DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS

UNITED STATES SENATE

"Protecting the Public Health: Examining FDA's Initiatives and Priorities"

MARCH 13, 2014

RELEASE ONLY UPON DELIVERY

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 provide an overview of the important actions and initiatives FDA has been working on over the last year, including implementation of several new laws passed with this Committee's leadership: the FDA Food Safety Modernization Act (FSMA), Public Law 111-353; the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144; and the Drug Quality and Security Act (DQSA), Public Law 113-54.

I would like to express my gratitude to you and the Members of this Committee for championing passage of these landmark laws, all of which directly impact the public health. Their importance cannot be overstated, and the breadth of their provisions touch and guide so much of what we do every day. I appreciate the opportunity to provide this Committee with an overview of the Agency's implementation of various provisions of these laws. I'd also like to take this opportunity to share FDA's broader strategic efforts to enhance areas such as innovation, quality and safety, smart regulation, and the increasing globalization of the food and medical products we regulate.

FSMA Implementation

In January 2011, building on the bipartisan work of Congress, the President signed FSMA, the most sweeping reform of our Nation's food safety laws in more than 70 years. I commend this Committee for its leadership in passing this landmark legislation. As you know, FSMA aims to

enhance the safety of the U.S. food supply by shifting the focus from responding to contamination to preventing it. The modernization of FDA's regulatory framework for the oversight of food is one of the most challenging initiatives in FDA's history, but one that will have public health and economic benefits that could save thousands of lives and billions of dollars annually.

Preventive Standards

I would like to highlight the Agency's activities related to the seven foundational rules that form FSMA's central framework aimed at systematically building preventive measures across the food system, from the farm to the table. This framework is comprised of measures to keep produce safe, implement modern preventive controls in human and animal food/feed facilities, modernize oversight of imported foods, guard against intentional contamination, and help ensure the safe transport of food and feed. Since January 2013, FDA has released seven proposed rules on these topics for public comment.

The proposed rules were the result of extensive outreach by FDA with consumers, government, industry, researchers, and many others. Since their release, we have made every effort to solicit input on the proposed rules, not only through the standard rulemaking process, but also by participating in webinars, listening sessions, public meetings, and other activities with industry, consumer, and other stakeholder groups across the country and internationally.

Based on our conversations, the Agency has learned a great deal, and, in some areas, our thinking has evolved. For example, with regard to the preventive controls for human food rule and the produce safety rule, we recognize that the new safety standards must be flexible enough to accommodate reasonably the great diversity of the produce sector, practical to implement, and

based on the best available science. To achieve this goal, we believe that significant changes will be needed to key provisions of the two proposed rules affecting small and large farmers. We intend to publish revised proposed rule language on certain provisions by early summer 2014 and accept comments on those provisions. We value our ongoing dialogue with produce farmers and others in the sector on the proposed rules, and we want to ensure that we implement FSMA in a way that improves public health protections while minimizing undue burden on farmers and food processors.

FDA also recognizes that FSMA will only be as effective as its on-the-ground implementation. Our implementation strategy includes collaborating with industry, Federal, state, and local partners, tribal and territorial authorities, and foreign governments to ensure mutual reliance and appropriate and efficient oversight and compliance. It is also a concerted effort, prior to enforcement, to facilitate compliance through education, technical assistance, and regulatory guidance.

Resources

Our work together to improve the safety of our food supply requires two fundamental steps. The first was to give FDA authority and tools to modernize the food safety system, which FSMA did. The second is to give FDA the capacity to carry out the numerous changes embodied in the law. The President's FY 2015 Budget proposes a registration fee and an import user fee that will help FDA meet its food safety obligations under FSMA, while also benefitting industry and our state, local, territorial, and tribal partners.

We are, of course, grateful for the additional food safety funding that the Agency has received to date through the appropriations process. As documented in the FSMA capacity and funding

report that Secretary Sebelius submitted to Congress in May 2013, however, implementing the law in a manner that achieves its food safety goals, while minimizing costs and disruptions for industry, will require additional resources above FDA's current base funding for food safety. For example, we need to invest in training and new tools to modernize FDA and state inspection activity in keeping with FSMA's science-based prevention framework and to improve the quality and consistency of inspections. We need to invest in guidance, training, and other technical assistance for small- and mid-size growers and processors. And we need to invest in building FSMA's innovative new import oversight system, which is vital to support international trade in safe food. FDA looks forward to working with you and the stakeholder community to develop these user fees.

Looking Forward

It is gratifying to FDA that in our meetings around the country, we have received broad support for moving forward in implementing FSMA in a timely and appropriate manner in light of its importance to food safety and to the economic success of the food industry. We will continue our collaborative approach as we move down the pathway to final rules and to full implementation of FSMA. Successfully implementing the broad prevention framework required by FSMA is critical to food safety and consumer confidence in the food supply and is an important priority for the Agency.

FDASIA Implementation

In 2012 the Congress passed—and on July 9, 2012, President Obama signed into law—FDASIA, reauthorizing user fee programs for innovator drugs and medical devices and establishing two new user fee programs for generic drugs and biosimilar biological products. The law also gave FDA new authority to better protect the drug supply chain, which is critical in an increasingly

global marketplace. In addition, FDASIA provided the Agency with new authorities to combat drug shortages and stimulate antibacterial drug development, made permanent programs to enhance development of products used to treat pediatric populations, included provisions intended to encourage drug innovation, made a number of important changes to medical device regulation, and added a number of other important provisions.

