preferred solution to a shortage is a supply of approved drugs sufficient to meet patient demand. However, FDA recognizes that there can also be risks to patients when treatment options are not available for critical conditions, and understands the importance of using the appropriate tools to prevent or mitigate a shortage. FDA also makes certain that drug shortages are considered before taking an enforcement action or issuing a Warning Letter. In appropriate cases, temporary exercise of regulatory flexibility has proven to be an important tool in ensuring access to treatment options for health care practitioners and patients in critical need.

For example, when particulate matter (including glass and metal particles) was found in an injectable drug product that was medically necessary and vulnerable to shortage, FDA exercised discretion to allow distribution of the product along with a letter, included in the drug's packaging, warning health care professionals to use a filter when administering the drug. The exercise of discretion was temporary, and was conditioned on the manufacturer's ability to demonstrate to FDA that the filter did not affect the way the drug works and could successfully remove the particulate. FDA also worked with the manufacturer while the manufacturer identified and addressed the root cause of the problem, so that it could resume producing a drug product that did not need the work-around involving the filter. In the last two years, FDA has exercised temporary regulatory flexibility involving the use of filters for eight important drugs, including life-saving components of IV nutrition for newborns, children, and other patients who are unable to eat or drink by mouth.

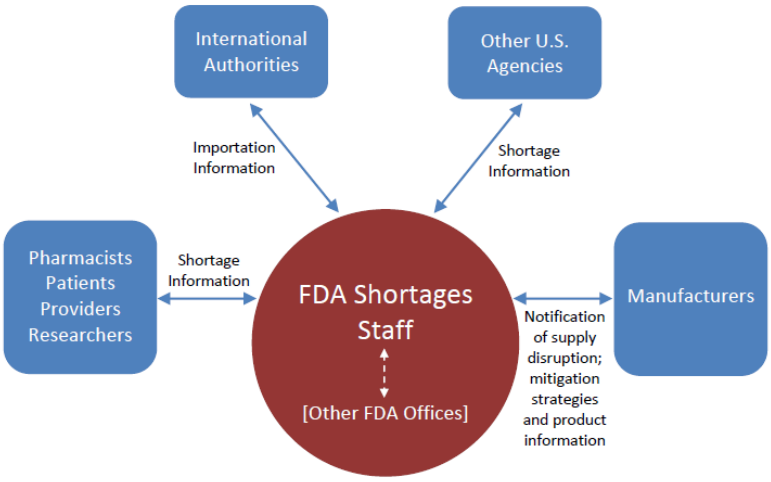
In contrast, a drug that is contaminated with bacteria or fungi presents a more extreme risk to patients, one that cannot be mitigated through a work-around such as the one described above. In such cases, the manufacturer must correct the conditions leading to the contamination before the product is safe for use, even if correcting the conditions ultimately leads to a shortage. Each

situation must be carefully evaluated to determine the public health impact, keeping in mind that a given action may have unintended, and potentially long-term, consequences.[19]

D. Internal and External Communication and Engagement

FDA communication and collaboration processes are essential to effectively prevent and manage drug shortages. These types of interactions, both internally and externally, occur in a variety of ways and with a variety of stakeholders (Figure 3).

Figure 3. Internal and External Communication During Shortage Management



1. Internal Coordination

The Agency's response to a notification of a discontinuance or production disruption involves multiple offices within FDA and often requires a cross-functional team of up to 25 individuals to respond to a specific shortage or potential shortage. Appendix D lists examples of specific offices and their roles in managing drug shortages. Appendix E lists specific examples of the types of communication that occur within the Center for Drug Evaluation and Research (CDER) to manage a drug shortage.

In response to the recent increase in drug shortages, CDER has nearly tripled the number of staff directly responsible for shortages, from 4 employees in 2011 to 11 employees in 2013. The office has also been elevated within the Center to indicate the priority FDA has placed on this topic. Although this staff serves as the primary point of contact for drug shortage-related issues, shortage staff members work with a large number of other offices and divisions within FDA.

[19] For example, if the use of enforcement discretion signals to industry that FDA is willing to exercise flexibility to ensure the availability of any critical product, this could create a long-term disincentive for manufacturers to invest in manufacturing upgrades or other quality improvements to avoid disruptions in supply, exacerbating the risk of shortages over the long term.

2. External Communication and Engagement

In addition to internal communication and coordination to facilitate FDA decision-making, it is essential for FDA to adequately maintain communication with the many external groups affected by drug shortages, including patients, health professionals, federal partners, and international groups. Appendix F describes these communications in greater detail.

One straightforward and accessible method for enhancing communication with these groups has been through FDA's website. In response to feedback from numerous stakeholders, including those who responded to the *Federal Register* notice, FDA has significantly improved its drug and biologics shortage websites in the past year. For example, CDER's website now includes the following features:

- More frequent updates to the CDER shortage website, including biweekly updates on postings from manufacturers about progress on specific shortages
- Icons to highlight *new* listings and *update* dates
- Improved layout for easier navigation, including the creation of a Current Drug Shortage Index, and separating the shortage list into sections of the alphabet for each page
- Information about the causes of shortages
- A page for additional news and information, such as extensions of expiry date for a specific lot of product to prevent shortage

Another important shortage website is maintained by the American Society of Health-System Pharmacists (ASHP) and the Drug Information Service at the University of Utah.[20] FDA, the Drug Information Service, and ASHP exchange information on a routine basis, sharing notifications and public information on the status of the drug supply. This collaborative effort has greatly improved FDA's ability to monitor product disruptions. ASHP's website also provides recommendations about therapeutic alternatives.

Communication with manufacturers is also a key component of FDA's coordination efforts. FDA's drug shortages staff interact with manufacturers on an ongoing basis to understand specific issues related to possible or ongoing shortages. For example, when the shortage staff hears about a potential disruption in production, FDA may contact other manufacturers to see if they have experienced an increase in demand; determine the status of their on-hand supply; and if a shortage appears imminent, determine whether the manufacturer is willing to initiate or increase production. FDA then works with those manufacturers as they increase production.

