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PROTECTING THE PUBLIC HEALTH: EXAMINING FDA'S INITIATIVES AND PRIORITIES

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED THIRTEENTH CONGRESS

SECOND SESSION

ON

EXAMINING THE FOOD AND DRUG ADMINISTRATION'S INITIATIVES AND PRIORITIES, FOCUSING ON PROTECTING THE PUBLIC HEALTH

MARCH 13, 2014

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C O N T E N T S

STATEMENTS

THURSDAY, MARCH 13, 2014

PROTECTING THE PUBLIC HEALTH: EXAMINING FDA'S INITIATIVES AND PRIORITIES

THURSDAY, MARCH 13, 2014

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 9:32 a.m., in room SD–430, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Casey, Franken, Bennet, Baldwin, Warren, Alexander, Enzi, Isakson, Roberts, and Murkowski.

OPENING STATEMENT OF SENATOR HARKIN

The CHAIRMAN. Good morning. The Senate Committee on Health, Education, Labor, and Pensions will come to order. We have convened this hearing to examine FDA's implementation of key public health initiatives being undertaken by the agency, including several significant reforms passed out of this committee over the last few years.

Our Nation faces a variety of public health challenges in this early part of the 21st century. There have been rapid changes in where our products are made and how they're made and where our food comes from. There have been major innovations, including treatments that save lives, and a better and more diversified food supply. But these new dynamics also present new risks and greater challenges for regulatory oversight.

The HELP Committee has been able to address many of these challenges in recent years, proving that things can still get done in Washington. I want to thank Ranking Member Alexander for being a great partner and also Senator Enzi and all the members on this committee and their staffs. We've worked together in a collaborative and bipartisan manner to address these public health issues head on.

Let me just summarize a few. Last fall, a year after the meningitis outbreak from compounded sterile drugs killed 64 people and sickened 751 patients across 20 States, we passed the Drug Quality and Security Act, which clarifies and strengthens oversight of compounded drugs.

In 2012, we passed the Food and Drug Administration Safety and Innovation Act, which, along with authorizing several FDA user fee programs, sped up patients' access to generic drugs, modernized FDA's ability to regulate the global drug supply chain, established tools to prevent and mitigate shortages of prescription

drugs, and implemented reforms to help bring critical drugs and medical devices to market faster.

In 2011, we enacted the Food Safety Modernization Act, a landmark law that brings America's food safety system into the 21st century to better protect Americans from contaminated food and food-borne illness.

Finally, in 2009, the Family Smoking Prevention and Tobacco Control Act, which this committee spearheaded, became law. It gives the FDA the authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health. So this committee, I believe, has been very active in addressing the health and safety needs of Americans.

I also want to take this opportunity to thank you, Commissioner Hamburg, and to commend the FDA for the recent proposal to update the Nutrition Facts Panel we see on packaged food. The last update to these labels, in 2006, prompted manufacturers to reduce trans fat in many of their products, and I'm hopeful that this new proposal will further support Americans in their efforts to make healthy decisions for themselves and their families.

So this hearing will focus on FDA's implementation of these reforms, as well as other key public health initiatives that are now confronting us and being undertaken by the agency, and other concerns to members of this committee. We are pleased to have Commissioner Hamburg of the FDA here to talk to us about their efforts and answer our questions.

I'll turn now to Senator Alexander for his opening remarks.

OPENING STATEMENT OF SENATOR ALEXANDER

Senator ALEXANDER. Thanks, Mr. Chairman. Thanks for having this very timely hearing.

Dr. Hamburg, thank you for being here today. We look forward to visiting with you.

I'm going to devote most of my attention to the Drug Quality and Security Act, which was signed into law last fall to clarify FDA authority over compounding pharmacies. That's very important to many States, but especially to Tennessee. The fungal meningitis outbreak in 2012 was a nightmare for us, as 137 Tennesseans became sick and 16 others died from the outbreak which was caused by contaminated steroid injections distributed by a poorly regulated compounding facility in Massachusetts.

While the final legislation, the law, was not as strong as the bill that passed this committee, the law does make it clear that either the FDA or the State is overseeing each compounding facility. And just to review, the law says that large facilities compounding sterile drugs without prescriptions now have the ability to voluntarily register with the FDA as outsourcing facilities committed to higher standards for sterile compounded drugs, to report adverse events, put on certain labels, and list all the products they make with the FDA.

The legislation, the new law, kept State oversight of traditional pharmacies, the corner drug store, and FDA oversight over drug manufacturers. The FDA gets plenty of criticism from time to time. But I want to give credit where credit is due on this one.

You have responded to a crisis—and it was—as if it was a crisis. You're off to a fast start in implementing this important legislation, I appreciate that.

On December 4, just 1 week after the legislation was signed into law, FDA published three guidance documents. It's been just a little over 100 days since the President signed the law, and in that time, 30 facilities have registered as outsourcing facilities nationwide. They've done this voluntarily. And these 30 facilities have done this without receiving guidance on the requirements they'll have to meet for the sterile drugs they make. So that's a good sign. And I believe that once we have more clarity, the number of outsourcing facilities will go up significantly.

Now that the law is established, who is on the flag pole? FDA and States can take the action necessary to make sure compounded drugs are safer in the future. You've continued inspections and enforcement actions, and you've sent numerous warning letters, referrals to State boards, and publishing inspection observations for many pharmacies.

In the question time, I hope to learn what policies you're developing and when we will see the guidance on the quality standards outsourcing facilities must comply with; and, No. 2, what your enforcement priorities are and how you plan to followup on the warning letters. The New England Compounding Pharmacy had received a warning letter, and I want to ensure there will be appropriate followup from the agency this time. And, third, now that we've established who's on the flag pole, how are you coordinating with States on what they're doing?

I thank you for your quick work in implementing this law, and I look forward to hearing about future plans on some other areas where the FDA's pace seems to be moving rather slowly. I hope the way you've worked on compounding pharmacies might set an example for how you might move ahead, for example, on the Center for Tobacco Products. You've gotten $1.7 billion in user fees to date for tobacco. Over 4,000 applications are filed. You've acted on 34.

Congress also instructed FDA to set up a regulatory pathway for biosimilars—that was March 2010—and established a biosimilar user fee 2 years later. Almost 4 years later, we don't have an approved biosimilar product in the United States, and many questions linger.

My last example comes from the implementation of the Food Safety Modernization Act. My understanding is that the FDA is going to re-propose parts of the proposed regulation due to widespread stakeholder concern about the cost and complexity of these regulations after the law emphasized the need for a science- and risk-based flexible approach.

I urge the FDA to improve responsiveness to congressional inquiries. There is one letter I sent last July to which I have not yet received a response. And in that light, I will send in writing a question that Senator Fischer of Nebraska has that she'd like answered. I won't deal with that orally, but I'll provide that to you separately.

