DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

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UNITED STATES SENATE

"Continuing America's Leadership in Medical Innovation for Patients"

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Margaret Hamburg, Commissioner of Food and Drugs 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 discovery and development of innovative medical products. My FDA colleagues and I appreciate the Committee's interest in advancing legislation to support our shared goal of speeding delivery of innovative, safe, and effective treatments and cures to patients who need them. We look forward to working with you on this effort.

FDA has helped make America's biomedical industry the global leader

Over the past century, remarkable biomedical discoveries have led to the development of medical products responsible for rescuing millions of patients from devastating diseases that previously had led to loss of life or severe reductions in quality of life. The evolution of modern medicine is a story of tremendous hope, learning, and achievement—and one that we all fervently wish to build upon. I am proud of the role that FDA has played in helping these discoveries become safe and effective treatments for patients.

America has long been at the forefront of biomedical discovery. Decades of taxpayer investments in biomedical research, including a focused investment in cancer research, launched in the 1970s, produced fundamental scientific advancements. Significant investments by U.S. pharmaceutical and biotechnology companies, along with the work of NIH-funded investigators across the country, have helped to translate these insights into innovative medical products for

patients. FDA oversight of product approvals has built public trust in the safety and efficacy of new drugs and devices and confidence in America's biomedical industry. Major improvements in public health resulted and vital industries flourished. As FDA, Congress, and stakeholders pursue opportunities that provide the most promise for continued development, it is critical that we maintain safety and efficacy of products on which patients and physicians depend.

Public health crises led Congress to establish standards for safety and effectiveness

It is important to recognize that innovative medical products will only save lives if they work properly. As a result of strong standards for medical product approval, our citizens now depend upon FDA to ensure that the drugs and devices they rely on are safe and effective.

Concerns about the safety and effectiveness of medical products are deeply rooted in our history. In the 19th Century, enterprising traveling salesmen hawked questionable medical products. When newspapers gained widespread circulation, sellers of medical products became leading advertisers of cure-alls containing unlabeled ingredients such as alcohol and narcotics. Eventually, Congress responded by giving FDA authority to review new drugs for safety before they could be marketed.

In 1961, reports started to surface connecting thalidomide, which was widely prescribed in other countries to treat morning sickness during pregnancy, to severe birth defects. Thousands of children in Europe were born with severe birth defects. In response to the public uproar, in 1962, Congress enacted the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Thanks to these new amendments, manufacturers had to prove that a drug was

not only safe, but also effective. Approvals had to be based on sound science. Companies had to monitor safety reports that emerged in the post-market and adhere to good manufacturing practices that would lead to consistently safe products. The amendments not only benefited patients, they helped industry by raising scientific standards that ushered in today's sophisticated, science-based life sciences industry.

As we seek to accelerate medical product development, it is essential to take care to maintain those critical aspects of the FD&C Act that ensure the safety and efficacy of these products. History has shown that allowing inadequately tested drugs and devices on the market can cause significant harm to patients, both because of unexpected dangers and, in many cases, because patients may use ineffective products when effective alternatives exist.

FDA has dramatically accelerated access to innovative medical products

This past calendar year, FDA approved 51 novel drugs and biologics, the most in almost 20 years. Today, FDA's average drug review times are consistently faster than other advanced regulatory agencies around the world, providing Americans earlier access to new, innovative drugs than patients in any other country.

In achieving these outcomes, FDA has maintained its commitment to high standards to protect the public health, while also exercising regulatory flexibility in order to help promote medical product development. This flexibility, along with FDA's work to collaborate with industry, has helped reduce product development and review times. As a result, Americans are seeing more

products being approved, and in many cases, they have access earlier than patients anywhere else in the world.