User Fee Program Implementation

FDASIA includes the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which was first enacted in 1992, and the third authorization of the Medical Device User Fee Act (MDUFA III), which was first enacted in 2002. Two new user fee programs, for generic drugs and for biosimilar biological products, build on the successes of these two established user fee programs. Coming at a time of continuing budget restraints, this steady source of funding is essential to support and maintain FDA's staff of experts who review the thousands of product submissions we receive every year, and do so in a timely and thoughtful manner. Over the years, our user fee programs have ensured predictable, consistent, and streamlined premarket programs for industry and have helped speed patient access to safe and effective new products.

PDUFA

PDUFA V addressed many of the top priorities identified by public stakeholders, the top concerns identified by industry, and the most important challenges identified within FDA. PDUFA V enhancements included increased interaction during regulatory review of New Molecular Entity New Drug Applications (NME NDAs) and original Biologics License Applications (BLAs); regulatory science enhancements to expedite drug development; development of important new guidance for drug developers; a commitment to develop a structured framework for benefit-risk assessment; various enhancements to the drug safety

system; and requirements for electronic submissions and standardization of electronic application data. This additional work was funded by a modest 6 percent increase in PDUFA user fees.

MDUFA

Reauthorization of the medical device user fee program has helped to expedite innovative new products to market by boosting the medical devices regulatory review capacity through hiring new review staff. MDUFA III represented a commitment between the U.S. medical device industry and FDA to increase the efficiency of regulatory processes in order to reduce the total time it takes to make decisions on safe and effective medical devices. It was the result of more than a year of public input, negotiations with industry representatives, and discussions with patient and consumer representatives.

Prior to MDUFA III, beginning in 2010, we put in place a series of reforms designed to improve predictability, consistency, and clarity in the device review process.[1] We were seeing results from these reforms before enactment of MDUFA III,[2] but the additional user fee funding authorized under FDASIA enhances our ability to implement positive changes for patients and industry. Under MDUFA III, FDA is authorized to collect user fees that will total approximately $595 million over five years. With this additional funding, plus stable appropriated funding, FDA intends to hire more than 200 full-time-equivalent (FTE) workers over the course of

[1] For example, in January 2011, FDA's Center for Devices and Radiological Health (CDRH) announced a Plan of Action that included 25 specific actions we would take in 2011 to improve the predictability, consistency, and transparency of our premarket programs. The following month, CDRH announced its Innovation Initiative, which included several proposals to help maintain the position of the United States as the world's leader in medical device innovation, including the creation of a new approach for important new technologies. See FDA, "CDRH Plan of Action for 510(k) and Science," available at *http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm239448.htm*, and documents cited therein.

[2] For example, in 2011, CDRH, for the first time, began reducing what previously was an increasing backlog of unresolved 510(k) submissions. In addition, in February 2012, CDRH reported that the "not substantially equivalent" (NSE) rate for 510(k) submissions had decreased to 5 percent in 2011 from a peak of 8 percent in 2010. See Testimony of Jeffrey Shuren, M.D., J.D., before the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health (February 15, 2012), available at *http://www.fda.gov/NewsEvents/Testimony/ucm290707.htm*.

MDUFA III. Between passage of MUDUFA III and October 1, 2013, we have hired more than 90 new employees in support of the medical device review process.

In exchange for the additional user fees, FDA committed to meet much-enhanced performance goals for the device review process. Preliminary data indicate that FDA has the potential to meet all of its FY 2013 MDUFA III performance goals, and the program has already seen a 27 percent decrease in the backlog of 510(k)s compared to FY 2010, a 10 percent decrease in average total time for review of 510(k)s compared to FY 2010, a 43 percent decrease in the backlog of Premarket Approval (PMA) applications compared to FY 2010, and a 32 percent decrease in average total time for review of a PMA application compared to FY 2009. Also, FDA is providing substantially more detailed quarterly reporting on our progress in implementing those performance goals, and our quarterly performance reports are online and available to the public.[3] These reports are also presented and discussed at FDA-conducted, quarterly meetings with representatives from medical device member organizations.

In addition, FDA and the medical device industry agreed in MDUFA III to have an independent contractor conduct a two-phase assessment for performing technical analysis, a management assessment, and program evaluation, required to objectively assess FDA's premarket review processes for medical devices. Phase 1 of this assessment required the publication of high-priority recommendations within six months of contract award.[4] The following high-priority recommendations were published on December 11, 2013:

[3] See CDRH, "MDUFMA Reports," available at *http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/medicaldeviceuserfeeandmodernizationactmdufma/ucm109210.htm*.

[4] See Booz Allen Hamilton, "Evaluations and Studies of Premarket Device Reviews under Medical Device User Fee Amendments (MDUFA) II/III for the Food and Drug Administration -- MDUFA II/III Evaluation -- Priority Recommendations" (Contract No. HHSF223201010017B, Order No. 22313004) (Dec. 11, 2013), available at *http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/overview/mdufaiii/ucm378202.pdf*.