But all in all, Commissioner, I thank you for the FDA's fast start on implementing the compounding pharmacy legislation, and we welcome you to the hearing.

The CHAIRMAN. Thank you very much, Senator Alexander.

On behalf of the committee, I'd like to welcome our witness today, Dr. Margaret Hamburg, the 21st Commissioner of the U.S. Food and Drug Administration since 2009. She is the top official of the FDA, an agency with the fundamental mission to protect and promote the public health.

Dr. Hamburg received her M.D. from Harvard Medical School and completed her residency at what is now New York Presbyterian Hospital/Weill Cornell Medical Center. Commissioner Hamburg has an impressive background as a doctor, an NIH scientist, and has significant public health experience from her previous post at New York's Department of Public Health and Mental Hygiene and the U.S. Department of Health and Human Services.

Dr. Hamburg, we thank you for sharing your expertise with the committee and being here today. Your statement, which is an extensive statement, which I got through yesterday and last night, will be made a part of the record in its entirety. I'd like to maybe give you up to 10 minutes to go through that, if you would like, rather than just 5—however close you can keep it, but below 10 minutes. And I'm going to request that the record remain open for 10 days for Senators to submit statements or questions for the record.

A couple of things—at 10:30, I have to leave. Both of us have to leave.

Senator ALEXANDER. Senator Enzi will stay.

The CHAIRMAN. OK. Good. I think Senator Franken said he would take over at that time if we continue on beyond that time. But we're managing a bill on the floor that we have to leave for at 10:30.

Again, Dr. Hamburg, welcome and please proceed.

STATEMENT OF MARGARET HAMBURG, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, SILVER SPRING, MD

Dr. HAMBURG. Thank you very much, and I know that you are pressed for time, so I wanted to keep my oral statement relatively short. I really thank you, Mr. Chairman and members of the committee, for the opportunity to be here to discuss some of the important initiatives that FDA has been working on with regard to the implementation of several new laws recently passed with this committee's leadership: the Food Safety Modernization Act, the Food and Drug Administration Safety and Innovation Act, and the Drug Quality and Security Act.

I also really want to express my gratitude to you and the members of the committee for championing the passage of these landmark laws. They all represent remarkable accomplishments done, as you noted, in a bipartisan way, and their importance to public health really cannot be overstated.

We also welcome the opportunity to return to the committee to provide a more detailed review of our implementation of the 2009 Family Smoking Prevention Tobacco Control Act, as you requested, which really lays a strong foundation for protecting the public health from the harms of tobacco products.

First, food safety. Reducing foodborne illness in the United States is one of the FDA's most important responsibilities. The toll that it takes on public health is profound: an estimated 48 million illnesses, 128,000 hospitalizations, and 3,000 deaths every year from foodborne illness. Moreover, the overall negative economic impact of foodborne illness in the United States, including cost to farmers, food processors, and consumers, may be as high as $77 billion per year.

Thanks to you and your colleagues, who enacted the Food Safety Modernization Act, FDA now has tools to significantly lessen these impacts. FSMA's central framework, as you know, is aimed at building preventive measures across the food system from farm to table, including produce safety, modern preventive controls, guarding against intentional contamination, modernizing oversight of imported foods, and ensuring safe transport.

Over the past year, FDA has put forth seven proposed rules on these topics for public comment. But new rules alone won't get us to our goal. FDA must have the resources to implement them; to provide the technical assistance to small food processors, for example; to build the capacity of our States as partners in this important effort; and also, very importantly, to begin the long delayed process of better oversight of imported foods, which are increasingly important in our food supply.

Simply put, without a significant increase in resources, we will not achieve FSMA's vision of a modern food safety system and a safer food supply.

With respect to FDASIA, building on a successful model, the Food and Drug Administration Safety and Innovation Act reauthorized user fee programs for innovator drugs and medical devices and also established two new important user fee programs for biosimilars and for generic drugs. Coming at a time of continuing budget constraints, this steady source of funding is really essential for speeding safe and effective new products to patients and providing predictability and consistency for industry.

The law also gave FDA new authority to better protect the drug supply chain in an increasingly global marketplace. In addition, FDASIA provided the agency with new authorities to combat drug shortages and also to stimulate antibacterial drug development, enhanced development of pediatric medicines, and encourage drug and device product innovation.

I want to highlight just a few of the successes that we've already seen. As part of the negotiated agreement with industry, FDA committed to meet much-enhanced performance goals for medical device reviews. Since fiscal year 2010, we have achieved a 27 percent decrease in the backlog of lower device applications and a 10 percent decrease in average total review time. For higher risk devices, we've seen a 43 percent decrease in the backlog and a 32 percent decrease in average total review time.

Recognizing the need to stimulate investments in antibacterial drugs, FDASIA created incentives for their development. Since the passage of FDASIA, FDA has granted 41 qualified infectious disease product designations under this new program, which I think is a promising start. I'm pleased that after a series of interventions, including use of new authority provided under FDASIA, the

number of new drug shortages declined very significantly from 251 to 117 between 2011 and 2012, and then fell even further to 44 in 2013. However, there do continue to be shortages that persist for longer periods, and we're working aggressively with all the tools at our disposal to prevent and mitigate them.

With respect to the Drug Quality and Security Act, the last time, as was noted, that I appeared before this committee, we were in the midst of a nationwide public health crisis related to the fungal meningitis outbreak caused by compounded medications. Thanks, truly, to this committee's leadership, we now have the Drug Quality and Security Act, which contains important provisions relating to compounding oversight and also outlines steps to an interoperable system to identify and trace certain prescription drugs.

As was noted, within 1 week of passage of DQSA, FDA took several actions to begin implementation, including the issuance of three draft guidances, three notices soliciting nominations for drugs that can and cannot be compounded, and significant stakeholder outreach has been undertaken. As of this week, 35 firms have, in fact, registered with FDA as outsourcing facilities. We intend to continue inspections of compounding pharmacies and to take enforcement actions as appropriate to protect patients.

So without a doubt, FDA's responsibilities have undergone huge transformation through these important new laws. Our commitment to implementing the responsibilities entrusted to this agency by Congress to improve the lives of the American public, to protect their health, safety, and welfare is unwavering.

We are committed to working closely with you on these important new laws, as well as so many other issues. We really believe that our work is vital and the partnership with you is vital, and that we are making a difference in the lives of Americans.

Thank you.

[The prepared statement of Dr. Hamburg follows:]

PREPARED STATEMENT OF MARGARET A. HAMBURG, M.D.

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 land-

mark 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 dialog 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 fiscal year 2015 budget proposes a registration fee and an import user fee that will help FDA meet its food safety obligations under FSMA, while also benefiting 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 imple-

menting 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]

[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*.