During a shortage, FDA also continues to work with the manufacturer causing the shortage to aid in recovery efforts. For instance, when a firm shuts down to address manufacturing and/or quality problems, FDA works with the firm as it remediates the problem to restore or maintain the availability of critical medicines. To maintain some level of supply during remediation, FDA may recommend creating a priority list that emphasizes continued manufacture of shortage

[20] Available at http://www.ashp.org/shortages.

products; encourage allocation programs to hold back supply of shortage products; or recommend third-party quality review for release of manufactured batches.

Finally, FDA understands the important role that the public plays in discussing and identifying solutions to drug shortage issues. FDA is actively involved in meetings with outside stakeholders to help guide FDA's regulatory and policy decision making, as well as to increase our understanding of the issues facing these stakeholders. In 2012, FDA staff participated in more than 45 such meetings with academics, patient groups, pharmacy organizations, distributors, and manufacturers.

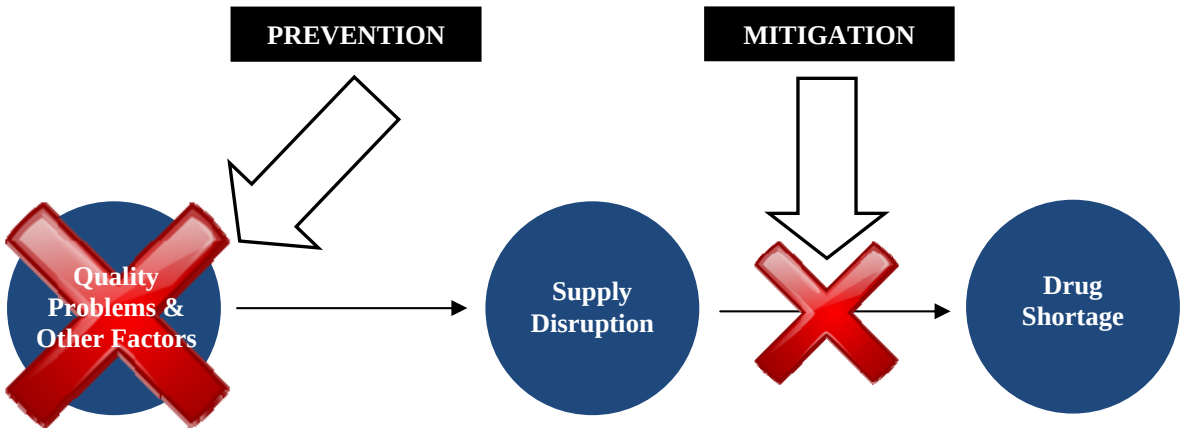
II. Continuing Progress: FDA's Strategic Plan

As described previously, Title X of FDASIA requires FDA to establish a task force to develop and submit to Congress a Strategic Plan to enhance FDA's ability to address drug shortages. In response, FDA convened a Task Force representing multiple centers, offices, and disciplines within FDA. The Task Force has identified two central goals and related tasks for FDA to focus on to address drug shortages, stated below. Specific tasks are discussed in further detail in the sections that follow.

Goal #1	**STRENGTHEN MITIGATION RESPONSE.** Improve and streamline FDA's current mitigation activities once the Agency is notified of a supply disruption or shortage.
Goal #2	**DEVELOP LONG-TERM PREVENTION STRATEGIES.** Develop prevention strategies to address the underlying causes of production disruptions to prevent drug shortages.

As depicted in the Figure 4, mitigation activities are directed at preventing supply disruptions from turning into actual shortages. Long-term prevention strategies are intended to address the underlying causes of shortages to prevent supply disruptions from occurring in the first place.

Figure 4. Addressing Drug Shortages: Mitigation Activities and Long-Term Prevention



A. GOAL #1: Strengthen Mitigation Response

The Task Force identified the following tasks to strengthen FDA's ability to respond to a notification of a production disruption to prevent a shortage or to mitigate an unavoidable shortage.

TASK 1.1: Develop and/or Streamline Internal FDA Processes

While coordinating the increased number of drug shortages over the last few years, FDA has continued to improve its approaches to the management of shortages. Revising and standardizing procedures will more accurately reflect and enhance the working interactions between units within FDA and will maximize the efficiency of FDA's response to a shortage. As a part of this work, the Center 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.[21] In addition, CDER is revising its Manual of Policies and Procedures (MAPP) on Drug Shortage Management.[22] Specifically, FDA intends to:

- Standardize the risk-benefit assessment process prior to compliance actions[23]
- Update the process for interacting with the Drug Enforcement Administration (DEA) in the event of a shortage of a controlled substance, including updating a memorandum of understanding between the two agencies that will improve the sharing of important information
- Develop and implement a process for issuing a noncompliance letter for failure to notify FDA as required by FDASIA
- Explore new approaches to extend expiration dating to temporarily mitigate a shortage

TASK 1.2: Improve Data and Response Tracking

FDA is working to improve its databases related to shortages and the tracking procedures it uses to manage them. FDA has several databases that it uses to support efforts to address shortages, but they were not created specifically for the purposes of assisting shortage-related activities.[24]

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[21] CBER Standard Operating Policy and Procedure 8506, Management of Shortages of CBER-Regulated Products, available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm299304.htm.

[22] CDER MAPP 6003.1, Drug Shortage Management.

[23] This work is also responsive to FDASIA, which directed FDA to evaluate certain risks and benefits prior to an enforcement action or issuance of a warning letter that could reasonably be expected to lead to a meaningful disruption in the supply of a drug covered by section 506C. FD&C Act § 506D(c).

[24] Examples include databases supporting the Orange and Red Books, and the databases that collect information about the inspections of manufacturing facilities.

In addition to these more general databases, CDER has created a dedicated database that focuses solely on collecting data related to shortages. This improved tracking 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.