- Develop criteria and establish mechanisms to improve consistency in decision-making throughout the review process;
- Provide mandatory full staff training for the three primary information technology (IT) systems that support MDUFA III reviews;
- Identify metrics and incorporate methods to better assess review process training satisfaction, learning, and staff behavior changes; and
- Adopt a holistic, multi-pronged approach to address five quality component areas to standardize process life-cycle management activities and improve consistency of reviews.

The remainder of the Phase 1 assessment is currently in process and is expected to be completed in June 2014.

Generic Drug User Fee Amendments of 2012

One of FDA's major undertakings since July 2012 has been putting in place the infrastructure for a new user fee program under the Generic Drug User Fee Amendments of 2012 (GDUFA) that will expedite the availability of low-cost, high-quality generic drugs. The program has already achieved several milestones, including making significant strides in reducing the backlog of pre-GDUFA applications and enhancing review efficiencies. FDA has completed scientific review of approximately 40 percent of GDUFA backlog applications, since the program launch. In addition, FDA has conducted completeness assessments for over 1,500 drug master files and has launched the creation of a public list of drug master files available for reference[5] to expedite review of applications containing referenced active pharmaceutical ingredients. Further, FDA

[5] *www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls*.

held a public meeting on June 21, 2013, to discuss regulatory science priorities to expand the availability and quality of generic drugs and solicit input from stakeholders. The Agency streamlined the hiring process to recruit new scientific reviewers, project managers, investigators, and support staff, and met its ambitious year-one GDUFA hiring goal by bringing on board at least 25 percent of GDUFA program hires by October 1, 2013.

Lastly, FDA has facilitated development of the most comprehensive list of generic drug industry participants: more than 3,500 manufacturing and testing facilities have submitted self-identification information to FDA during the FY 2013 annual reporting period, enhancing the quality and transparency of our knowledge of the generics industry.

Biosimilars User Fee Act (BsUFA)

The Biologics Price Competition and Innovation Act, which was enacted as part of the Affordable Care Act, established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. Approved biosimilars are expected to be less expensive than the reference products, providing clinicians and their patients access to more affordable treatments that are biosimilar or interchangeable.

BsUFA addresses many of the top priorities identified by public and industry stakeholders and the most important challenges identified by FDA in bringing biosimilar products to market. The BsUFA program is similar to the PDUFA program in that it includes fees associated with marketing applications, manufacturing establishments, and products. However, there are some differences between BsUFA and PDUFA because of the nascent state of the biosimilars industry in the United States. For example, there are currently no FDA-approved biosimilar biological

products; accordingly, the BsUFA program includes fees for products that are in the development phase to generate fee revenue in the near-term and to enable sponsors to have meetings with FDA early in the development of biosimilar biological product candidates.

In March 2013, FDA published draft guidance for industry entitled "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants."[6] This draft guidance provides recommendations to industry on formal meetings between FDA and sponsors or applicants relating to the development and review of biosimilar biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The guidance assists sponsors and applicants in generating and submitting a meeting request and the associated meeting package to FDA for biosimilar biological products.

Development of Antibacterial Drugs

Recognizing the need to stimulate investments in antibacterial drugs, Congress passed—and the President signed into law—the Generating Antibiotic Incentives Now (GAIN) title of FDASIA to create an incentive system. The primary framework for encouraging antibacterial development authorizes FDA to designate human antibacterial or antifungal drugs that are intended to treat "serious or life-threatening infections" as "qualified infectious disease products (QIDP)." With certain limitations set forth in the statute, a sponsor of an application for an antibacterial or antifungal drug that receives a QIDP designation gains an additional five years of exclusivity to be added to certain existing exclusivity periods. A drug that receives a QIDP designation is also eligible for designation as a fast-track product, and the application for that drug is eligible for priority review. Between July 9, 2012 (when the GAIN title of FDASIA went

[6] *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf*

into effect), and February 19, 2014, FDA granted 40 QIDP designations representing 27 unique molecules. Consistent with the statute, on June 12, 2013, FDA issued a proposed rule to establish a legislatively mandated list of "qualifying pathogens" that have the potential to pose a serious threat to public health and make public the methodology for developing the list, as required by FDASIA.

In addition to this initiative under FDASIA, FDA's Center for Veterinary Medicine (CVM) has introduced a judicious-use strategy to help protect the efficacy of anti-microbial drugs that are currently used in animal agriculture but are also important for treating human infection ("medically important antimicrobials"). The plan includes phasing out the use of medically important antimicrobials for food animal production uses, such as to enhance growth or improve feed efficiency, and bringing under veterinary oversight all remaining therapeutic uses of such drugs in food-producing animals in order to ensure such uses are consistent with the judicious-use principles in CVM's recently issued Guidance for Industry (GFI) #213 entitled "New Animal Drugs and New Animal Drug Combination Products, Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209."[7] FDA is committed to the success of this initiative as an element of its overall strategy to address the public health problem of antimicrobial resistance.