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 5 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 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 fiscal year 2013 MDUFA III performance goals, and the program has already seen a 27 percent decrease in the backlog of 510(k)'s compared to fiscal year 2010, a 10 percent decrease in average total time for review of 510(k)'s compared to fiscal year 2010, a 43 percent decrease in the backlog of Premarket Approval (PMA) applications compared to fiscal year 2010, and a 32 percent decrease in average total time for review of a PMA application compared to fiscal year 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 6 months of contract award.[4] The following high-priority recommendations were published on December 11, 2013:

- 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 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.

Last, FDA has facilitated development of the most comprehensive list of generic drug industry participants: more than 3,500 manufacturing and testing facilities

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[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*.

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

have submitted self-identification information to FDA during the fiscal year 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 5 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 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

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

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

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 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 3-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 5-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 2-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.

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

[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*.

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 decisionmaking, (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.

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

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

[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*.

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 Web sites 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 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, 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 3-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.

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[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*.

[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.

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.

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[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*.

[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*.

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 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 5 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 Regu-

latory 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 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.

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

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.

The CHAIRMAN. Thank you very much, Dr. Hamburg. We'll start a round of 5-minute questions. I have two tracks I want to go on. I don't know if I can get them in in 5 minutes, but I'll try. I'd like to have you address, if you can—perhaps I'll submit the question in writing—sodium consumption and the reduction of sodium in our foods.

But I really want to focus my question on opioids. In 2002, doctors in America wrote 144 million prescriptions for opioids, 144 million. Ten years later, they wrote 241 million prescriptions for opioids. In 1999, 4,030 people died from prescription opioids overdose, and 16,651 died in 2010, more than heroin, opium, everything else combined. That's OxyContin, Percocet, Vicodin, all those.

On October 25, 2013, the FDA approved a new hydrocodone, Zohydro. Forty experts urged the FDA to reconsider its approval, and here's a statement they made,

> "In the midst of a severe drug addiction epidemic fueled by overprescribing of opioids, the very last thing the country needs is a new, dangerous, high-dose opioid."

One expert said, "It's a whopping dose of hydrocodone packed in an easy to crush capsule. It will kill people as soon as it's released." And then I found in the newspaper this morning—the *Washington Post*, where I'm getting some of this information—I don't know if it's right, but I'm just reporting what they said. The advisory panel, your advisory panel, voted 11 to 2 against approving Zohydro, and yet the FDA went ahead and approved it.

What I find startling is that in the United States, we have 5 percent of the world's population, but we have 99 percent of the world's consumption of hydrocodone. Hydrocodone-based pain killers are the most prescribed pharmacy drugs in the United States—as I said, 241 million for hydrocodone. It was 131 million prescriptions in 2011.

I didn't realize we were so painful in this country. What's happened? We had a hearing on pain here last year. I may have to have another one. Pain clinics, all these—you go to a doctor, and they're prescribing pain killers, opioids. People go back and get them refilled. You've got a pain, you go to the doctor, and they prescribe this. What's happening to our doctors in this country?

We had a panel here last year that said a lot of it is not physiologically caused. It may have a physiological manifestation, but it's not physiologically caused. And now the FDA comes along and approves what I understand to be something that is 10 to 20 times more powerful than OxyContin when your advisory panel voted 11 to two.

There was an editorial in the *Post* this morning plus another story in the Post. Could you address that, please?

Dr. HAMBURG. As you know, it's a very complex problem, a very serious public health threat. We are working very hard to address what FDA can do to make sure that patients with legitimate pain needs get what they need, but also to recognize the serious addiction potential of these drugs and that we need to do what we can internally and, of course, work more broadly with all the components. As you noted, prescriber practices is an important component of this overall problem.

With respect to your question on Zohydro, let me address it as best I can. Hydrocodone is a very important opiate for the treatment of legitimate pain, and we do have many medical needs for both acute and chronic pain management. Hydrocodone, up until the approval of Zohydro, was only available in a product that also included acetaminophen, which has significant liver toxicity.

As you know, some patients respond to different drugs differently, and some can tolerate hydrocodone much better than they can tolerate other opiate drugs. But at the lower doses, where it was available in the combination product, there are serious risks, if you upped the dose of the hydrocodone, of liver toxicity and serious life-threatening complications from the acetaminophen. So this product is unique in terms of its availability as a single hydrocodone product without that associated liver toxicity risk.

The advisory committee met, actually, before we put in place more stringent labeling requirements around the use of this class of drugs that we think are important for assuring appropriate use for patients with legitimate pain. It is approved as a Schedule II drug, which means that there are additional restrictions on prescribing. Physicians have to have a special license. There are limits on prescriptions—no refills. There are special security precautions and requirements that have to be undertaken with respect to the storage of the drug and reporting requirements.

It's a Schedule II drug, which has these additional requirements to limit its use and, hopefully, to make sure that it is prescribed and used appropriately for pain where it is required. In addition, there is a REMS for this drug product that places further restrictions on the use and also requires the company to make available physician training for its appropriate use.

So we recognize that this is a powerful drug. But we also believe that, appropriately used, it serves an important and unique niche with respect to pain medication, and it meets the standards for safety and efficacy. Recognizing its addiction potential and understanding, of course, the broader context of the serious problem of opiate medication abuse and misuse in this country, we weigh carefully risks and benefits.

We hope that as a Nation, we can make progress in addressing all of the issues that contribute to this ongoing and very serious opiate misuse and abuse epidemic, and we will continue to push hard. We also are trying to ensure that work is going forward with respect to the science and technology of abuse deterrent formulations so that, hopefully, we can move in that direction going forward.

The CHAIRMAN. Thank you, Commissioner. I have followup questions, but my time is out. I'll submit those in writing.

Senator Alexander.

Senator ALEXANDER. Thanks, Mr. Chairman.

Dr. Hamburg, I've complimented you and the FDA for your fast start on implementing the compounding pharmacy. I'd like to just discuss that with you a little bit. I think we understand each other on this. One of the reasons, in my opinion, for the tragedy was some confusion about who was on the flag pole, whose job it was to regulate the Massachusetts facility.

My understanding is that now the law clears that up, that a compounding pharmacy that compounds sterile drugs may choose to be regulated by you, or, if not, they're regulated by the States. Is that right?

Dr. HAMBURG. First, let me thank you for your leadership on this issue and the important issue of trying to clarify through legislation important aspects of the compounding pharmacy law and requirements for oversight. I would say that this is a very, very important step forward in terms of that effort and also really defining a new role for the FDA.

I do have some concerns, and I think that you're aware that FDA, as the legislation was being shaped, was concerned about the fact that even with clarifying 503A, so we now know that it does apply nationwide, it is still possible that a compounding pharmacy could be in compliance with some aspects of 503A, compounding a specific product for a specific patient with a prescription, ET cetera, but might be out of compliance with other components, such as compounding an FDA approved drug or other aspects. So there still is an opportunity for some confusion there.