TASK 1.3: Clarify Roles/Responsibility of Manufacturers

Patients expect and deserve high-quality drugs, and it is the manufacturer's responsibility to ensure that its products are safe, effective, and of high quality. FDA is committed to working with industry to resolve quality or manufacturing problems that arise, or avoid them if possible. Where justified, FDA may exercise regulatory flexibility to prevent or mitigate a shortage. To facilitate its work with industry, FDA intends to:

- Finalize the proposed rule on Notification to FDA of a Discontinuance or Interruption in Supply of Certain Drug or Biological Products
- Work with manufacturers as needed to remediate manufacturing problems, facilitate their return to full production, and discuss how to prioritize drugs in shortage as they address manufacturing deficiencies
- Encourage manufacturers to engage in practices to avoid or mitigate shortages. These practices are listed in the table below:

Practices to Avoid or Mitigate Shortages	
Create Allocation Plans	Design an allocation plan in advance, in the event that a product shortage occurs.
Communicate with Contract Manufacturing Organizations	Communicate frequently with contract manufacturers to ensure up-to-date knowledge of their manufacturing processes and facilities and to anticipate potential problems that might lead to a shortage
Manage Inventory	Build robust inventories before major manufacturing changes, such as upgrades to manufacturing facilities or transfer of facility ownership
Develop Short- and Long-Term Proposals	Provide short- and long-term proposals to address issues that could cause a shortage, either as part of the notification to FDA of a potential shortage or shortly thereafter
Communicate with FDA	Engage in dialogue with FDA to work on a long-term solution to a shortage, including remediation efforts
Investigate Root Causes	Provide a realistic timeline for investigation of product defects and scheduled restart after shut downs
Consider Clinical Trials	Consider the possibility of shortages during initial clinical trial design and developing and implementing contingency plans for handling a shortage during the clinical trial, should one arise (see Appendix F for additional discussion of this point).

TASK 1.4: Enhance Public Communications about Drug Shortages

Comments received in response to the *Federal Register* notice made clear that ongoing efforts by FDA to improve external communications have enhanced our response to shortages or potential

shortages. Additionally, groups requested up-to-the-minute and customized information about shortages. FDA will continue to improve our public communications about drug shortages by:

- Developing a smartphone application so that individuals can access the drug shortage information currently posted online instantaneously from their mobile phones or tablets
- Updating the website to include the therapeutic category (or categories) for the products listed in shortage
- 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. GOAL #2: Develop Long-Term Prevention Strategies

Developing long-term strategies focused on the underlying causes of production disruptions can, ultimately, prevent drug shortages. Efforts to build on existing tools to mitigate or prevent existing shortages are an important piece of the Strategic Plan. However, a comprehensive strategy must also recognize the importance of addressing the underlying causes of shortages, including sustaining manufacturing quality. While keeping in mind the role other stakeholders play in ensuring manufacturing quality, FDA is also exploring actions it can take, both alone and in collaboration with other groups.

TASK 2.1: Develop Methods to Incentivize and Prioritize Manufacturing Quality

The majority of drug shortages are the result of production disruptions caused by manufacturing problems, particularly problems that affect product quality (see Figure 2). Ultimately, prevention of future drug shortages means improving the quality of manufacturing facilities and manufactured products. In addition to regulatory enforcement, FDA is exploring what it can do to provide more positive incentives for quality improvements and to make manufacturing quality a priority, taking into account the responses we received to the *Federal Register* notice. For example, FDA is:

- Examining the broader use of manufacturing quality metrics to assist in the evaluation of product manufacturing quality
- Implementing internal organizational improvements to focus on quality, including the creation of an Office of Pharmaceutical Quality within CDER
- Considering public recognition of manufacturers who have demonstrated a consistent record of high quality manufacturing
- Continuing expedited review to mitigate shortages, including the review of submissions for facility upgrades to improve quality

TASK 2.2: Use Regulatory Science to Identify Early Warning Signals of Shortages

Understanding the factors contributing to supply disruptions and drug shortages and identifying potential warning signals of future production disruptions could help FDA and manufacturers in their efforts to prevent them. However, identifying these factors and signals is a challenging

undertaking. To further this effort, FDA will explore risk-based approaches to identifying the early warning signals of manufacturing and quality problems that could lead to production disruptions. In addition, to gain a better understanding of the factors and forces contributing to manufacturing and quality problems, FDA will work with stakeholders to identify vulnerabilities at manufacturing sites that could put the production of quality drugs at that facility at risk, and thereby contribute to shortages.

TASK 2.3: Increase Knowledge to Develop New Strategies to Address Shortages

A wide variety of stakeholders have collected and analyzed data on drug shortages and potential approaches to their prevention, and it is essential that FDA continue to work with these stakeholders to fill gaps in our understanding of issues around shortages. This additional information could help inform new strategies to address shortages. Specifically, FDA intends to:

- Work with the International Society for Pharmaceutical Engineering (ISPE) to analyze data from a recent global survey ISPE conducted on the technical, scientific, manufacturing, quality, and compliance issues that have resulted in drug shortages
- Join with other stakeholder groups, such as groups convened by the American Society of Anesthesiologists and ASHP, and with individual companies, patient groups, and group purchasing organizations to discuss shortages
- Work with manufacturers to identify *best practices* for avoiding disruptions in production
- Continue to explore (through the Department of Health and Human Services) the potential benefit, and assess the identified challenges, of establishing a Qualified Manufacturing Partner Program (QMPP)[25]

III. Actions Other Stakeholders Should Consider

FDA can play a significant role in addressing drug shortages and has identified several additional ways to enhance its efforts. It is clear, however, that FDA cannot address the threat of drug shortages alone. Success in addressing drug shortages requires a collective effort by all stakeholders—manufacturers, federal partners, researchers, professional organizations, and patients. In preparing this Strategic Plan, FDA has identified four key areas that merit consideration by the broader community for their potential to reduce drug shortages. FDA limitations in these areas and possible roles for others are discussed in the following sections.

[25] FDASIA requires FDA to examine the value of establishing a QMPP. FDA asked for public input on the feasibility and advisability of a QMPP in the *Federal Register* notice. We asked commenters to address several significant challenges FDA identified with such a program, including lack of funding to incentivize participation and a potentially unlimited scope of applicable products. Many public comments supported the idea of a QMPP, but did not address the challenges FDA raised. In follow up to these comments, the Department of Health and Human Services will explore further the feasibility of creating a QMPP.