Breakthrough Therapies

FDASIA created a powerful new tool to facilitate the development and review of "breakthrough therapies," instructing FDA to take actions appropriate to expedite the development and review

[7] *http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm299624.pdf*

of a drug or biologic, if preliminary clinical evidence indicates that it may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. This offers real opportunities to get promising drugs more quickly to patients who need them. In fact, using this new approach, FDA recently approved two advanced treatments for rare types of cancer and one for hepatitis C. As of December 31, 2013, CDER had received 121 requests for breakthrough therapy designation, and CDER has already granted the breakthrough therapy designation to 36 potential innovative new drugs, many of which have been for rare disease indications, that have shown encouraging early clinical results in treating conditions such as cystic fibrosis, hepatitis C infection, and breast cancer.

Pediatrics

FDASIA strengthened and made permanent provisions to improve the safety and effectiveness of drugs, biological products, and medical devices intended for use in pediatric populations. It made permanent the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), and authorized certain funding associated with pediatric device development. We recently marked the 16-year anniversary of BPCA and the 10-year anniversary of PREA and are pleased to report that, since passage of those important pieces of legislation, labeling for more than 500 drug products have been revised to contain information about use of products in pediatric populations.

Under FDASIA, PREA was amended to require the submission of initial pediatric study plans, typically at the end of Phase 2. This provision provides an opportunity to improve the pace of pediatric drug development by requiring sponsors to submit pediatric study plans early in a product's development program; it is consistent with FDA's stated regulatory objectives and facilitates alignment with European efforts in the arena of pediatric product development. FDA

implemented this provision in early January 2013. In addition, FDA has published draft guidance to industry, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans."

FDA has also issued a Final Rule, as required under FDASIA, relating to the tracking of pediatric use of devices. This rule requires applicants to include in certain premarket submissions readily available information on pediatric subpopulations who suffer from the disease or condition that the device is intended to treat, diagnose, or cure. The information submitted will be used to help FDA better track the number of approved devices for which there is a pediatric subpopulation that suffers from the disease or condition that the device is intended to treat, diagnose, or cure. FDA would like to use this data to identify unmet pediatric needs in medical device development.

Rare Disease Initiatives and Other Rare Disease Programs

FDASIA added a number of new provisions for rare diseases, including the rare pediatric disease priority review voucher program, consultation with external experts on rare diseases, and a pediatric rare diseases public meeting. Under PDUFA V, CDER has a rare diseases program that is fully staffed and operational, and a rare diseases liaison in CBER has been planned. Also, a three-day public meeting on complex issues in rare disease drug development, which included the pediatric rare diseases public meeting, was recently held on January 6-8, 2014.

FDASIA also broadened the circumstances under which a sponsor of a device approved under the humanitarian device exemption (HDE) pathway could make a profit, in order to further encourage the development of medical devices for rare diseases and conditions, without undermining the incentive for sponsors to develop these devices for pediatric populations. To

encourage the development of medical devices intended to benefit patients in the treatment and diagnosis of rare diseases, sponsors of certain devices for rare diseases or conditions may apply for marketing approval under the HDE pathway, which allows the sponsor to seek FDA approval for the device by demonstrating only a reasonable assurance of safety and not a reasonable assurance of effectiveness. FDA approval of an HDE authorizes an applicant to market a device subject to certain profit and use restrictions set forth in section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Previously, only sponsors of devices that were intended and labeled for use in pediatric patients after the date of the enactment of the Pediatric Medical Device Safety and Improvement Act of 2007 could seek to make a profit on their HDE-approved devices. FDASIA expanded this profit prohibition exemption to include HDE-approved devices intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe. FDA has approved five HDE supplements for HDE device sponsors, under this modified provision.

Patient Engagement

In accordance with our commitments in PDUFA V, FDA has initiated the Patient-Focused Drug Development Program. The objective of this five-year effort is to more systematically obtain the patient's perspective on a disease and its impact on patients' daily lives, the types of treatment benefit that matter most to patients, and the adequacy of the available therapies for the disease. As part of this commitment, FDA is holding at least 20 public meetings over the course of PDUFA V; each will focus on a specific disease area. We have already held patient meetings on several major diseases.

CDRH launched a comprehensive Patient Preference Initiative last year. This Initiative builds upon our 2012 Benefit-Risk Guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications,"[8] which outlines the principal factors that FDA considers, including patient perspectives on meaningful benefits and acceptable risks, when making benefit-risk determinations during the premarket review process for certain medical devices. This guidance outlines a strategy for how patient preference results should be compared to other sections of an application.

CDRH established the Patient Preference Initiative to address issues not in the guidance, such as available methods, tools, and approaches that can be used to collect patient views, how to establish and evaluate the validity of the data, and how patient preference data may be used in a broader context of the total product cycle of medical devices.

The Initiative intends to provide the information, guidance, and framework necessary to incorporate patient preferences on the benefit-risk assessment of medical devices into the full spectrum of CDRH's regulatory processes and to inform medical device innovation by the larger medical device community. CDRH held a two-day public workshop in September 2013 to engage and solicit information on patient preference from stakeholders, including patients, health care providers, industry, and academic leaders. CDRH has also recently completed an obesity pilot study that has developed new tools that can be used to measure patient preferences. Finally, CDRH is working to expand both the number of patient Special Government Employees and the ways in which FDA uses these expert patients throughout the Agency.