FDA routinely works closely with sponsors to facilitate flexible approaches to drug development. One example is FDA's engagement with sponsors to expedite drug development under the breakthrough therapy program. We have also worked with sponsors on the use of surrogate endpoints, non-traditional trial designs, and other available tools to expedite the development of products to treat both common and rare diseases. In fact, more than one-third (69) of the new drug applications approved by the Center for Drug Evaluation and Research (CDER) from 2008 through 2013 were approved on the basis of one human study and supporting evidence. This included 167 novel drugs, some with multiple indications (for a total of 184 new indications). Almost two-thirds (112) have characteristics of a flexible development program and/or engaged in one or more of FDA's expedited development programs (fast track, breakthrough, accelerated approval, priority review), without undermining or diminishing FDA's commitment to a strong safety and effectiveness standard. These many innovative and flexible approaches underscore FDA's commitment to making drugs that are shown to be safe and effective available as rapidly as possible.

Early and frequent communication between sponsors and FDA is significantly reducing overall drug development times. For instance, an analysis of 184 new drug applications approved from 2008-2013 concluded that the median clinical development time for drugs that were the subject of a Pre-IND or "early" meeting was 1.4 years faster than drugs without such meetings. Similarly, drug development was reduced by more than a year for companies that sought an End-

of-Phase I meeting with FDA, compared to companies that did not request such meetings; and companies that had End-of-Phase II meetings with FDA had higher first-cycle approval rates than those that did not. This analysis includes drugs that did not qualify for an expedited development program.

For devices, FDA's Center for Devices and Radiological Health (CDRH) is focusing on improving investigational device exemption (IDE) submissions to allow earlier and more efficient clinical study enrollment for devices. CDRH has reduced, by 34 percent, the number of IDEs requiring more than two cycles to full approval. These improvements resulted in reducing by over half the median time to full-study approval. From 2011 to 2014, the median number of days to full IDE approval has decreased from 442 to only 101, cutting the time it takes to bring a new medical device to market by nearly a full year. In addition, improvements to the *de novo* program have resulted in a 70 percent reduction in the average total time to decision for these submissions.

As a result of these improvements, patients are able to receive important treatments sooner. Today, 76 percent of the new drugs approved by Japan, the European Union (EU) and FDA from 2009 to 2013 were approved first by FDA, according to a report released in May by the British-based Centre for Innovation in Regulatory Science.[1]

In addition to earlier access to innovative products, patients are also seeing substantial numbers of new treatment options on the market. Of the 51 new molecular entities and new biological

[1] "New Drug Approvals in ICH Countries, 2004-2013," Centre for Innovation in Regulatory Science, R&D Briefing 54, 2014.

products approved by FDA in 2014, 17 new approvals are "first-in-class" therapies, which represent new approaches in the treatment of disease. The greatest number of new drugs approved for "orphan" diseases, since Congress enacted the Orphan Drug Act over 30 years ago, also was seen in 2014. These approvals represent important advances for patients who may have limited treatment options available. Among CDER's 2014 approvals are treatments for cancer, hepatitis C, and type-2 diabetes, as well. CBER approved many important biological products in 2014, including a groundbreaking vaccine for meningitis B and a vaccine to prevent certain cancers and other diseases caused by a broader range of Human Papillomaviruses.

There are even more opportunities to accelerate medical product development

While tremendous progress has been made thus far, it is important that FDA, Congress, and stakeholders continue working to promote medical product development. In order to ensure that we are promoting the development of products that work properly, it is important that advances are grounded in science. Where there are gaps in scientific understanding, stakeholders can work together to address these gaps so that the public remains confident in the safety and efficacy of products on the market and to ensure that investments in research and development are more likely to have meaningful results.

I would like to share FDA's thoughts on some of the most promising areas that we believe could truly reach our common goal of speeding delivery of innovative, safe, and effective products to American patients, focusing primarily on transformation of the early stages of drug development and increased efficiency of drug testing and manufacturing. Opportunities to achieve these priorities include: promoting precision medicine; encouraging collaboration and data sharing

among scientists; incorporating patient perspectives and experiences; bridging gaps in the science of biomarkers; streamlining clinical trials; modernizing drug manufacturing; obtaining the best experts to help accelerate cures; and reducing administrative burdens and duplication.