A. Manufacturing Incentives

Advances in drug discovery and development have been and continue to be encouraged and supported through a variety of economic incentives, such as listed patent protection, various forms of statutory market exclusivity, and tax credits. Yet, the need for innovation goes beyond drug discovery and approval—manufacturing processes and technologies must keep pace with advances in drug research and development. In many cases pharmaceutical manufacturing processes, facilities, and equipment lag behind innovation in drug development. Some processes and facilities have become outdated, resulting in quality problems that can lead to drug shortages.

FDA Limitations: FDA is exploring ways to use its existing authorities to promote and sustain quality manufacturing. However, our ability to offer financial or other economic means to promote innovation in quality manufacturing is limited.

Opportunities for Others: Given the importance of quality and its link to shortages, other stakeholders might explore economic, financial, or other means to incentivize innovation and new investments in manufacturing quality drugs to reduce the occurrence and severity of shortages.

B. Use of Data on Manufacturing Quality

Within the limits set by disclosure law, FDA makes certain information publicly available about the historical ability of manufacturers to produce quality products. Several indicators of historical quality, including a manufacturer's history of inspection outcomes and classification, recalls, and shortages, are publicly available. Nevertheless, numerous comments to the *Federal Register* notice suggested that buyers (e.g., hospitals, health maintenance organizations, group purchasing organizations, and others) do not consider or value this potentially important information. This decoupling of quality considerations from purchasing decisions makes cost the major factor in purchasing decisions, most likely intensifying price competition, leading manufacturers to focus more on reducing costs than on maintaining quality, and potentially contributing to shortages.

FDA Limitations: Although FDA makes certain quality information public, buyers ultimately decide how or whether they will use this data when they make purchasing decisions.

Opportunities for Others: An effort by buyers to use publicly available information to take quality into account when making drug purchasing decisions—for example, by buying only from manufacturers with a history of good quality, or including "failure to supply" clauses in purchasing contracts—could further incentivize manufacturers to invest in quality improvements, and ultimately prevent drug shortages.

C. Redundancy, Capability, and Capacity

A disruption in supply is exacerbated by limited manufacturing capacity and capability, market concentration, and just-in-time inventory practices that result in minimal product inventory being on hand at any given time. If these factors are present, a disruption in supply is more likely to result in a nationwide shortage. Many stakeholders, including commenters to the *Federal Register* notice, have suggested that building redundancy, holding spare capacity, and increasing inventory levels could lower the risks of shortages.

FDA Limitations: FDA does not regulate manufacturing concentration and cannot require redundancy of manufacturing capability or capacity. Nor can FDA require a company to manufacture a drug, maintain a certain level of inventory of drug product, or reverse a business decision to cease manufacturing.

Opportunities for Others: Manufacturers could explore building redundant manufacturing capacity, holding spare capacity, or increasing inventory levels to lower the risks of shortages. Other stakeholders could consider how to incentivize such practices.

D. The Gray Market

In the context of drug shortages, the term *gray market* is often used to reference the downstream distribution of approved drug products at significantly marked-up prices. A shortage offers a unique opportunity for this to occur, because large-scale buyers are often willing to pay any price to obtain a much-needed product in short supply. When a gray market distributor handles a product that it normally would not distribute, there can also be safety issues that put patients at risk – if, for example, the product is not stored or handled appropriately. These activities do not cause shortages, but may exacerbate the impact of an existing shortage.

FDA Limitations: FDA has limited data on the gray market and limited influence on its workings (including no authority regarding product pricing). However, there is evidence that gray market activities exacerbate the impact of drug shortages.

Opportunities for Others: Actions on the part of other stakeholders to minimize gray market activities could play a role in mitigating the impact of shortages and reducing risks to patients.

Conclusion

Drug shortages remain a significant public health issue in the United States and a top priority for FDA. FDA works with manufacturers to help prevent shortages from occurring. In this respect, early and open dialogue between FDA and manufacturers is critical to successfully preventing a shortage. Because of recent important actions by the President and Congress, FDA has been able to learn of many possible shortages before they occur. These actions, along with increases in the

resources FDA is devoting to drug shortages, have helped prevent numerous recent shortages—more than 280 in 2012.

Despite these achievements, substantial challenges remain, and more work is needed on the part of manufacturers and other relevant stakeholders. This Strategic Plan identifies a number of activities to improve the Agency's ability to address drug shortages. Activities center around two key goals: (1) strengthening FDA's ability to respond to notices of a disruption in supply, including improving our mitigation tools, and (2) developing long-term strategies to prevent drug shortages by addressing the underlying causes of shortages.

FDA recognizes that manufacturers and other stakeholders have important roles to play in ensuring that drugs are available to the patients who need them. Thus, the Task Force has also identified actions outside stakeholders can consider that show promise in helping to prevent shortages.

FDA looks forward to implementing this Strategic Plan as part of a collaborative and sustained effort to address drug shortages in the United States.

APPENDIX A: Federal Register Notice

http://www.gpo.gov/fdsys/pkg/FR-2013-02-12/html/2013-03198.htm

[Federal Register Volume 78, Number 29 (Tuesday, February 12, 2013)]
[Notices]
[Pages 9928-9929]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2013-03198]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
[Docket No. FDA-2013-N-0124]
Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments
AGENCY: Food and Drug Administration, HHS.
ACTION: Notice; request for comments.