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[8] CDRH, "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" (March 28, 2012), available at *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf*.

In addition to these efforts, CDER established the Professional Affairs and Stakeholder Engagement program that will serve as a focal point and enhance two-way communication and collaboration with health professional organizations and patient advocacy and consumer groups about drug products.

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. 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 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, shortages continue to persist for longer periods, and at the end of 2013, FDA was 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 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 could help revitalize pharmaceutical manufacturing.

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"),[9] 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.

Supply Chain

Title VII of FDASIA strengthens drug safety by giving FDA new authorities to protect the integrity of an increasingly global drug supply chain in which nearly 40 percent of finished drugs and 80 percent of APIs are imported. Title VII allows FDA to protect the global drug supply chain by: (1) increasing FDA's ability to collect and analyze data to enable risk-informed decision-making, (2) advancing risk-based approaches to facility inspection, (3) partnering with foreign regulatory authorities, and (4) driving safety and quality throughout the supply chain through strengthened enforcement tools.

[9] *http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf*.

Since enactment of FDASIA, FDA has been working diligently to implement the Title VII supply chain authorities in a meaningful way that strives to maximize its public health impact. For example, FDA issued a proposed rule to extend the Agency's administrative detention authority to include drugs intended for human or animal use, in addition to the authority that is already in place for foods, tobacco, and devices; issued draft guidance defining conduct that the Agency considers delaying, denying, limiting, or refusing inspection, resulting in a drug being deemed adulterated; and issued draft guidance addressing specification of the unique facility identifier system for drug establishment registration.

The Agency already had taken steps toward development of a risk-based inspection schedule, prior to FDASIA. However, the enhancements provided by FDASIA will further assist the Agency in responding to the complexities of an increasingly globalized supply chain. For example, provisions in FDASIA that permit FDA to request records in advance or in lieu of an inspection and that require firms to submit a unique facility identifier will allow FDA to increase its inspectional efficiency and its knowledge base.

In addition, FDA hosted a public meeting in July 2013 to solicit comments from the public about implementation of Title VII generally, and to specifically address the provisions related to standards for admission of imported drugs and commercial drug importers, including registration requirements and good importer practices.

Title VII implementation requires not only the development of new regulations, guidance, and reports, but also major changes in FDA information systems, processes, and policy—a challenging task, given that Title VII was not additionally funded through user fee support or otherwise. However, FDA has worked to make progress in each of these areas, prioritizing the

Agency's efforts to achieve the greatest public health impact and deploy its limited resources most effectively.

Unique Device Identification (UDI) System

On September 20, 2013, FDA announced the Final Rule for a UDI system,[10] which, once implemented, will provide a consistent, standardized, unambiguous way to identify medical devices. The UDI system will be phased in over several years, focusing first on the highest-risk medical devices. Once fully implemented, the UDI system rule is expected to have many benefits for patients, the health care system, and the device industry. It will provide improved visibility as devices move through the distribution chain, enhancing the ability to quickly and efficiently identify marketed devices when recalled and improve the accuracy and specificity of adverse event reports; it will also offer a clear way of documenting device use in electronic health records and clinical information systems.

Health Information Technology (Health IT)

Pursuant to section 618 of FDASIA, FDA, in collaboration with the Federal Communications Commission (FCC) and the HHS Office of the National Coordinator for Health IT (ONC), will soon publish on our respective websites a report containing a proposed strategy and recommendations on an appropriate risk-based regulatory framework pertaining to health IT that promotes innovation, protects patient safety, and avoids duplicative regulation. FDA, FCC, and ONC convened a working group of external stakeholders and experts under ONC's Health IT Policy Committee to provide appropriate input on the strategy and recommendations for this report. This working group held open meetings, made documents and information discussed

[10] FDA, "Final Rule: Unique Device Identification System," Docket No. FDA–2011–N–0090, 78 *Fed. Reg.* 58786 (Sept. 24, 2013), available at *http://www.gpo.gov/fdsys/pkg/FR-2013-09-24/pdf/2013-23059.pdf*.

available to the public, and solicited public input during every meeting and through a public docket. In developing the report, FDA, FCC and ONC took into account all of ONC's Health IT Policy Committee's recommendations. The Committee adopted in full the external stakeholder working group's recommendations.

Complementary to the FDASIA section 618 report in development, on September 25, 2013, FDA published its final guidance on mobile medical applications (mobile medical apps).[11] FDA issued the mobile medical apps guidance to provide clarity and predictability for manufacturers of mobile apps. This guidance informs manufacturers, distributors, and other entities about how FDA intends to apply its regulatory authorities to software applications intended for use on mobile devices that perform the same functions as traditional medical devices.

Consistent with FDA's existing oversight approach, which considers functionality rather than platform, the Agency intends a tailored approach. The Agency intends to exercise enforcement discretion for the majority of mobile apps as they pose low risk to consumers. FDA intends to focus its regulatory oversight on the subset of mobile apps that are medical devices that present risks to patients if they do not work as intended. FDA has cleared more than 75 such mobile medical apps since the late 1990s.

