DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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STATEMENT

OF

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"EXAMINING DRUG SHORTAGES AND RECENT EFFORTS TO ADDRESS THEM"

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Douglas Throckmorton, Deputy Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to speak with you today about the progress FDA has made in preventing and mitigating drug shortages.

Drug shortages pose a significant public health threat, affecting individual patients from across the United States, including patients who are in need of drugs to treat life-threatening diseases such as cancer, serious infections, and malnutrition. Recently, for example, there have been reported stock shortages of normal saline, a critical fluid used in the treatment of shock. These shortages can result in delaying or denying needed care to patients and may lead practitioners to prescribe an alternative therapy that may be less effective for the patient or that poses greater risk. Shortages have occurred, impacting care delivered by care providers in our Emergency Medical Services and in our emergency departments. Drug shortages have even disrupted clinical trials, potentially delaying research on important new therapies.

The number of new drug shortages in the United States rose steadily between 2005, when FDA began tracking 60 new shortages and the all-time high in 2011, when 251 new shortages were reported. After a series of interventions, including a Presidential Executive Order, enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA outreach, and work with the pharmaceutical community, the number of new drug shortages declined significantly in 2012 to 117 and fell even further to 44 in 2013. However, there continue to be

shortages that persist for longer periods, and currently, FDA is tracking 97 total shortages that began in 2013 or earlier.

Preventing drug shortages has been, and continues to be, a top priority for FDA. Recognizing the importance of this issue, we have increased substantially the resources we devote to drug shortages and expanded our work to prevent them. While the Agency cannot solve the problem alone, working in partnership with manufacturers and other stakeholders, and within the confines of the current statutory and regulatory framework, FDA helped prevent 170 shortages in 2013, 282 shortages in 2012, and 195 shortages in 2011. FDA has also identified future actions that can help prevent shortages, including important work to support new manufacturing methods that promise high-quality drug manufacturing, that would help to ensure patients have needed access to lifesaving medicines and help revitalize pharmaceutical manufacturing in the United States. In my testimony, I'd like to share with the Committee some of the work FDA is doing, and the plans the Agency has to continue to work to address this important public health issue.

Causes of Drug Shortages in the United States Today

Addressing the issue of drug shortages first requires an understanding of the causes of drug shortages. While increases in demand for a given drug can sometimes challenge the drug supply, drug shortages are usually preceded by a production disruption, which can be either a permanent product discontinuation or temporary interruption in manufacturing. Once a manufacturer experiences a discontinuance or interruption in manufacturing, a shortage may 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.

These production disruptions can be triggered by several factors, including factors within the control of manufacturers, such as a decision to permanently discontinue production of a drug because the product is no longer profitable. Production disruptions can also be caused by factors outside of the manufacturer's control, such as natural disasters or the unavailability of raw materials or needed materials for drug manufacturing. For example, shortages have resulted when raw material manufacturers discontinue the production of a needed ingredient for business reasons. In these circumstances, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. This is a particular vulnerability, if the ingredient is only available from one supplier (so-called 'sole-source').

FDA has had to intervene in the past to prevent shortages resulting from problems with non-U.S.-based suppliers. For example, shortages have resulted when raw material manufacturers discontinue an ingredient for business reasons. As noted above, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. Examples of critical drugs currently or recently in shortage with an active ingredient and/or finished goods sourced primarily from overseas include propofol, heparin, and Tamiflu. In some instances, our reliance on non-U.S.-sourced materials affect response to public health vulnerabilities.

Most often, however, production disruptions leading to shortages are the result of failures within manufacturing facilities that result in failures of product or facility quality. These quality failures include failing to follow proper operator procedures on sterile lines, allowing the growth

of bacteria and fungus. Moreover, just like an older car, aging production lines and the facilities that house them require significantly more upkeep. For example, poorly maintained old equipment has led to the introduction of steel and iron particulates into injectable products. Addressing these quality problems can result in a supply disruption that can result in a drug shortage. In 2012, for example, based on information collected from manufacturers, FDA determined that 66 percent of production disruptions leading to a shortage resulted from either (1) efforts to address product-specific quality problems (31 percent) or (2) efforts to address broader problems at a manufacturing facility (35 percent). As discussed below, preventing these disruptions requires a commitment on the part of the manufacturer to quality manufacturing, putting in place controlled production that ensures consistent drug quality. When these systems fail, a production can be disrupted and a firm may initiate a recall that leads to a shortage. In such cases, FDA can work with firms to remediate quality issues while production continues, however, some firms have taken the unilateral decision to shut down operations.