SUMMARY: To assist the Food and Drug Administration (FDA or Agency) in drafting a strategic plan on drug shortages as required by the Food and Drug Administration Safety and Innovation Act, the Agency is seeking public comment from interested persons on certain questions related to drug and biological product shortages.
DATES: Submit either electronic or written comments by March 14, 2013.
ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-0124, by any of the following methods:
Electronic Submissions:
Submit electronic comments in the following way:
Federal eRulemaking Portal: http://www.regulations.gov.
Follow the instructions for submitting comments.
Written Submissions:
Submit written submissions in the following way:
Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-0124. All comments received may be posted without change to http://www.regulations.gov, including any personal information provided. For additional information on submitting comments, see the ``Comments'' heading of the SUPPLEMENTARY INFORMATION section of this document.
Docket: For access to the docket to read background documents or comments received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the ``Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
FOR FURTHER INFORMATION CONTACT: Kalah Auchincloss, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6208; Silver Spring, MD 20993, 301-796-0659.
SUPPLEMENTARY INFORMATION:
I. Background
On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144). Section 1003 of FDASIA adds section 506D to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to require the formation of a task force to

develop and implement a strategic plan for enhancing the Agency's response to preventing and mitigating drug shortages. Section 506D of the FD&C Act (21 U.S.C. 356D) requires that the drug shortages strategic plan include the following:

-Plans for enhanced interagency and intra-agency coordination, communication, and decisionmaking;

-Plans for ensuring that drug shortages are considered when the Secretary initiates a regulatory action that could precipitate a drug shortage or exacerbate an existing drug shortage;

-Plans for effective communication with outside stakeholders, including who the Secretary should alert about potential or actual drug shortages, how the communication should occur, and what types of information should be shared;

-Plans for considering the impact of drug shortages on research and clinical trials; and

-An examination of whether to establish a ``qualified manufacturing partner program'' as described in section 506D(a)(1)(C) of the FD&C Act.

II. Scope of Public Input Requested

Per the directive in section 506D, FDA has formed an internal Drug Shortages Task Force (Task Force) to develop and implement the drug shortages strategic plan. The Task Force is seeking comments from the public on issues related to the development of this strategic plan. Importantly, although FDASIA refers only to a drug shortages strategic plan, we anticipate that the strategic plan will consider prevention and mitigation of both drug and biological product shortages. Accordingly, we are interested in receiving comments on these questions from all parties, including those with an interest in biological products. The Task Force is specifically interested in seeking public input on the following questions:

1. In an effort to address the major underlying causes of drug and biological product shortages, FDA is seeking new ideas to encourage high-quality manufacturing and to facilitate expansion of manufacturing capacity.

a. To assist in the evaluation of product manufacturing quality, FDA is exploring the broader use of manufacturing quality metrics. With that in mind, FDA would like input on the following issues: What metrics do manufacturers currently use to monitor production quality? To what extent do purchasers and prescribers use information about manufacturing quality when deciding how to purchase or utilize products? What kinds of manufacturing quality metrics might be valuable for purchasers and prescribers when determining which manufacturers to purchase from or which manufacturers' products to prescribe? What kinds of manufacturing quality metrics might be valuable for manufacturers when choosing a contract manufacturer? How frequently would such metrics need to be updated to be meaningful?

b. The use of a qualified manufacturing partner program similar to one used under the Biomedical Advanced Research and Development Authority (BARDA) has been suggested as a potentially useful approach to expanding manufacturing capacity and preventing shortages. FDA recognizes that there are important potential differences between the BARDA program and the use of a parallel program to address shortages. For example, the BARDA program covers a relatively stable and limited number of products, but drugs at risk of shortage are many, may change rapidly over time, and are difficult to predict in advance. In addition, FDA does not have funding to pay manufacturers to participate in a drug shortages qualified manufacturing partner program or to

guarantee purchase of the end product. With these differences in mind, is it possible to design a qualified manufacturing partner program that would have a positive impact on shortages?

c. Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and/or to create other conditions to prevent or mitigate shortages?

2. In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies. Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?

3. When notified of a potential or actual drug or biological product shortage, FDA may take certain actions to mitigate the impact of the shortage, including expediting review of regulatory submissions, expediting inspections, exercising enforcement discretion, identifying alternative manufacturing sources, extending expiration dates based on stability data, and working with the manufacturer to resolve the underlying cause of the shortage. Are there changes to these existing tools that FDA can make to improve their utility in managing shortages? Are there other actions that FDA can take under its existing authority to address impending shortages?

4. To manage communications to help alleviate potential or actual shortages, FDA uses a variety of tools, including posting information on our public shortages Web sites and sending targeted notifications to specialty groups. Are there other communication tools that FDA should use or additional information the Agency should share to help health care professionals, manufacturers, distributors, patients, and others manage shortages more effectively? Are there changes to our public shortage Web sites that would help enhance their utility for patients, prescribers, and others in managing shortages?

5. What impact do drug and biological product shortages have on research and clinical trials? What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?

6. What other actions or activities should FDA consider including in the strategic plan to help prevent or mitigate shortages?

III. Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

Dated: February 7, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-03198 Filed 2-11-13; 8:45 am]

APPENDIX B: Statutory Elements[26]

The following table indicates where in this Strategic Plan the reader can find discussion of specific topics required by FDASIA.

Element	Section & Task
Enhanced inter-agency and intra-agency coordination, communication, and decision-making	Task 1.1 Section I.C.2 Section II.A
Ensure drug shortages are considered before initiating a regulatory action that could precipitate or exacerbate a drug shortage	Task 1.1 Section 1.C.1
Effective communication with external stakeholders	Task 1.4 Task 2.3 Section I.C.2 Section II.A
Impact of drug shortages on research and clinical trials	Task 1.3 Section I.C.2
Examination of establishing a "qualified manufacturing partner program"	Task 2.3 Section II.B