Implementing FDASIA is a considerable undertaking, requiring detailed planning to integrate these tasks with the rest of FDA's workload. All told, the 140-page law called for multiple deliverables of all types, including more than 30 proposed and final rules, more than 40 draft and final guidance documents, more than 20 reports to Congress, and many other additional reports,

[11] CDRH, "Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff" (September 25 2013), available at *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf*.

assessments, public meetings, and plans. FDA continues to meet most of its FDASIA milestones and is on track to implement more provisions very soon. To help the public keep track of our progress on these and other provisions, we established a FDASIA web portal that includes a link to our three-year implementation plan, which we update regularly.[12]

DQSA Implementation

This past fall, Congress passed—and on November 27, 2013, the President signed—DQSA. This new law contains important provisions relating to the oversight of compounding of human drugs and outlines steps to an interoperable system to identify and trace certain prescription drugs as they are distributed in the United States.

Compounding

Title I of DQSA, the Compounding Quality Act, removes certain provisions from section 503A of the FD&C Act that were found to be unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide. In addition, the new law creates a new section 503B in the FD&C Act. Under section 503B, a compounder can become an "outsourcing facility." An outsourcing facility will be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from current good manufacturing practice (CGMP) requirements. Outsourcing facilities must comply with CGMP requirements, will be inspected by FDA according to a risk-based schedule, and must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

[12] *http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm20027187.htm*.

If compounders register with FDA as outsourcing facilities, hospitals and other health care providers that purchase drugs necessary to meet the medical needs of their patients can provide patients with drugs that were compounded in outsourcing facilities, subject to CGMP requirements and Federal oversight.

On December 4, 2013, a week after the bill was signed, FDA took several actions to implement the Compounding Quality Act. These included issuance of three draft guidances related to implementation of sections 503A and 503B of the law, three *Federal Register* Notices soliciting nominations for various lists of drugs that can and cannot be compounded, and significant stakeholder outreach.

Since then, FDA has solicited nominations for members of the Pharmacy Compounding Advisory Committee and published a list of compounders that have registered with FDA as outsourcing facilities under section 503B of the law. As of February 28, 2014, 30 companies had registered.[13] FDA has also scheduled a 50-state meeting for March 20-21, 2014, to discuss implementation of the Compounding Quality Act.

New problems continue to be identified at compounding pharmacies across the country, and FDA intends to continue its inspection and enforcement efforts to address these problems using currently available resources. FDA intends to continue proactive and for-cause inspections of compounding pharmacies and plans to take action, including enforcement actions, as appropriate to protect the public health.

[13] Company list, facility information, and information about what it means to register as an outsourcing facility are available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm*

Track and Trace

DQSA also outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. The development of the system will be phased in with new requirements over a 10-year period. These requirements will include placing unique product identifiers on individual drug packages and providing product and transaction information at each sale with lot level information, in paper or electronic format.

Ten years after enactment, the system will facilitate the exchange of information at the individual package level about where a drug has been in the supply chain. The new system will:

- Enable verification of the legitimacy of the drug product identifier down to the package level;
- Enhance detection and notification of illegitimate product in the drug supply chain; and
- Facilitate more efficient recalls of drug products.

This system will enhance FDA's ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful. The system will improve detection and removal of potentially dangerous drugs from the drug supply chain to protect U.S. consumers. Failure to comply with the requirements of the law can result in penalties.

Drug manufacturers, wholesale drug distributors, repackagers, and many dispensers (primarily pharmacies) will be called on to work in cooperation with FDA to develop the new system over the next 10 years.

The law requires FDA to develop standards, guidance documents, and pilot programs and to conduct public meetings, in addition to other efforts necessary to support efficient and effective implementation. FDA developed a schedule for implementing the law's requirements.[14] In addition, last month we established a docket and requested comments on standards for the interoperable exchange of information for tracing of human, finished, prescription drugs, in paper or electronic format.[15]

FDA's Efforts to Protect the Public Health—Now and in the Future

FDA's mission is to promote and protect the public health, and FDA's core responsibilities include ensuring the safety and efficacy of medical products while fostering medical product innovation, overseeing the safety and nutritional quality of four-fifths of America's food supply, the safety of the blood supply and animal feed, and regulating tobacco products. These responsibilities are enormous and the products FDA regulates represent over 20 cents of every consumer dollar spent on products in the United States.

Quality and Safety

Quality and safety are integral to FDA's mission. Food safety and medical product quality depend primarily on the industry, requiring top-level management commitment; a clear and in-depth knowledge of the product and the system; supply chain management throughout the entire life of a product; proactive and continuous management of risk; and continuous and consistent monitoring of quality management systems and processes. Unfortunately, serious quality lapses in recent years have presented serious public health challenges, most notably those involving

[14] *http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm382022.htm*.
[15] *https://www.federalregister.gov/articles/2014/02/20/2014-03592/standards-for-interoperable-exchange-of-information-for-tracing-of-human-finished-prescription-drugs*

foodborne illness, drug shortages, and the compounding of unsafe drugs. Food safety and medical product quality issues lead to higher risks to public health, increased costs, inefficiencies, shortages and recalls, market damage, and, ultimately, loss of consumer trust. FSMA, FDASIA, and DQSA respond to these challenges and present the opportunity to re-think traditional approaches to quality.

