



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

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BEFORE THE

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COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

FDA CHECK UP: DRUG DEVELOPMENT AND MANUFACTURING CHALLENGES

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INTRODUCTION

Mr. Chairman, Ranking Member Speier, and Members of the Subcommittee, I am Dr. Janet Woodcock, 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 be here today to discuss the important issue of modernizing the manufacturing of pharmaceuticals.

The United States, through its investment in biomedical research, has become a world leader in drug discovery and development, but it is no longer in the forefront of drug manufacturing. Historically, the production of medicines for the U.S. population has been domestically-based. However, in recent decades, drug manufacturing has gradually moved out of the United States. It is currently estimated that 40 percent of the finished drugs taken by U.S. patients and 80 percent of the active ingredients come from sources overseas, including some of the drugs in shortage as noted below. While there are multiple reasons for this shift, common underlying factors include the fact that most traditional drug production processes require a large footprint, often have environmental liabilities, and can utilize a low-cost labor force.

Use of foreign-sourced materials creates vulnerabilities in the U.S. drug supply. The Department of Commerce's Office of Technology Evaluation, in its 2011 report entitled "Reliance on Foreign Sourcing in the Healthcare and Public Health (HPH) Sector: Pharmaceuticals, Medical Devices and Surgical Equipment," identified a high degree of foreign sourcing and dependency for critical components, materials, and finished products in the pharmaceutical sector. For example, most of the U.S. heparin supply comes from non-U.S. sources. When contaminated heparin, sourced from China, was found in the United States, FDA had to urgently devise several

tests to detect the contaminant and screen out contaminated product, because heparin is a critical drug for U.S. patients, and there was no adequate alternative source.

FDA also has had to intervene 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. In these circumstances, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. Shortages can occur when transport and shipping delays occur due to severe weather and other unforeseen events. In recent years, flight cancellations and potential shipping difficulties could have been caused by the Iceland volcano, the tsunami in Japan, or a threatened cargo ship strike. 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. Our reliance on foreign-sourced materials continues to create ongoing vulnerabilities.

Advances in pharmaceutical manufacturing technology in the last decade provide new opportunities to address this situation and to reinvigorate the pharmaceutical manufacturing sector in the United States. FDA has been working to stimulate development of novel manufacturing technologies in collaboration with academic and industry experts. The new technologies enable forms of “continuous manufacturing,” wherein the finished drug product is produced in a continuous stream, as opposed to traditional methods that involve a series of so-called “unit operations,” such as milling, mixing, granulation, and so forth. In examples of advanced novel manufacturing, production is continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage form. This type of manufacturing is on the verge of entering commercial production. There are a multitude of advantages of this type of production, when done well. Product quality can be precisely controlled. Production scale-up

issues, which frequently bedevil drug development, will likely be much less of an issue.

Increases in capacity can be handled in a straightforward manner. A range of strengths or doses may be prepared more easily, which may be important for personalized medicine. However, other key advantages do not relate to the specific drug product being made. For example, continuous manufacturing plants require a smaller footprint and can be located closer to markets, thus reducing the need for transcontinental shipping of components.

FDA has been working for over a decade to stimulate modernization of drug manufacturing; however, the Agency's efforts alone cannot reinvigorate the pharmaceutical manufacturing sector in the United States. Other essential actions include support for academic research in this area and opportunities for collaboration, possibly through public-private partnerships or consortia. In parallel with FDA's initiatives, we have seen a resurgence in academic research supporting modern pharmaceutical manufacturing. FDA works cooperatively with many of these academic groups to help advance the science of pharmaceutical manufacturing. For example, Cooperative Research and Development Agreements (CRADA) have been established with several academic groups to enhance understanding of concepts of manufacturing science. Utilizing a CRADA, one or more FDA laboratories may work with one or more non-Federal parties to conduct specified research or development efforts. FDA participates in a number of collaborative research projects being conducted by the Product Quality Research Institute and the National Institute for Pharmaceutical Technology and Education. However, these efforts are relatively small in scale, given the impact and criticality of the drug supply.

The future of drug manufacturing lies in high-technology, computer-controlled production facilities that can rapidly respond to changes in demand and are capable of seamlessly producing a variety of dosages and even dosage forms. This future can unfold within the United States, or

it may take place elsewhere, forcing U.S. patients to continue to rely on drugs produced on other continents.

The following discussion describes FDA's efforts to stimulate modernization of drug manufacturing.

What is FDA doing to encourage modern manufacturing?

In August 2002, FDA announced a significant new initiative, Pharmaceutical current Good Manufacturing Practice (cGMP) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This initiative had a number of objectives, including encouraging early adoption of new technological advances in the pharmaceutical industry, facilitating industry application of modern quality management techniques, implementing risk-based approaches, and ensuring that regulatory policies and decisions are based on state-of-the-art pharmaceutical science. In 2004, FDA issued a final report on the initiative, highlighting the Agency's commitment to restructuring its oversight of pharmaceutical quality systems.

In 2006, FDA issued a final guidance, "Quality Systems Approach to Pharmaceutical cGMP Regulations." This guidance not only provides information to help in implementing quality systems and risk management approaches, but also provides the framework for integrating these approaches into existing programs with the goal of encouraging industry to adopt modern and innovative manufacturing technologies. Additionally, in 2011, we released a final version of the process validation guidance, which modernized recommendations and expectations of how pharmaceutical manufacturers should ensure a state of control of their commercial manufacturing processes over the life cycle of the product.

Additionally, collaboration with international health and regulatory organizations has been a vital part of the modernization efforts. FDA has participated in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use (ICH) to help with the development of pharmaceutical quality systems based on an integrated approach to risk management and pharmaceutical science. These ICH guidances have become the international foundation for Quality by Design (QbD) and modern pharmaceutical manufacturing approaches. FDA is also participating in various expert working groups within ICH to develop guidelines to help ensure that drug regulatory processes are more efficient and uniform in the three regulatory regions.