Responding to Drug Shortages

While manufacturers have a central role in ensuring that drugs are manufactured to a consistently high quality, FDA and other stakeholders have important roles to play in addressing drug shortages in the United States. When FDA is aware of an imminent or ongoing shortage, the Agency is well-positioned to work with the affected manufacturer to find ways to prevent or mitigate the shortage and lessen a shortage's impact on patients. The numbers are worth repeating: with early and timely notification by manufacturers, FDA helped prevent 170 shortages in 2013, 282 shortages in 2012, and 195 shortages in 2011. These numbers illustrate the value of FDA's receiving early notification of potential drug shortages. Several recent actions have supported such early notification. First, President Obama issued Executive Order 13588, "Reducing Prescription Drug Shortages," on October 31, 2011, which immediately

strengthened the Agency's response to shortages by directing FDA to use all appropriate administrative tools to improve manufacturers' notifications of potential shortages. In response, FDA issued an interim final rule to require early notification from certain manufacturers. In addition, on July 9, 2012, the Congress provided FDA with new authorities as part of FDASIA. Section 1001 of FDASIA broadened the scope of the early notification provisions by requiring all manufacturers of all covered prescription drugs (approved or unapproved) to notify FDA of a permanent discontinuance or temporary interruption in manufacturing. FDASIA also allowed FDA to require, by regulation, early notification of discontinuances or interruptions in the manufacturing of biologic products. In response to these actions, in October 2013, FDA issued a proposed rule. The proposed rule would implement the new reporting requirements, and would also extend these requirements to manufacturers of medically important biologic products. FDA is currently reviewing the comments on the proposed rule.

Since the Executive Order was issued in 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). FDA also learns about potential shortages from a variety of sources outside of the drug manufacturer—including professional organizations, interest groups, patients, and health care professionals—who report shortage information to multiple FDA offices. This work, coordinated through the Drug Shortage Staff, is included in the data we use when assessing a potential shortage, and helps ensure that FDA is aware of the shortages and their potential impact as early as possible.

FDA's staff has a variety of tools to help prevent or mitigate shortages. FDA staff, led by the Drug Shortage Staff, begins by verifying that an actual shortage exists or may occur. When the

shortage staff determines that a shortage either exists or is likely to occur, 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. 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.

FDA can and does take a variety of actions to mitigate or prevent shortages:

- Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap
- 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 quality problem
- Explore risk-mitigation measures for products initially not meeting established standards to allow them to be used safely.

The decisions FDA makes regarding a given drug shortage take into account both the risks and the benefits of continuing to make a drug available for patients. While FDA's standards of safety, efficacy, and quality do not change in a shortage situation, the benefits and risks of providing patients access to the specific product are always considered as the Agency determines what the best approach is for a given shortage. Our goal is to ensure that an adequate supply of approved drugs for all patient needs is available. However, FDA recognizes that there may 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.

We also expect that an increase in availability of generic drugs on the market can help mitigate future drug shortages. Generic drug user fee resources, including those recently made available through the Generic Drugs User Fee Amendments of 2012 (GDUFA), can speed access to safe and effective generic drugs to the public.

Continuing FDA Progress on Drug Shortages: the FDA Strategic Plan

Responding to notifications about potential shortages has enabled FDA, working with other groups, to prevent a significant number of drug shortages. Going forward, there is important additional work to do to reduce the factors that lead to shortages. In October 2013, the Agency released a Strategic Plan ("the Plan"), called for in FDASIA, both to improve the Agency's

response to imminent or existing shortages and to advance longer-term approaches for addressing the underlying causes of shortages to prevent supply disruptions from occurring in the first place. The Plan also recognizes the important role of other groups in preventing drug shortages and highlights opportunities for drug manufacturers and others to prevent drug shortages by promoting and sustaining quality manufacturing. This Plan was created by a Task Force representing multiple Centers, Offices, and disciplines from across FDA—a group that continues to work to implement the actions identified in the Plan.