FDA plans to redouble its prevention efforts through a focus on quality. The Agency will promote the adoption of quality policies, practices, and standards, both domestically and internationally, aimed at reducing risks in the manufacturing, production, and distribution of FDA-regulated products.

FDA is already taking concrete steps to prioritize quality in the day-to-day work of staff across the Agency. For example, CDRH continues to advance the Case for Quality Initiative for medical devices and has established a Voluntary Compliance Improvement Program pilot. CDER is moving toward creating a new Office of Pharmaceutical Quality to highlight and consolidate quality principles and review throughout the life cycle of drugs. And the Office of Foods is fostering broad, consistent industry implementation of modern preventive practices under FSMA.

Ultimately, all stakeholders globally must work individually and collectively to foster food safety and medical product quality. Industry, regulators, international organizations, health professionals, purchasers, and consumers all have a role in demanding products that are what they say they are and do what they say they will do, delivered through a system that ensures the security and quality of the product.

Diet and Health

In addition to implementing FSMA's prevention framework for food safety, FDA is implementing a wide range of other high-priority food safety and nutrition initiatives aimed at improving consumer access to safe and nutritious food and to the information they need to choose a healthy diet.

For example, FDA has begun a public process to further reduce Trans Fat in the American diet and thereby reduce the risk of heart disease. We recently announced our tentative determination that partially hydrogenated oils, which contain industrially produced Trans Fat, do not meet the criteria for "generally recognized as safe" status under the statute. If, after reviewing the comments and scientific information submitted, FDA finalizes this determination, such oils would become unapproved food additives. That would make their use unlawful, unless a company or other petitioner could prove to FDA that one or more specific uses are safe. We have specifically solicited comment on how such a determination might impact small businesses and whether any special considerations could be made to reduce any burden on small businesses.

We are also addressing concerns raised about the proliferation of caffeine uses in energy drinks, conventional foods and dietary supplements, including products that are readily available and attractive to children. We do not have a concern about the use of caffeine within its traditional boundaries, but we are working with the scientific community and the food industry to ensure that higher levels of caffeine added to new foods and marketed for new purposes meet the relevant safety standards and bear any labeling that may be appropriate to help ensure safe use.

Several initiatives are underway at FDA to provide information to consumers that can help them make healthier food choices and thus could improve their diets in ways that can reduce the risk

and economic costs of chronic disease. Last month, First Lady Michelle Obama announced FDA's plans to update the iconic 20-year-old Nutrition Facts Label based on updated scientific information and data about consumer eating patterns. Among other things, the recently issued proposed rules to update the label propose changes that better highlight the calorie content of food, which is one tool to enable consumers to choose diets that can reduce the tragically high incidence of obesity in the United States. We expect and welcome a wide range of comments on the proposed label changes and look forward to working with industry, consumers, and nutrition experts to improve the food label.

In a similar vein, FDA is working on a final regulation implementing the legislative requirement for nutrition labeling of standard menu items in certain chain restaurants and similar retail food establishments with 20 or more locations. Again, the focus is on calories, so that consumers can readily know what they are getting and can make informed choices when eating out. We expect to issue the Final Rule this year.

Globalization

Just over a decade ago, FDA was responsible for overseeing a largely domestic market of foods and medical products comprised of manufacturers and producers within its borders who were relatively easy to oversee. Contrast that with today's marketplace, where information and goods flow freely across borders, and the development and production of FDA-regulated products has become increasingly complex, fragmented, and global.

These worldwide products create new public health challenges for the Agency. FDA's historical regulatory approaches and tools—such as hoping to intercept products at the border—are outdated and often insufficient. Border inspections will remain important but cannot reach even

a small fraction of the 24 million U.S. food and medical imports a year. To effectively protect the health of Americans, FDA must continue to transform itself—from a primarily domestic agency to one that uses innovative global strategies to secure our vast worldwide supply chain.

Globalization demands that we think, act, and engage globally. Acknowledging that we cannot respond to these challenges alone, over the next five years, FDA will continue expanding its regulatory enterprise, including medical product and food regulators at the international, Federal, and state levels, to build a stronger global product safety net.

Through global coalitions of regulators, FDA will continue developing procedures for more comprehensive and systematic information sharing and deployment of resources, with an ultimate goal of mutual reliance—a point where FDA and other regulators can rely on each other, as well as on private third parties, to protect and improve product safety.

"Smart" Regulation

In the midst of rapid scientific development and an increasingly global and complex marketplace, FDA's mission of promoting and protecting the public health has become even more challenging. FDA must address these new challenges expeditiously, as it continues to meet its core responsibilities. Public trust in FDA oversight breeds confidence in our regulated industries, at home and in the global marketplace. In order to keep the public trust and maintain FDA's global leadership role in fostering innovation, we must employ smart regulation.

The term "smart regulation" embodies the concept that protecting the public health while encouraging innovation is an attainable goal and it is attainable through smart, sound, science-based regulation. Smart regulation also necessitates that FDA remain dynamic; continually

respond to changing situations, new information, and new challenges; and that it always brings the best possible science to bear. Regulation, when done right, can be a pathway toward meaningful innovation; instill consumer confidence in products and treatments; prevent recalls that threaten industry reputation and consumer trust; and spur industry to excellence.