With respect to 503B, we are concerned that since it is voluntary and companies can choose to register with us and be under our oversight, some may not.

Senator ALEXANDER. True.

Dr. HAMBURG. And if they sort of hide out as 503A traditional compounders, we may not even know that they exist.

Senator ALEXANDER. I've only got 5 minutes here, so I want to get to—yes, I understand that. And the Senate bill, of course, wanted to go further, but the law didn't go that far. But, fundamentally, you've got 35 facilities that have already agreed to be regulated by you, and at the same time, you're able to and are—I mean, you're issuing warning letters to others.

Dr. HAMBURG. Yes.

Senator ALEXANDER. So I have a couple of questions on that. On your followup to the warning letters, I also understand that some States are indicating, I've heard, that they may require an outsourcing facility that has chosen to be regulated by the FDA also to be regulated by the State as a pharmacy. Have you heard that? That wasn't really the intent of the legislation. It was to permit a facility to choose one or the other.

Dr. HAMBURG. I have not heard that specific concern. States vary, as you know, considerably in terms of their laws and their resources for the oversight of compounding pharmacies. What I have heard from States is that when there are these large facilities that are manufacturing high-risk sterile injectable products, they

often don't feel equipped to provide that regulatory oversight. So they hope that those facilities will register with FDA.

Senator ALEXANDER. But at least under the law, manufacturers, you've got. You regulate manufacturing.

Dr. HAMBURG. Right.

Senator ALEXANDER. Outsourcing facilities are all yours. The rest are the States'. But when will you be issuing more—I guess you call them draft quality standards——

Dr. HAMBURG. Yes.

Senator ALEXANDER [continuing]. So that the other compounding pharmacies will know what will be expected of them if they choose to be an outsourcing facility.

Dr. HAMBURG. We are working to develop the good manufacturing practices guidelines for those outsourcing facilities, and we'll get that out as quickly as we can. I think that these kinds of facilities understand the sort of broad framework that they can expect in terms of good sterility practices, ET cetera. But this is very, very important and a high priority for us, and we will be moving forward.

Senator ALEXANDER. Do you have any estimate of how many of these facilities that compound sterile drugs exist that are eligible to be outsourcing facilities? Do you have any idea?

Dr. HAMBURG. We really don't know what that number is, and we're hoping that now, as we implement this important new law and begin this process, we'll begin to get a much better sense. And, of course, we are also increasing our partnership with the States, and, actually, we're having a second 50-State meeting next week to help strengthen the communication, both the understanding of what this new law means for all of us and also to make sure we've got the right systems for communication.

We've also been doing a lot of outreach with healthcare providers, hospital systems, ET cetera, because we hope that they will see this, the outsourcing facility mechanism, as what is best for their patients in terms of assuring quality and regulatory oversight, and that it will become the standard of care so that more and more companies will declare themselves to us and we will be able to work with them in this way.

Senator ALEXANDER. That is my hope, too, and I'll be anxious to watch this as it moves along.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Alexander.

I have in order here Senator Warren, Senator Isakson, Senator Bennet, Senator Enzi, Senator Murphy, and Senator Casey, and now Senator Franken.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you very much, Mr. Chairman and Ranking Member Alexander.

Welcome, Dr. Hamburg. It's good to see you here today. The CDC estimates that more than 2 million people develop antibiotic resistant infections in the United States every year. There's increasing scientific evidence that the overuse of antibiotics in animal agriculture is contributing to the rise in antibiotic resistance.

The more we use an antibiotic, the less effective it becomes at fighting resistant infections. If we continue to use 30 million pounds of antibiotics in food animals every year, which is about four times as much as we use in people, we're likely to have a lot more resistant infections and fewer antibiotics that work when we need them.

So the FDA's most recent guidance documents on this subject concluded that the use of antibiotics in animal agriculture for production purposes, to promote growth in animals—and I'll quote you here—"may contribute to antibiotic resistance." But the FDA says that antibiotic use for disease prevention is all right. And you've asked pharmaceutical companies that sell antibiotics to animal growers to voluntarily withdraw their FDA approvals for those uses.

Now, we've heard preliminary reports that all 27 companies that manufacture animal antibiotics agreed to comply with this directive and will submit supplemental new drug applications to revise their labels. Surely, the removal of production uses from the market is a good first step, and I'm hopeful that this is going to lead to decreasing use of antibiotics.

But the FDA's guidance doesn't guarantee the prudent use of antibiotics in the context of disease prevention. Even with every animal drug company agreeing to comply with the FDA's most recent guidance, there could still be a lot of antibiotic use in animals that is ostensibly for disease prevention, but it is still far more than necessary and will continue increasing resistance.

So how will these guidances and the FDA's review of labeling changes ensure that we're reducing the antibiotic use in agriculture and decreasing the risks of perpetuating resistance?

Dr. HAMBURG. Thank you for the question. It's such an important topic, and it's actually one that, on a personal level, I've been working on for most of my career. I really am encouraged by some of the steps that we are taking now, and I think they will make a real and an enduring difference.

As you noted, we put forward the guidance asking for companies, both innovator manufacturers and generics, to show us how, over a period of time, they will remove the products for the growth promotion purposes, what we call non-judicious use of the antibiotics. We've been very encouraged.

There was a 90-day period for the companies to report to us their plans for how they would voluntarily comply. That just closed, and we've gotten preliminary indications of very full participation. We'll obviously review what they have put in writing to make sure that we are comfortable, and we'll work with them if we don't think it adequately addresses.

With respect to your question about how we ensure that these antibiotics don't continue to be used inappropriately, although not targeted for the growth promotion, for prevention purposes, we're also going to be moving the oversight of the use of these products to the supervision of a veterinarian, which isn't the case now. So it'll be much more like what you're familiar with, with a prescription from a doctor and the release of a drug. The same will be true with veterinary oversight of the use of these products for the preventive and treatment purposes.

Of course, there will always be a need for antibiotics to treat animals for important illnesses they may have, and, also, there is a role for prevention. But we want to make sure that it's appropriate and adequately supervised, and, especially, that is of importance when they are antibiotics of importance for human medical needs as well.

Senator WARREN. I appreciate that, and I'm running out of time here. So I'll just make the note about the use—moving this over so that veterinarians have to prescribe. Again, I think it's a very good first step.

But veterinarians are permitted to prescribe for anything that's on-label use. And so long as they are permitted to use it effectively for prevention of disease, that means there's the possibility of just continuing to keep these drugs out in circulation, keeping them out there all the time, even with the approval of a veterinarian, and I'm just concerned.

I'll submit the rest of my questions for the record so we can go back to this in detail, including how you're going to track it.