Advancing precision medicine

Advances in a variety of fields, including genomics and systems biology, are beginning to produce highly tailored medical treatments based on unique patient characteristics. "Targeted drug development" is a growing area of drug discovery. It is the identification of patients for inclusion/exclusion either in the pivotal studies supporting approval or for the drug's use in the labeled indication based on a genetic test, biomarker, or susceptibility test (e.g., bacterial resistance, tumor genetic mutation). These treatments are specifically targeted to treat patients who are most likely to respond, or more safely receive, the medication based on specific tests. In the early 1990s, only 5 percent of FDA's new drug approvals were for targeted therapies. Twenty years later, that number had risen to a quarter of new approvals, and in 2013, approximately 45 percent of FDA's approvals were for targeted therapies.

President Obama recently announced a Precision Medicine Initiative to advance biomedical understanding by leveraging genomic advances, health information technologies, and new methods of analyzing large volumes of data. As part of that effort, FDA has been reviewing the current regulatory landscape involving next generation sequencing (NGS) as the technology moves rapidly from research to clinical practice. With NGS technology, a single test potentially can be employed to identify thousands—even millions—of genetic variants carried by a single individual. To get the dialogue started, FDA published a preliminary discussion paper in late

December that posed a series of questions about how to best ensure that tests are not only accurate and reliable, but are available for patients as soon as possible. Public comment is essential, so FDA opened a public docket and held a public meeting on NGS technology on February 20, 2015. As part of the President's Precision Medicine initiative, FDA will develop a new approach for evaluating NGS technologies to facilitate the generation of knowledge about which genetic changes are important to patient care and foster innovation in genetic sequencing technology, while ensuring that the tests are accurate and reliable.

Utilizing real-world observational data

Real-world observational data provides a vital tool to monitor medical product safety and identify and further evaluate concerns. With appropriate privacy protections, leveraging large databases containing patient EHRs, disease-specific registries, and claims data has resulted in significant advances in our understanding of health and disease, provided novel and sometimes surprising insights into potential relationships between health-related factors and outcomes, and provided important product safety data. FDA is currently querying large, diverse health care data for product safety through its Sentinel Initiative and exploring opportunities to expand the use of real-world observational data to optimize the performance of medical products.

Although there is reason to believe that in the appropriate setting these data may be helpful in providing information on the effectiveness of marketed products, such as for new uses of approved products to support label expansion, many experts in the field agree that more work is needed to make these data operational for and directly applicable to regulatory purposes. We

should move quickly to further develop methodologies needed to better understand and harness the promise of real-world observational data for regulatory purposes.

Incorporating patient perspectives

Patients are uniquely positioned to inform medical product development with firsthand experience gained from living with a disease, including their use of available therapies to treat their conditions. In Prescription Drug User Fee Act (PDUFA) V, FDA committed to a more systematic and expansive approach to obtaining patient perspectives through a Patient-Focused Drug Development Initiative. FDA has, so far, held 11 public meetings on specific disease areas and gleaned much valuable insight from patients. Important patient-focused work is also already underway through the Medical Device Innovation Consortium (MDIC). MDIC is developing a framework for incorporating patient preferences into the device development and assessment process, and compiling a catalog of methods for collecting patient-preference information that can be used to develop, design, and market devices that meet the needs of patients. One recent example, highlighting the impact of patient perspectives, was the decision to approve a device to treat obesity. The decision to approve the device was based in part on the data from a study that showed a substantial portion of obese patients would accept the risks associated with a surgically implanted device, if they lost a sufficient number of pounds.

We believe that more can be learned and applied by engaging in a transparent, multi-stakeholder approach, potentially through public-private partnerships, that identifies sound and rigorous methods to capture science-based, disease-specific patient input in an analytically meaningful and useful form that can be incorporated directly into drug and medical device development and

review processes. This should include capturing information on the natural history of diseases, including identifying and measuring aspects that matter most to patients. Developing guidance to enable patient groups to become active participants in this process and to help industry incorporate appropriate methods in drug development programs also will move the field forward.