Implementation of a Question-based Review (QbR) process has occurred in CDER's Office of Generic Drugs. QbR, a general framework for the assessment of the chemistry, manufacturing, and controls information submitted in abbreviated new drug applications (ANDA), incorporates the most important scientific and regulatory review questions that focus on critical pharmaceutical attributes essential for ensuring generic product quality. The QbR serves a dual purpose. First, it provides a guide to reviewers in preparing consistent and comprehensive evaluations of whether a product is of high quality and in the determination of the level of risk associated with the manufacture and design of the product. Second, it provides industry with transparency about the logic that reviewers invoke in their reviews. CDER is currently exploring the expansion of the QbR approach beyond generic drugs.

FDA's inspection and compliance focus has also changed in recent years. In addition to the publication of our 2006 quality systems guidance, we have enhanced our inspectorate capability and increased familiarity with the quality systems model. Some of these inspections have found

operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized.

What is Quality by Design (QbD)?

QbD offers an opportunity to reduce manufacturing costs while ensuring that consumers receive high-quality drug products. The focus of QbD is to build quality into a product using a thorough understanding of the risks of the product and process, and controlling those risks. QbD starts in development, and adaptation continues throughout the manufacturing life cycle if a firm has a strong quality management system. QbD utilizes a systematic approach to product design and development. It involves identifying what characteristics are important from the patient's perspective, identifying necessary material attributes and manufacturing parameters to achieve the quality characteristics, and then designing manufacturing controls and developing methods to assess process capability and make improvements. Instead of being in a reactive mode and taking corrective actions once failures occur, QbD causes manufacturers to focus on developing process understanding and supporting proactive actions to avoid failures through vigilant lifecycle quality risk management. It can enhance development capability, speed, manufacturing robustness, as well as the manufacturer's ability to identify the root cause of manufacturing failures. In certain cases, QbD can also help a manufacturer make post-approval changes and scale-up operations.

QbD and quality systems are beginning to gain ground in the pharmaceutical sector. A recent survey of pharmaceutical companies conducted by the International Society of Pharmaceutical Engineers Process Analytical Technology Community of Practice of United Kingdom/

Ireland (PAT COP UK/IR) indicated that significant cost benefits resulted from QbD-developed products. Benefits such as improved product quality and process robustness, increased process capability, and greater speed and reliability to market were also cited. This same organization found in another survey that inadequate manufacturing capability is a frequent cause of critical drug supply shortfalls, and cited lyophilization (freeze-drying) and sterile manufacturing as two areas in need of improvement.

From FDA's observations of industry, QbD in development is quickly becoming the standard way of doing business for small molecule innovator drugs. Biotech companies and generic companies are also shifting toward QbD for development, but at a slower pace. While QbD is catching on in development, manufacturers have been reluctant to modernize manufacturing methods by taking advantage of advances in modern facility and process design, such as replacing manually-intensive processes with automation, using closed systems, integrating process analytical technologies into operations for better process control, and adopting continuous manufacturing platforms. These technologies would help achieve improved manufacturing reliability, increased robustness, and lowered costs. Consequently, only part of the potential benefit of QbD and robust quality systems is currently being captured by much of the pharmaceutical sector. Increased efforts to better manage facility and process risks by making life cycle improvements are underway in the industry, and some transformative thinking at FDA has helped to promote this gradual evolution.

CDER's Office of New Drug Quality Assessment has conducted two pilot programs for implementing QbD. The first, announced in 2005 and now complete, allowed the Agency and industry to explore the scientific and regulatory aspects of QbD. The data from this pilot were incorporated in resulting ICH guidance documents. The second pilot, which started in 2011 and

is still ongoing, provides for collaboration with our European regulatory colleagues in review of applications that follow the QbD approach.

CDER's Office of Biotech Products has held similar piloting efforts. Its QbD pilot, which began in 2008 and is now closed to new applicants, is exploring the extension of QbD concepts to protein drugs. Additionally, we have also collaborated with our international colleagues to discuss QbD approaches in review.

What results could we expect to see from adoption of QbD?

Full implementation of QbD and modernization of manufacturing by the pharmaceutical industry in development through manufacturing is expected to provide lasting benefits to industry, regulators and patients. For industry, we expect the long-term benefits to include lower production costs which result from more efficient manufacturing, decreased failure rates, and lowered inventory costs. For regulators, we expect that application of science- and risk-based approaches will increase our work efficiency, so we can focus our efforts on higher risk products and processes. But most of all, we expect that application of QbD and modernizing manufacturing will benefit patients with higher assurance of product quality, greater availability, and a resulting decrease in drug shortages and recalls.

While this may require some investment for manufacturers who need to improve the infrastructure, the benefits of more dependable operations strongly aligns with the business goals of process predictability (e.g., Right First Time) and product dependability. Reduced variability will lead to reduced rejected goods, higher supply dependability, fewer defects, and overall better productivity and profitability. Modernizing drug manufacturing represents a great opportunity to

lower costs and develop more flexible manufacturing processes while continuing to ensure that the public receives high quality drug products. In addition, the public health will also be well served as modernization can help reduce the root causes of drug shortages, and industry's cost savings can be reinvested into developing new products to serve public health needs.

CONCLUSION

In summary, FDA has been working diligently for over a decade, in collaboration with the pharmaceutical industry, to improve drug manufacturing. Building on this foundation, and utilizing new technologies, groundbreaking new manufacturing methods are within reach. These new ways of making drugs could, with the proper strategies, revitalize pharmaceutical manufacturing in the United States.