Dr. HAMBURG. Yes. And I'm happy to discuss it further, and we will be able to work in oversight of the prescribing practices of veterinarians in ways that may be reassuring to you.

Senator WARREN. I appreciate that and just want to encourage you along these lines. Thank you very much, Dr. Hamburg.

The CHAIRMAN. Thank you, Senator Warren.

Senator Isakson.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Thank you, Mr. Chairman.

Dr. Hamburg, thank you for being here, and thanks for your service. I'm sure you're probably aware that skin cancer is reaching epidemic proportions in the United States. In fact, one person an hour dies now from melanoma, not to mention disfigurement of squamous cell and basal cell and other skin cancers. The last time the FDA approved an application for an enhanced ingredient for sun screening capability was in 1990. And there are some applications that have been pending longer than a decade for action.

Senator Reed, my Democratic co-sponsor, and myself—and you're familiar with, I think, some of the initiatives we've taken—will be introducing along with members of the House some legislation to make more transparent and more rapid the determination in terms of skin care ingredients in products. We don't want to, in any way, legislate what FDA should approve. But we want to get a more transparent and a more effective system of evaluating these important ingredients for this terrible cancer.

Would you commit to work with our offices on this to ensure that we get a more rapid response to these determinations?

Dr. HAMBURG. Absolutely, and I would agree with you that it has been taking too long. We are eager to work with you on that particular legislation. We are moving forward on our evaluation of the sun screen additives and getting back to sponsors on our assessments. We also are looking at whether we can modernize the overall framework for how some of the over-the-counter products submit applications and are overseen to really try to streamline it and make it more responsive to our modern world.

Senator ISAKSON. We'll certainly work with you and your office to be a positive influence. We don't want to make the decision, but we want to get the decisions to be made, and we know that's your responsibility.

Dr. HAMBURG. Absolutely.

Senator ISAKSON. My second question has arisen in my State from a couple of companies that have asked me questions. I'm not going to get into a specific question of their product, but I do want to ask you about the length of time it takes for FDA to respond to an appeal of an FDA decision.

A particular case was brought to my attention where a decision was made by FDA, and the company governed by that decision appealed the decision based on scientific facts and determinations that were submitted. It's been 2 years, and they still haven't gotten an answer.

Last July, when they called for an update, they were told the decision was pending and would be there any day, and that's been 8 or 9 months ago. So what can people expect on an appeal of a determination by the FDA in terms of a reasonable time within which to get an answer to that appeal?

Dr. HAMBURG. I think it would depend on the product, the nature of the appeal, the regulatory pathway that the appeal was being undertaken. So I can't give you a one-size-fits-all answer. But I would say that I recognize how important it is to make sure that these processes work well and that they are clearly understood by the companies in terms of what timelines will be.

I think it's, no doubt, an area where we can often be more efficient and responsive than we have been, and we really are committed to trying to do the best job possible. But, not knowing the specifics here, I can't tell you when—I do believe I saw a letter from you, and we are moving forward on that in a relatively timely way. But I will get back to you on your specific query.

More broadly, I would say that over the last couple of years, we've been working very hard to really streamline and modernize our regulatory systems to address some of the business process issues that slow things down and to recognize the importance of good, clear communication with companies around these kinds of activities.

Senator ISAKSON. And I understand with breakthroughs in medical science and pharmaceuticals and devices, sometimes devices use pharmaceuticals within themselves, and you've got to determine which one they are.

Dr. HAMBURG. That is true.

Senator ISAKSON. That can get very complicated.

Dr. HAMBURG. Yes. In this arena, as in many other arenas, the world in which our authorities were first established looks very different today. That's why we had to modernize through FDASIA and FSMA, updating the compounding pharmacy laws, ET cetera. We're always needing to really look at whether our systems match the real world needs.

Senator ISAKSON. I appreciate your attention very much. My time is almost up, so I'll just say I'm going to submit another question that is very important with regard to FDA's considering the regulation of medical IT.

Dr. HAMBURG. There is a great deal of interest in that topic.

Senator ISAKSON. We need to look at Congress' responsibility in that as well. So I'll look forward to talking to you about that. Thank you for your service.

Dr. HAMBURG. Thank you.

The CHAIRMAN. Thank you, Senator.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman. I'd like to thank you and the Ranking Member, Senator Alexander, for holding this important hearing.

Commissioner, welcome back. I want to take a minute before I ask my question to thank you for the FDA's work over the last few years. It hasn't been easy to implement a comprehensive FDA reform bill while beginning to also implement a track-and-trace and compounding bill. You came out to my home State of Colorado in 2011 and listened to many people in our bioscience community all across the State who were having difficulty communicating back and forth with the FDA, and you made a commitment then that things were going to get better.

I can tell you honestly that I've heard from many people back home that they've seen a very positive change at the FDA, and I think a lot of that is due to your leadership. Nothing is perfect, but I hear consistently how much things have improved at the FDA. And on behalf of my constituents, I want to thank you for that.

Dr. HAMBURG. Thank you.

Senator BENNET. I also was pleased to see the implementation of a bill that I worked on with Senators Burr and Hatch that created a breakthrough therapy designation for drugs that have shown dramatic results early in the approval process. To date, over 40 treatments have received this designation.

We passed that bill—if you had asked me if we'd be sitting here today with 40 drugs, I would have said you're delusional. But that is, in fact, what's happened. Drugs that are trying to cure various kinds of cancer, cystic fibrosis, hepatitis C, and many other life-threatening conditions.

I visited a number of Colorado patients who are receiving breakthrough therapies, and I can tell you firsthand that it has truly made a lifesaving difference for many who tell me that their dream is only to live a normal life. That's all they want to do, like everyone else, something the rest of us take for granted.

So as a result of this effort to get drugs to patients more efficiently, we've seen a number of people writing to our office asking for more direct dialog with FDA regarding groundbreaking drugs that should be considered to be breakthrough therapies. And while no one wants to unduly influence the science and data that FDA looks at, I believe there should be an avenue for patients to inform the FDA of their opinions about what might be considered for breakthrough.

So, Commissioner, in light of all the work that FDA has already done, I wonder whether you can talk a little bit about the effect this new designation has had at the agency and for the industry and for patients, and whether you might be willing to have more

open dialog with patients to consider information they would supply with respect to breakthrough therapy designation. I apologize for the long windup, but I'm excited to see something in our government working well, and I wanted to give you an opportunity to talk about it.

Dr. HAMBURG. I could give you an answer that would be very long, too. I'll try to be succinct, though. But it's been such an important and exciting new opportunity for us, and we appreciate that it was included in the legislation. Frankly, it has been much more popular and successful than we had anticipated. The other side of that is that we actually didn't get new resources to implement this program.

But we have been able to identify a very large number of exciting drugs that really hold promise to treat serious, often life-threatening illnesses. We've been able already to approve three different products for four different indications under this breakthrough therapy pathway. And I think that we will continue to see it as a very important program.