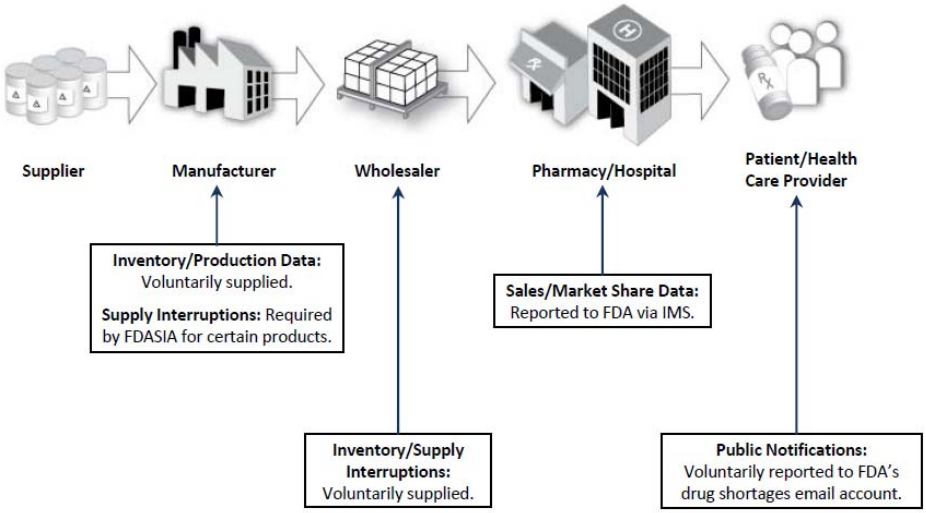
[26] Section 506D(a)(1)(B) (added by FDASIA) requires FDA to consider certain elements when developing the Strategic Plan.

APPENDIX C: Collecting Information on Drug Shortages

Recognizing the complexity of drug manufacturing and the importance of having up-to-date data to manage shortages, FDA draws on a variety of sources for information on whether a shortage exists and how best to manage a shortage. The table below lists various sources of information and the type of information obtained from each source. Figure 5 illustrates some of these sources of information in the context of the drug supply chain.

Source	Type of Information
Orange Book or Drugs@FDA	Information on therapeutic equivalents
National Drug Code (NDC) product directory	Identification of NDCs for products
Internal FDA databases	Information on managing and tracking drug and biologics license applications; inspections and registered manufacturing establishments; and lot distribution and release data
IMS Health (health care analytics firm)	Information on the pharmaceutical market, including historical supply and demand
Red Book	Information on current suppliers of products
Emails from prescribers, patients, pharmacies, manufacturers, and other stakeholders	Notifications of a disruption in supply and information on the impact of a shortage
ASHP shortage website	Additional information on existing shortages and therapeutic alternatives
Other agencies, such DEA, the Centers for Disease Control and Prevention (CDC), and NIH	Data on other factors that may be influencing the shortage

Figure 5. FDA's Key Supply Chain Information Sources



However, although extremely useful, these data provide only part of the picture. For example, key aspects of drug manufacture and distribution are not transparent, such as production schedules, distribution of production volume across various contract manufacturing facilities, the amount of inventory stored by a manufacturer, and wholesaler and pharmacy/hospital supply and purchasing practices. Additionally, the role that other sources of products (e.g., gray market distribution, compounding, unapproved drugs) play in contributing to shortages or in the reactions to shortages is not clearly understood.

APPENDIX D: FDA Offices Engaged in Drug Shortage Efforts

1. FDA's Drug Shortage Task Force

This overarching group, which includes individuals from across CBER, CDER, and the Office of Regulatory Affairs (ORA), was formed in 2012, per the directive in FDASIA. The Task Force coordinates the development of consistent policy with regard to FDA's handling of drug shortages, facilitates intra- and inter-agency communications around shortages, and provides a forum for individuals working on shortage issues within FDA to discuss policy issues related to shortages, including the development of this Strategic Plan.

2. CBER's Product Shortage Coordinator

The Product Shortage Coordinator within CBER's Office of Compliance and Biologics Quality, Immediate Office of the Director, is the primary contact for potential or actual shortages of biologics regulated by CBER. The relative infrequency of biologics shortages has enabled CBER to manage the workload with a shortage coordinator and staff support. When a potential or actual shortage is reported, CBER responds by gathering information through communications with manufacturers, other CBER and FDA offices, and external entities, such as ASHP, as well as through market research data when available. The CBER Product Shortage Coordinator is generally in close communication with other Department of Health and Human Services agencies, including the Biomedical Advanced Research and Development Authority (BARDA)[27] and the CDC. CBER can draw from an array of policy options when addressing a shortage situation, including: encouraging other manufacturers of the product (if available) to increase their production, expediting inspections of manufacturing facilities, and expediting review of biologics license applications, new drug applications, or abbreviated new drug applications.

To respond to the recent increase in shortages, CBER has revised its standard operating policy and procedure titled, *Management of Shortages of CBER-Regulated Products*[28]; created a new, robust database for internal tracking purposes; and significantly revised the CBER shortage website.

[27] Contracts for the procurement of medical countermeasures against chemical, biological, nuclear and radiological threat agents (e.g. smallpox and anthrax vaccines) are administered by BARDA, part of the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services (HHS). See http://www.hhs.gov/aspr.

[28] See CBER Standard Operation Policy and Procedure 8506.

3. CDER's Drug Shortage Staff

The CDER Drug Shortage Staff (DSS) is the primary contact for potential or actual shortages of products regulated by CDER. This group was established in 1999 and is located in the Office of the Center Director. DSS coordinates FDA's response to drug shortages and engages in the day-to-day management of specific shortages. DSS also works to integrate up-to-date information across products, manufacturers, review activities, and pending compliance actions to monitor shortages, and vulnerability for shortage, on an ongoing basis. Although the staff serves as the primary point of contact for shortage-related issues, it works with a large number of other offices and divisions within CDER and FDA.

To respond to the recent increase in shortages, CDER has made two major changes to the DSS. First, during the last two years, CDER has nearly tripled the number of staff directly responsible for shortages, from 4 employees in 2011 to 11 employees in 2013. Second, CDER elevated DSS from its original location within the Office of New Drugs to its current location in the Immediate Office of the Center Director. Now, DSS reports to the Deputy Director for Regulatory Programs. This location reflects the priority nature of responding to drug shortages for CDER and the reality that shortages affect both new drugs and generic products and require cross-functional coordination across CDER.