First, FDA is working to strengthen FDA's ability to respond to a notification of a production disruption to prevent a shortage or to mitigate an unavoidable shortage by improving the processes we use to respond to shortages. We are working to continue to improve communications within FDA to ensure that our decisions are made as efficiently as possible. Second, recognizing the importance of up-to-date and accurate data, we are also working on ways to improve our databases related to drug shortages as well as the tracking procedures we use to manage those databases. This is a complex task, as some of these data systems that support efforts to prevent shortages were not created specifically for the purposes of assisting shortage-related activities. As a result, in addition to these more general data systems, the Agency is creating a dedicated data system that focuses solely on collecting data related to shortages—a system that will be able to integrate data from the other general data systems. This new drug data system will enable FDA to more efficiently track and assess issues relating to drug mitigating shortages, including enhancing our tracking of time from notification of shortage to resolution. The new system also will enhance FDA's ability to compile the information necessary for the required annual report to Congress on drug shortages. Third, FDA understands the importance of timely and accurate information about shortages for patients and caregivers

who are concerned about the availability of a particular drug, and the Agency continues to work to improve our communications about drug shortages.

The Future—Developing Long-Term Prevention Strategies

In addition to the activities FDA is taking to address current drug shortages, our Strategic Plan also addresses the development of long-term strategies focused on the underlying causes of production disruptions. While keeping in mind the critical role other stakeholders play in ensuring manufacturing quality, FDA is also exploring actions it can take, both alone and in collaboration with other groups, to address the issue of manufacturing quality.

FDA is exploring how we can use the tools we have to help support manufacturing quality through our own actions. We are also continuing to work with other stakeholders to understand and identify potential warning signals that could put the production of quality drugs at a given facility at risk. Early identification of these signals could allow for actions by the manufacturer to prevent shortages. Identifying these signals is a challenging undertaking, and FDA will work with a wide variety of stakeholders, who have collected and analyzed data about drug shortages and potential approaches to predict the risk for shortage, earlier.

FDA also recognizes that other proposals to reduce the risk of drug shortages would rely on actions by other stakeholders. Opportunities for others to explore could include better planning to prepare for potential manufacturing disruptions; the use of economic, financial, or other incentives for innovation and new investments in manufacturing quality drugs to reduce the occurrence and severity of shortages; and efforts to address concerns about the impact of

secondary distribution of approved drug products in shortage that can lead to higher prices (so-called 'Gray Market' activities).

The Future—Manufacturing Modernization and Shortage Prevention

Recognizing that shortages commonly begin with a supply disruption related to product or facility quality, FDA's efforts include a focus on encouraging and sustaining improvements in manufacturing quality. For over a decade, FDA has been working with academic and industry experts to stimulate development of novel manufacturing technologies with a goal of supporting these needed improvements. This work has supported advances in pharmaceutical manufacturing technology in the last decade that provide new opportunities to address the primary drivers of drug shortages and, potentially, to reinvigorate the pharmaceutical manufacturing sector in the United States. This work has included guidance and other actions to encourage manufacturers to adopt new manufacturing technologies, to facilitate their use of modern quality management techniques, and to ensure that FDA regulatory policies reflect state-of-the-art manufacturing science. Importantly, these efforts by FDA have focused on the need to encourage the adoption of new technologies and do not impact the standards for existing appropriate technologies or raise the bar on their use.

FDA is actively encouraging development of techniques that can help advance drug manufacturing. One example of a technique that holds promise is "continuous manufacturing," wherein the finished drug product is produced in a continuous manufacturing process, as opposed to traditional methods that involve a series of so-called "unit operations," such as milling, mixing, and granulation. Production can be continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage form, which can support

better control of product quality and can make changes in product, such as scale-up, easier to accomplish.

CONCLUSION

Drug shortages remain a significant public health issue in the United States, and addressing them is a top priority for the Agency. 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. Although the number of new shortages decreased in 2012 and 2013, and FDA has been able to prevent many shortages, nearly 100 drugs were in active shortages as of December 31, 2013. Many of the remaining drugs in shortage have been in ongoing shortage for the past several years because manufacturers have been unable to address the issues that led to the shortage or have chosen not to continue their availability. FDA will continue to work with manufacturers and other stakeholders to search for new tools to address these long-term shortages. However, an examination of the sources of drug shortages underscores the fact that FDA cannot do this alone and reinforces the importance of strong collaboration and constant communication between FDA, industry, health professionals, and patients. Because the majority of drug shortages begin with quality manufacturing problems, supporting sustained investment in reliable, high-quality modern drug manufacturing is an important target for future work. FDA has been working for over a decade, in collaboration with the pharmaceutical industry, to modernize drug manufacturing. These activities, combined with the other important work by FDA and other stakeholders, hold the key to preventing drug shortages from occurring, addressing them when they do occur, and providing patients with access to medicines they need.

I am happy to answer any questions you may have.