It underscores, I think, another set of important points that have broader ramifications for our work at the FDA. One of the aspects of it that's been so successful is the early engagement with the FDA review teams and senior level scientists at the FDA to really help shape what the best development strategy is, so that we can ask and answer all the critical questions to address the safety and efficacy questions, but actually move it through the system as quickly as possible so these promising drug candidates can get to the people who need them. And in that regard, the opportunity for engagement of patients is critical.

In another aspect of FDASIA and our FDA work, we actually have been also establishing a series of meetings with patients around some critical disease areas to get their input in terms of how the disease or condition manifests itself in their lives, how we should be thinking about patient-reported outcomes in many instances as an integral part of our study designs, and how to really make sure that we are helping to address critical unmet medical care and public health needs while trying to help speed innovation and product development.

Senator BENNET. My time is up because of my long wind-up, but I want to thank you.

And, Mr. Chairman, I want to thank you, because your leadership in including this really has made a material difference. I think as we see the FDA exercising its muscles around this one part of the pipeline, my hope is that, as you sort of implied, we're going to be able to see it across the FDA as we think about how to make sure that the United States maintains its leadership in bioscience going into the 21st century. So thank you.

Dr. HAMBURG. Thank you.

The CHAIRMAN. Thank you, Senator Bennet. But, again, my thanks to you, because you were the person on this committee who spearheaded that effort for a couple of years, and so I'm very grateful for you sort of taking that over and running with it. I appreciate it very, very much.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

The CHAIRMAN. And you, too. Senator Roberts was also—I forgot. Both Bennet and Roberts were on that issue, now that I think about it. Thank you.

Senator Enzi.

STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman. That used up 10 seconds of my time.

[Laughter.]

I would followup on what Senator Warren was asking about, the animal antibiotics. That's very important in Wyoming, and now there's a proposed veterinary fee directive. She comes from a very heavily populated State. I come from a very sparsely populated State and one that's underserved by large animal veterinarians. So we have some different problems with that.

In light of her one question taking up all 5 minutes, I'm going to submit that one in writing.

Dr. HAMBURG. OK.

Senator ENZI. I worked with Senator Tester on the Tester amendment which was the Food Modernization Act that provides specific accommodations for preventive controls in the law for small farmers and producers. What is the status of the implementation of that?

Dr. HAMBURG. The Tester amendment, in particular, or more broadly?

Senator ENZI. Yes, in particular.

Dr. HAMBURG. One of the things—as we have been doing outreach in response to developing our proposed rules and now as we are taking comments—one of the things more broadly than just the Tester amendment is the impact on small farmers and the fact that we have a system where there are very different types of food producers, and we need to find a way to ensure greater food safety, but not impose undue burdens.

Senator ENZI. I'll submit that one with more detail, too.

Dr. HAMBURG. OK.

Senator ENZI. I have heard a number of concerns from food producers about the overly prescriptive framework when considering the preventive controls for human food. What concerns me even more is that it doesn't appear as though the FDA has adhered to the requirements of the Administrative Procedures Act in how it went about publicizing the proposed rule.

Can you provide this committee with a commitment that you'll adhere to the requirements of the Administrative Procedures Act on further rulemaking?

Dr. HAMBURG. I certainly can. And I had not heard that concern. I would say, if anything, we have really done a remarkable job in terms of outreach and engagement and taking comment and responding to comment. So I will go back and ask some questions about that, and we'll certainly followup with you.

Senator ENZI. We'll provide more detail on that, too, then.

For my next question, we're concerned about the abuse deterrent formulations, of course, to make pills harder to crush and inject and use. If the agency establishes a clear pathway and standards for abuse deterrent claims, companies, of course, I think, will con-

tinue to invest in this kind of research. I've been troubled to hear from the drug manufacturers who are working toward that and who would like to adopt abuse deterrent formulations that they are kind of stymied and confused by the FDA's lack of clear and consistent standards.

When do you plan to finalize the guidance, and can we expect the guidance to also include generic versions? It's integral in the fight for prescription drug abuse to use all the available tools, and the regulatory uncertainty is slowing down the particular tool, and I think that's unacceptable. So could you commit to me to finalize the guidance in maybe the next 6 months?

Dr. HAMBURG. I think the guidance is very important and lays out how we're thinking about it. I think, in all honesty, the science and the technology also needs to be developed here, though. We really need to incentivize companies to work hard on this. That's what we want to do. We want to be able to provide them with as much clarity as possible, because it's such an important area, and we need to develop abuse deterrent approaches for these powerful drugs.

Senator ENZI. But there's no time table laid out for it?

Dr. HAMBURG. I am not sure what the timeframe is. I know we issued the guidance maybe a few months ago when—a year ago, and so we——

Senator ENZI. I'll submit that as well, because I know it's a very complicated thing, and I would like a fairly extensive answer on it. I appreciate the efforts on it.

There's also a new pathway to approve biosimilars, and I was very involved in crafting the bipartisan proposal to create a pathway, and then helped lead discussions to ratify a user fee to support that program. You mentioned resources earlier. And I'm very interested in how both are implemented and particularly committed to ensuring that the implementation is consensus-driven with the original law.

Again, I'm looking for a commitment that the FDA will be transparent, that you'll issue guidance as needed to ensure we all understand, and also give the stakeholders, which, of course, would include us, the opportunity to engage with you around the key policy questions before the final decisions are made.

Dr. HAMBURG. Absolutely committed to that. We are standing up the program, as you well know, and have had many discussions with companies that are either developing or interested in developing biosimilars as part of that new program and pathway.

Senator ENZI. Thank you, and I've got some additional questions, but my time is out. So thank you.

The CHAIRMAN. Thank you, Senator Enzi. Let's see. Where are we now? Senator Murphy, Senator Casey.

STATEMENT OF SENATOR CASEY

Senator CASEY. Mr. Chairman, thank you very much.

Dr. Hamburg, we're grateful for your presence here and your good work. I wanted to try to get to at least two areas. One is on this issue of naloxone, and the question of whether law enforcement and others should be able to administer this drug in the case of an overdose to reverse it. In particular, I wanted to highlight an

element of legislation. Tom Udall, Senator Udall, has Senate bill 1657, which is the Increasing the Safety of Prescription Drug Use Act of 2013.

One of the provisions asks the FDA to reconsider the status of naloxone as a prescription drug. I just wanted to have you speak to that. I know you can't make a determination here today, but I just wanted to have you speak to that issue in terms of its value in the context of law enforcement, but, more particularly, as a way to deal with a crisis situation when there's an overdose.