4. Office of Regulatory Affairs District Drug Shortage Coordinators

Communication between ORA and FDA's medical product centers is critical in effectively managing product shortages. District Drug Shortage Coordinators are the points of contact in each of the district offices. They are responsible for notifying the relevant center of any issue that has the potential to lead to a product shortage (e.g., information obtained during an inspection or other field activities). The creation of Field Management Directive (FMD) #15, Product Shortage Communication, in July 2012, established a mutual understanding of communication roles, responsibilities, and expectations involving both potential and current product shortage situations between ORA and the centers. Effective sharing of information and coordination of efforts has optimized the outcomes and use of resources by both ORA and center staff (e.g., when there is an emergency need to conduct an inspection to resolve a shortage issue).

5. CDER and CBER Offices of Compliance

Interaction and coordination with the Offices of Compliance in CDER and CBER (and ORA, as needed) are integral to the prevention and management of potential shortages. Located within CDER's Office of Compliance is the Office of Drug Security, Integrity and Recalls (ODSIR), and within ODSIR is the Recalls and Shortages Branch Shortage Coordination Team. This team ensures that the relevant CDER Compliance and ORA personnel are involved in a shortage issue and works diligently to coordinate efforts for the evaluating and determining whether to use enforcement discretion, as warranted by medical necessity, clinical and chemistry review, and shortage need.

6. Other Center Offices

The drug shortages staff in FDA centers also communicate extensively with other offices within CBER and CDER to determine the medical necessity of a product in shortage or at risk of shortage to assess whether there are pending applications in FDA that may address a shortage, to obtain information from clinicians and scientists to inform the risk–benefit calculation, and to work with communication specialists to alert the public about important drug shortage developments.

APPENDIX E: Coordinating Drug Shortage Efforts in CDER

The following table highlights the extensive coordination and interaction that takes place in CDER to assess and address a drug shortage.

Coordinating Offices	Examples of Information Shared	Examples of Decisions Made
DSS Office of New Drugs (OND)	DSS ⟶ OND[29] • Shortage evaluation • Marketing status, including whether alternate manufacturers are available OND ⟶ DSS • Evaluation of medical necessity, including off-label use and potential alternative therapies • Clinical perspective of risk–benefit calculation to inform whether enforcement discretion is appropriate • Information on review of supplements related to the drug in shortage	Medical necessity Revisions to proposed labeling and Dear Healthcare Provider letter to mitigate shortage
DSS Office of Compliance (OC)	OC ⟶ DSS • Compliance status of a foreign or domestic site • Compliance perspective of risk–benefit calculus, which may include a Health Hazard Evaluation DSS ⟶ OC • Medical necessity determination from OND • Shortage evaluation • Marketing status, including whether alternate manufacturers are available • Shortage memo, which provides the medical necessity determination and what may be	Warning Letter or other action Need for product recall Revisions to proposed labeling and Dear Healthcare Provider letter to mitigate shortage Expediting inspections to address shortage Temporary enforcement discretion to maintain availability of medically necessary drugs

[29] Arrows specify the direction of information flow. For example, in the first row, DSS → OND indicates that DSS shared with OND the shortage evaluation and marketing status.

	the impact of an enforcement action	
DSS OC Office of Regulatory Affairs (ORA)	<u>ORA/OC ⟶ DSS</u> • Upcoming firm decisions to recall that may impact an existing or potential drug shortage • Number of lots involved in recall, estimated impact to market of recall • Alternative product availability • Manufacturer assessment of risk involved with product and proposed risk mitigation strategy • Alternatives to product recall, if any <u>DSS ⟶ ORA/OC</u> • Shortage evaluation • Marketing status, including whether alternate manufacturers are available	Need for product recall
DSS Office of Generic Drugs (OGD) Office of Pharmaceutical Science (OPS)	<u>DSS ⟶ OGD/OPS</u> • Shortage evaluation • Marketing status, including whether alternate manufacturers are available • Medical necessity determination from OND • Pending shortage due to product expiration (if applicable) <u>OGD/OPS ⟶ DSS</u> • Assessment of pending applications in-house for products in shortage • Chemistry and microbiology perspective of risk–benefit calculus • Assessment of potential extension	Expediting review Enforcement discretion on supplement filing category Enforcement discretion on post-market commitments Extension of shelf life/expiration dating

	of shelf life based on data from manufacturer	
DSS OND OGD OPS OC ORA	<u>DSS ⟶ OND/OGD/ OPS/OC/ORA</u> • Shortage evaluation • Marketing status, including whether alternate manufacturers are available <u>OND ⟶ DSS</u> • Medical necessity determination • Clinical perspective of risk–benefit calculus <u>OGD/OPS ⟶ DSS</u> • Chemistry and microbiology perspective of risk involved and how to address <u>OC and/or ORA ⟶ DSS</u> • Compliance status of a foreign or domestic site • Compliance and ORA perspective of risk involved and how to address	Actions on import-related issues
DSS Office of Communications (OCOMM)	<u>DSS ⟶ OCOMM</u> Information relevant to shortage that may need to be broadly communicated to public, such as recalls or resolution of the shortage	Press release, Frequently Asked Questions (FAQ) document, or other form of communication to the public to convey necessary information (in addition to posting on DSS website)

APPENDIX F: Communicating With External Groups

1. Patients, Prescribers, and Pharmacists

Keeping the public informed about shortages is essential to help support the fullest access possible to drugs in shortage and to ensure that patients, prescribers, and others are aware of progress in resolving each drug shortage. CBER and CDER maintain shortage websites as key resources for external stakeholders.[30] Since they were first launched, these FDA websites have served as a vehicle for making publicly available the latest information provided by manufacturers on each shortage, including information about the reasons for the shortage, places where additional information can be found (e.g., company contacts for allocations of products in shortage), and any estimates on when a given shortage might be resolved. FDA updates this information daily. The websites also include links to resolved shortages (once FDA determines that the shortage is over).

FDA also employs a wide range of other tools to communicate information about drug shortages to specific populations. These include collaborating with manufacturers on information sent directly to health care professionals in the form of Dear Healthcare Provider letters, press releases, and communications with groups representing specific patient populations affected by a particular drug shortage. For example, FDA worked closely with the American Society of Parenteral and Enteral Nutrition on recent shortages of components of total parenteral nutrition, including trace elements, which provide essential nutrients for patients (including neonates) who are unable to eat or drink by mouth.