Bridging gaps in the science of biomarkers

FDA believes that accelerating the development of reliable biomarkers is essential to advancing important new therapies. FDA already accepts the use of hundreds of biomarkers for a variety of purposes throughout drug development, such as proof-of-concept, diagnosis of disease, enrichment of trials with patients most likely to respond, and as surrogate endpoints that can support accelerated or traditional drug approval. For example, 45 percent of drugs were approved by FDA on the basis of a surrogate endpoint between 2010 and 2012. There remain, however, many diseases such as Alzheimer's disease for which disease-specific biomarkers have not yet been developed, or shown to be reliable for use in the regulatory review process. When we do not understand the disease pathways, biomarkers appearing to be linked to disease progression can fail because they are not, in fact, in the causal pathway for the disease. A wide range of stakeholders is necessary to achieve meaningful progress in developing additional biomarkers that can be used by the scientific community. Important work is already underway through the National Institutes of Health (NIH), the Biomarkers Consortium in which FDA participates, and the Critical Path Institute.

The principal barrier to biomarker development is the lack of scientific understanding about the causes and biochemical pathways of many diseases. Continued public and private investment in

biomedical research is key to filling this knowledge gap and to improving understanding of how to show whether a biomarker is clinically meaningful. Collaboration among NIH, FDA, academia, industry, and patient groups can lead to development of standards of evidence for using biomarkers for regulatory decisions.

Leveraging clinical trial networks

The time and expense associated with designing and conducting clinical trials is one of the most significant limiting factors to drug and device development. Widespread use of clinical trial networks and master protocols could dramatically improve clinical trial efficiency—and create a new drug and device development paradigm that benefits both patients and industry. The recently initiated Lung Cancer Master Protocol (Lung-MAP) is an excellent example. A master protocol creates a single clinical trial infrastructure to test many drugs at the same time. In the case of Lung-MAP, patients are assigned to one of five different drugs being simultaneously tested, based on the results of genomic profiling to screen for alterations in more than 200 cancer-related genes. Additional drugs can be added, or dropped, as appropriate, over time. FDA is highly supportive of the use of master protocols, and we are working with key stakeholders to advance their use.

Modernizing drug manufacturing

Advances in pharmaceutical manufacturing technology provide new opportunities to lower costs, limit drug shortages, and reduce supply chain vulnerabilities—and reinvigorate U.S. pharmaceutical manufacturing. A promising example is the new technology that enables forms of "continuous manufacturing" to produce a finished drug product in a continuous stream, as

opposed to traditional methods that involve a series of sequential and discrete "unit operations," such as milling, mixing, and granulation. Unlike traditional manufacturing, which can take close to a year from start to finish, continuous manufacturing could take only a few days, increase equipment utilization rates up to 95 percent, and dramatically reduce the risk of production failure and negative environmental impacts. Continuous manufacturing could also reduce the likelihood of drug shortages. FDA has been working for over a decade to stimulate modernization of U.S. drug manufacturing, but more work is needed, including supporting academic research in this area and expanding opportunities for collaboration, possibly through public-private partnerships or consortia.

Hiring and retaining highly qualified experts

In order to achieve its mission in a complex, global, and rapidly evolving scientific arena, FDA and industry agree: the Agency must be able to attract, recruit, and retain talented leaders, physicians, scientists, and other experts to effectively review cutting-edge products and conduct post-market surveillance activities. Delays in bringing selected candidates on board may prompt highly qualified experts to pursue opportunities elsewhere.

Allowing use of central Institutional Review Boards (IRB)

The FD&C Act mandates review of a clinical trial on a device by a "local" IRB, or by FDA in rare circumstances, although there is no comparable requirement for drug trials. This can require review of multi-site studies by many different IRBs, and each IRB may require the study sponsor to meet different, sometimes inconsistent requirements for study approval, increasing the length and cost of trials. Studies have shown that the use of a central IRB for multi-site drug studies

can significantly improve efficiency, without undermining trial participants' protections. A modification of the FD&C Act to bring IRB review of device studies in line with drug studies would accomplish the goal of greater efficiency, without sacrificing oversight.

CONCLUSION

I am incredibly proud of the progress that FDA has made during my tenure to speed medical products to patients. I look forward to working with Congress to accelerate product development more while continuing to ensure that American families can rely on the safety and effectiveness of products on the market.