Dr. HAMBURG. Naloxone, as you know, is a very, very important medicine in terms of being able to reverse opiate overdose and certainly used on a very frequent basis and very effectively in the healthcare setting. We have been concerned that many opportunities when it could save a life have been limited because they occur in the community, not in a healthcare setting.

We've actually encouraged and reached out to manufacturers of this product to consider coming in to us with a formulation that could be provided as an auto injector or nasal inhaler that could be more available in community settings. Law enforcement or others, potentially, could take advantage of this kind of formulation, and it could, I think, save lives. So we're encouraged, actually, by the response that we've had from the manufacturers, and we will continue to work on this important issue.

Senator CASEY. I appreciate that. I know that the chairman has raised this issue. A lot of people are working on this. It is stunning, as Chairman Harkin said, the numbers we've seen. The one number that I keep coming back to is people who abuse prescription drugs are 19 times more likely to abuse heroin—just stunning.

Our State of Pennsylvania unfortunately has a third place finish that we did not want to have in terms of heroin abuse. So it's substantial, and we're seeing it not in the stereotypical fashion, not urban communities or places where you might—you know, the popular image of this kind of abuse is in big cities. We're seeing it in rural areas and small towns. So it's very substantial.

Let me just move to one more issue that the chairman also raised—Zohydro, if I'm pronouncing that right. One issue that the chairman raised is the question of the advisory committee recommending against the approval of the product. But also, apparently, the product was approved without any abuse deterrent properties. Is that correct?

Dr. HAMBURG. That is correct.

Senator CASEY. I guess a related question to what the chairman asked is the concern that I think a number of us have—and I'm sure you share this concern—about the implications of allowing this new product on the market without these abuse deterrent properties. Can you speak to that?

Dr. HAMBURG. I would love it if we had abuse deterrent formulations that were actually meaningful and effective at deterring abuse in all instances. We are moving in that direction. We put out, as was noted, guidance for how we would be thinking about reviewing and approving abuse deterrent formulations. What they would need to be able to demonstrate—because it doesn't do any good to label something as abuse deterrent if it actually isn't abuse deterrent.

Right now, unfortunately, the technology is poor. There's one abuse deterrent formulation that is in the marketplace, recently approved. It's abuse deterrent in terms of immediate crushing for uses, injection or for sniffing. It doesn't prevent abuse or misuse when taken orally, and it's, frankly, not where we need to be. It's an important step forward. It demonstrates utility and opportunity, but we need to continue to work with companies and the broader scientific and engineering community to come up with better abuse deterrent formulations that will really work.

We also are committed to working on developing non-opioid pain medicines, because that would make a huge difference as well. You know, acute and chronic pain needs to be treated. Opiates are very effective for acute pain and less effective for chronic pain. But we don't have a lot of good alternatives at the present time. So that's another commitment that FDA has made, to work with companies to try to develop non-opioid pain medicines that really will make a difference for patients.

Senator CASEY. Thank you. I'm out of time. I'll submit some more for the record. Thank you.

Senator FRANKEN [presiding]. We'll go next to Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Thank you, Mr. Chairman.

Dr. Hamburg, thank you so much for coming. I know your time is very valuable. This is a Senator Enzi question, too. It's the same question he asked. I think he pretty well summed it up. But it gets pretty specific, so I'd like to go through it, and I think your answer to Senator Enzi was yes. That's the answer I'm looking for. So we'll give that a try.

There is concern, as you know, from our food industry leaders about the implementation of the Food Safety and Modernization Act, specifically, concerns related to the preventive controls for human food, a proposed rule that I believe is still open for comment. They are specifically interested in the proposed rule mentioning testing and supplier verification requirements in the preamble, but does not provide the specific requirements in the rule.

This can get pretty expensive, to say the least, and there is a whole host of organizations, which I will not go into, that are very worried about this. Can you assure me that you will not finalize the rule with these more prescriptive testing and supplier verification requirements, the ones that are so expensive, unless they go through a full notice and comment period regulatory process, including the revised economic analysis? And can you also assure me that this will not be issued as an interim final rule?

Dr. HAMBURG. What I can assure you is that we have really, from the very beginning, tried to reach out to all of the different stakeholders, hear their concerns, and we've done lots of public meetings, visits, meetings with specific groups and individuals, all trying to get input. It has been a complex set of rules to put forward with many different, sometimes competing interests and concerns.

We have gotten a lot of response back. We're going to be carefully going through all of the comments when the different comment periods end on the rules. We may well reissue codified language on

certain key provisions because of some of the kinds of concerns that you've raised, and I have heard the concerns about some of the economic impacts and analyses as well. So, yes, we will work in a very deliberate, transparent way and continue to try to drill down on these critical questions so that we end up with something that will really work.

Senator ROBERTS. I appreciate that. I think that's a long yes, and I thank you for going into that. In the Food and Drug Administration Safety and Innovation Act, we asked the GAO to look into how regulations and guidance, policies and practices could be modified, streamlined, expanded, or discontinued in order to reduce or prevent such drug shortages. This was also discussed at length with the FDA staff during the drafting of the legislation.

Can you tell me where the FDA is in regards to their internal review of their regulations and what's been done to address instances in which the FDA policies are or were leading to drug shortages?

Dr. HAMBURG. I think a huge amount of progress has been made in the drug shortage area. Certainly, our team, which has been expanded as well, has been working, I think, long hours and very diligently to address both existing shortages and eminent potential shortages in this country. Obviously, industry plays a critical role, and the shortages that occur generally occur because of issues with either their supply chains of products or, importantly, quality concerns in the manufacturing.

But we have seen real improvement in the number of shortages in recent years. The passage of FDASIA has helped to strengthen progress that was being made and really enables us to institutionalize important ways of interacting with industry and important activities within FDA. So we are moving forward and, I think, have made real progress, and I think we have systems that are working and need to continue to be strengthened, of course.

Senator ROBERTS. I understand you're making progress. And pardon me for the interruption. I have about 11 seconds here. But where is your internal review of the regulations? Where would you say that stands now? Are you halfway done, or where are we?

Dr. HAMBURG. I'm not quite sure when you say the internal review with respect to regulations. We had some delays in getting the reports up to you——

Senator ROBERTS. Well, it's an ongoing process.

Dr. HAMBURG [continuing]. But we are——

Senator ROBERTS. But you're getting there.

Dr. HAMBURG. We're getting there, and I really do think that it is a system that is working.

Senator ROBERTS. OK. I appreciate that.

Thank you, Mr. Chairman.

Senator FRANKEN. Before we go to Senator Baldwin, I just want to thank Senator Roberts for your work on the compounding bill.

Senator ROBERTS. Well, thank you, Mr. Chairman. I appreciate that. I'm happy to compound with you any time.

[Laughter.]

Senator FRANKEN. OK. We'll go to Senator Baldwin.