2. Clinical Researchers and Sponsors of Clinical Trials

One particularly challenging issue that has confronted industry and the academic community is consistent access to products for use in clinical trials. FDA recognizes that shortages may affect clinical research and the conduct of clinical trials. Generally, shortages affect trials designed to compare a new product with an existing product. For example, according to comments in response to the *Federal Register* notice, many oncology trials and studies of new antibiotics use such a design—i.e., comparing a candidate drug to one already approved, rather than using a placebo controlled clinical trial. If the approved drug goes into shortage, the trial may need to be delayed or stopped, halting research on important new products. FDA is continuing to explore how shortages affect clinical trials and how best to address this issue. While FDA works to identify long-term solutions, we encourage trial sponsors to consider the possibility of shortages during initial trial design and to develop and implement contingency plans for handling a shortage, should one arise.

[30] For drugs and therapeutic biologics regulated in CDER, see http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm. For products regulated by CBER, see http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm.

3. Manufacturers

Ultimately, shortages cannot be resolved until one or more manufacturers commit to fill in for lost production. FDA is in a unique position to coordinate such a response.

FDA's drug shortages staff interacts with manufacturers on an ongoing basis to understand specific issues related to possible or ongoing shortages. For example, when the shortage staff hears about a potential disruption in production, FDA contacts other manufacturers to see if they have experienced an increase in demand; determines the status of their on-hand supply; and when a shortage looms, determines if they are willing to initiate or increase production to cover expected gaps in supply. FDA then works with those manufacturers in their efforts to increase production.

During a shortage, FDA continues to work with manufacturers to aide in recovery efforts. For instance, when a firm shuts down to address manufacturing and/or quality problems, FDA works with the firm as it remediates to maintain the availability of critical medicines.

To maintain some level of supply during remediation, FDA may recommend creating a priority list that emphasizes continued manufacture of shortage products; encourage allocation programs to hold back supply of shortage products; or recommend third-party quality review for release of manufactured batches. FDA may also work with the manufacturer to assist it in providing drop shipments[31] of available supply to hospitals to speed the delivery of the drug to patients. If new raw materials are needed, FDA can facilitate the qualification of new or additional sources of raw materials.

4. Other Governmental Agencies

FDA recognizes the important roles that other U.S. governmental agencies play in shortage mitigation efforts. For example, FDA worked closely with NIH to address a shortage of doxorubicin, a drug needed for clinical cancer trials. In another recent case, FDA alerted CDC as soon as we were informed of the potential shortage of rifampin injection, a drug used in the treatment of seriously ill patients with tuberculosis who require intravenous treatment. In addition, under the President's Executive Order 13588 (October 2011), FDA has been sending information to the Department of Justice that could be indicative of stockpiling or exorbitant pricing.

One particularly important interaction related to shortages is between FDA and DEA. Among other things with input from FDA, DEA is responsible for setting aggregate limits on the amount of each basic class of controlled substance that may be manufactured. DEA is also responsible for approving requests by manufacturers for a specific amount of the aggregate limit (a *quota*). This tight control over the manufacturing of controlled substances requires FDA and DEA to

[31] A *drop shipment* is a shipment directly from a manufacturer to the end purchaser or user (e.g., hospital or pharmacist) that bypasses the intermediate distributor from whom the end purchaser originally bought the product.

coordinate when there is a shortage of a controlled substance. Recognizing this need, FDASIA includes new provisions requiring improved coordination and communication between FDA and DEA when there is a shortage of a controlled substance.

5. International Authorities

FDA interactions with international authorities have been critical to successfully mitigating drug shortages. One important area of interaction has been around the importation of drugs from other countries to address shortages in the United States.[32] Numerous comments to the *Federal Register* notice asked FDA to expand the use of temporary importation of unapproved drugs to address shortages. FDA has used this tool to address shortages a number of times in recent years. For example, in 2012, FDA worked to facilitate the importation of propofol injection, which was in critical shortage when two firms discontinued the drug because of quality problems, including contamination with particulates and endotoxin.

Working through FDA's Office of International Programs, FDA has established ties with many regulatory agencies in other countries and maintains ongoing dialogues with those agencies through existing confidentiality agreements. FDA has worked with these agencies on a variety of issues related to importation, for example, requesting recent documents from foreign regulatory authorities who have audited manufacturing sites and tested products. An example of the value of this international cooperation is the recent importation of sodium bicarbonate injection, a critical drug for use in the intensive care unit that was in shortage. With cooperation of the Australian authorities, this critical drug was temporarily imported by a firm willing and able to supply their Australian product to the United States to address the U.S. shortage.

Not all drugs that are manufactured by foreign firms are appropriate for importation, and setting up a process to explore the possibility of importation required the cooperation of many stakeholders. When a foreign-registered drug manufacturer has been willing to supply a drug in shortage, FDA has worked closely with the company and assembled an internal cross-functional team to evaluate the drug and the facility in which it is made. Where the requested information has been found acceptable, considering risks associated with the drug and the risk to patients if it is not available, FDA has exercised enforcement discretion for temporary importation to provide treatment options for patients in critical need during the shortage.[33]

In addition to contacting foreign authorities for assistance with importation to address a specific shortage, FDA has begun discussing shortages more broadly with regulatory agencies in other regions. For example, to harmonize the international approach to shortage communications,

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[32] FDA is aware of the recent decision in *Cook v. FDA* (D.C. Circuit, Case No. 12-5176). We are currently reviewing the decision in the context of our drug shortages program.

[33] See also FDA's Regulatory Procedures Manual Chapter 9, Section 2 available at http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074300.pdf; and CPG Sec. 440.100 Marketed New Drugs Without Approved NDAs and ANDAs available at http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm

FDA meets regularly with the European Medicines Agency (EMA) to discuss various drug shortage issues. FDA has also spoken with the Canadian health authority about its approach to shortages, particularly those shortages that may cross U.S./Canadian borders and affect both countries.