Over the last few years, FDA has worked hard to keep the public trust and maintain its global leadership role in fostering innovation by deploying smart regulatory approaches to streamline and modernize its regulatory programs and minimize regulatory uncertainty for industry, without compromising safety. This commitment will continue into the future.

Regulatory Science

The 21st century has seen rapid advances in biomedical research. New cutting-edge technologies that have led to thousands of new drug candidates include: the sequencing of the human genome; combinatorial chemistry, a new method of chemical synthesis that makes it possible to prepare thousands of compounds in a single process; biosynthesis, which enables scientists to synthesize complex chemicals in living cells; and high throughput screening, which allows researchers to quickly conduct millions of genetic, chemical, or pharmacological tests. In addition, cutting-edge electronics and materials science have the power to transform medical devices, and research on nanotechnology-based materials will provide a better understanding of the safety of the use of nanomaterials in food, over-the-counter drugs, and cosmetics. FDA's regulatory science research agenda is critical to help translate new technologies and basic science discoveries into safe and effective real-world diagnostics, treatments, and cures and reduce the time, complexity, and cost of product development.

In 2011, FDA recognized that advancing regulatory science was necessary to enable FDA to keep abreast of emerging technologies, and indeed, to stay ahead of the curve. That year, the Agency released its strategic plan entitled "Advancing Regulatory Science at FDA."[16] Since that time, FDA has been modernizing its scientific infrastructure by enhancing its internal research capacity and access to outside scientific expertise, and by expanding external collaborations. Early efforts have included:

- The Medical Countermeasures Regulatory Science Program—this program funds a number of projects conducted by internal FDA scientists, external organizations, and public-private partnerships;
- The Biomarker Qualification Program—this program was established to support CDER's work with external scientists and clinicians in developing biomarkers;
- Modernizing Toxicology Safety Assessments—FDA has worked in collaboration with the National Center for Toxicological Research to modernize toxicology safety assessments;
- The Entrepreneurs in Residence Program in CDRH—this program enables the Center to recruit world-class entrepreneurs and innovators to join highly qualified FDA scientists to develop solutions that impact innovation; and
- Public-Private Partnerships—these partnerships include: the Centers for Excellence at the University of Maryland and Georgetown University and the virtual Center of Excellence in Regulatory Science formed with the State of Arkansas, which promote cross-disciplinary regulatory science training, scientific exchanges, and research; and the Medical Device Innovation Consortium, a partnership between FDA, NIH, CMS, medical

[16] *http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm*

device companies, patient advocacy groups, and non-profit organizations, such as the Pew Charitable Trusts, to advance regulatory science for devices.

In addition, in October 2013, FDA issued a report entitled "Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development" to help the industry capitalize on advances in personalized medicine. FDA has long understood that therapies targeted toward individual patients were a major wave of the future.

Stewardship

During these challenging fiscal times, maximizing public health value from each federal dollar has become increasingly demanding for FDA as the Agency attempts to keep pace with the dramatic technological and market-based changes, impacting how foods, drugs, biologics, and devices are produced. From personalized medicine and nanotechnology to the globalization of our food and medical product supplies to an array of new laws passed by the Congress that expand FDA's oversight responsibilities, these complicated issues do not always include additional resources to support FDA's new responsibilities. Therefore, it is critical that FDA continues to effectively and efficiently utilize its limited resources to increase productivity while also maintaining program integrity.

In today's era of budget constraints and ever-increasing requirements to do more with less, it is imperative that FDA takes a hard look at how it approaches its work to identify ways to modernize and maximize efficiency. The Agency will continue to prioritize recruiting, developing, and retaining a high-quality workforce; fostering a culture of continuous improvement; emphasizing customer satisfaction; and embracing excellence from its programs. FDA has established operational excellence and accountability objectives to align resource

planning, allocation, and management with the Agency's strategic priorities to better ensure timely delivery of services critical to the fulfillment of FDA's mission.

FDA must be an organization that delivers smart regulation through lean management that relies on the best available evidence and science to drive decision-making. Responsible stewardship of our public funding and user fees requires collaboration across FDA to perform the mission-specific core regulatory activities, which engage not only the regulatory science disciplines but also Agency experts in policy, planning, informatics, analysis, management, and communications. FDA is continuing to invest in a talented and diverse workforce that can help to fulfill the Agency's important public health and regulatory roles. FDA is improving its systems and process for hiring, paying, training, assessing, and retaining staff.

The Agency is fostering a culture of continuous improvement that includes encouraging programs to prioritize actions that have the most public health impact, communicating with and learning from others to innovate and solve problems, and quickly reassessing when outcomes are not ideal or do not move forward. FDA is also developing performance metrics that align with program requirements to help drive outcomes.

Focusing on customer improvement and expectations of excellence, both internally and externally, FDA is allowing for more timely information sharing and collaboration. This includes systems that track critical resources and support functions.

CONCLUSION

FDA's responsibilities have undergone huge transformations through such important laws as FSMA, FDASIA and DQSA. Our commitment to implementing the responsibilities entrusted to

the Agency by Congress, to improve the lives of the American public with integrity, is unwavering. We look forward to continuing and improving on the critical work we do.

I am happy to answer any questions you may have.