STATEMENT OF SENATOR BALDWIN

Senator BALDWIN. Thank you. And I want to thank, in their absence, Chairman Harkin and Ranking Member Alexander for convening this hearing and giving us the opportunity to ask questions of you. Welcome, Dr. Hamburg.

Dr. HAMBURG. Thank you.

Senator BALDWIN. Wisconsin is home to a vibrant community of innovative medical device companies. There's always interesting things going on. Wisconsin innovators are making significant contributions to medical treatment with breakthrough technologies, such as a state-of-the-art colon cancer screening test and a pioneering sepsis detection device.

In the last several years, the FDA has taken some encouraging steps to enhance patient access to safe devices and to spur product innovation, and we're very excited about some of those, in particular, the FDA's pilot program of parallel review that allows both the FDA and CMS to simultaneously review innovative devices for market approval and coverage determinations. This will help streamline the process for companies and the patients who are served by those innovations.

So, Commissioner, the FDA Center for Devices recently indicated that the agency plans on establishing a new pathway to accelerate the approval of certain devices for patients with serious unmet medical needs. Under this approach, as I've heard, some of the data that typically is collected in device studies could be submitted to the FDA once the device is already approved for use with patients.

This proposal not only has the potential to improve treatment options for patients in need, but also to empower smaller companies to bring new and cutting edge technologies to market by allowing them to target their resources most efficiently and effectively throughout the approval process. So I'm hoping that today you could elaborate on the development of this new pathway and, specifically, if you could tell me how the FDA will assure predictability throughout the process for the device companies, and, importantly, how the agency will make sure that the needed evidence is collected in a post-market setting to guarantee patient safety.

Dr. HAMBURG. That's an important question. There's so much exciting innovation in the medical device arena. The center has been working hard in a number of arenas to really harness those opportunities in science and technology for innovation—the innovation pathway, the entrepreneurs and residence program—and looking now at how we can learn, in some ways, from the drug center and pathways there to try to build in some new mechanisms, recognizing that really understanding safety and effectiveness and benefits to patients of a product has to be sort of a life cycle of the product approach, and that as we look at the preapproval, we also have opportunities to deepen our understanding in real world use with post-marketing surveillance and collection of data and additional studies that are continued.

That's been a theme on the drug side for quite a number of years and continuing now, and I think that is part of the Center for Devices strategic plan going forward. As you noted, this approach of really integrating post-market studies into the overall assessment

and ongoing understanding of a device is very, very key, and it's being shaped, and we are going to be eager to work with industry and patients and consumers and other stakeholders as it moves forward.

Senator BALDWIN. Thank you. We'll follow this and look for more details with great interest.

Mr. Chairman, I'm going to submit some additional questions for the record, but thank you again for the opportunity.

Senator FRANKEN. Thank you. We'll do that.

Senator Murkowski.

STATEMENT OF SENATOR MURKOWSKI

Senator MURKOWSKI. Thank you, Mr. Chairman.

Dr. Hamburg, welcome. We appreciate all that you do. There have been good questions asked about FDA approval of certain drugs, drug shortages. These are issues that I have concern with. But in fairness to your time, I want to shift to a couple of subjects that probably have not been brought up.

One is the shellfish ban that the Chinese have imposed on shellfish coming out of parts of Alaska and the West Coast. This is an issue that might be very narrow in its scope, but has great impact in certainly a portion of my State, impacting some basically family-owned businesses that are really taking a real hit right now.

We sent a letter on March 6 to encourage that there be a delegation to go to China to discuss this issue with the Chinese to see if we can't get faster resolution of this. I understand from NOAA that this meeting is scheduled in China for March 21. The U.S. delegation is going to include NOAA, USTR, and USDA's Foreign Ag Service, but not FDA.

The question to you this morning is: Can you give me any assurances that we are fast-tracking a resolution of this issue, what FDA's role is, and if you will be sending somebody as part of that delegation, and, if not, why not?

Dr. HAMBURG. Well, this is an issue that, obviously, has great importance. It is something where NOAA and the Department of Commerce has the lead in terms of the interactions with the Chinese. We have been providing information and support to them, as well as information about public health assessments to our Chinese counterparts as well.

We are not going to be formally part of the delegation, but we will be in contact with them. We'll be working with them and supporting them, and we also do have an office in China to provide additional support. So we will have input, but we are not in the lead on this. Our focus is really on the public health assessment.

Senator MURKOWSKI. Well, I understand. I appreciate that. My only concern is that if there are issues that arise in this meeting that speak to the specific jurisdiction of FDA, I would hate for things to be held——

Dr. HAMBURG. And we will be available to them—and they know it—24 hours a day to provide that technical support.

Senator MURKOWSKI. All right. Then I would like to turn to a subject that I have brought up before this committee, and no offense to the chairman here, but we often refer to this alien species

of fish as a Frankenfish. No offense to Senator Franken here in any way, shape, or form.

Senator FRANKEN. Offense taken, however.

[Laughter.]

Dr. HAMBURG. There's actually an inflatable Frankenfish that I've seen.

Senator MURKOWSKI. Now, see, that's even worse.

Senator FRANKEN. That is worse.

Senator MURKOWSKI. That is worse.

[Laughter.]

I don't want to consume my time here talking about how bad the name is. We'll refer to it as genetically engineered fish, and, specifically, salmon. You know that I have very, very strong concerns and reservations. I don't need to show you pictures of beautiful wild Alaska salmon. I have them here.

But I will show you a picture of the eelpout, which is where the DNA is taken from—this kind of slimy, ugly eel, bottom-feeding fish—that is injected into a beautiful chinook salmon in an effort to cause these fish to grow quicker so that they can get to a market more readily. I continue to strongly oppose, strongly oppose, FDA approval of genetically engineered salmon. I don't believe that the FDA has adequately studied the environmental effects, the economic impacts, not only on the wild salmon themselves, but our seafood markets, and let alone the potential health impacts on humans.

Given the concerns that I have and many, many others have, can you assure me that FDA is prepared to deny approval of the sale of GE salmon to consumers if your agency determines that it cannot guarantee that it's safe to eat?

Dr. HAMBURG. If we could guarantee that it wasn't safe to eat, then it would not pass our approval standards.

Senator MURKOWSKI. All right, because what we're looking for is—we want this assurance, and we don't know that it is safe to eat. We don't believe that it has been determined that this genetically engineered salmon would be safe to eat. We also haven't been able to determine whether or not it would impact negatively and jeopardize the wild Alaska salmon.

So I would ask again that you look very critically at this. The threat, I believe, is not only to humans for consumption of this bizarre fish, but is a threat to our wild stocks. And then if, in fact—if, in fact—FDA should advance to a level of approval for sale to consumers, I have been demanding that the agency provide very clear labeling to consumers that that is, in fact, what they would be purchasing for consumption.

So what I'm seeking is, first of all, a level of assurance that if it's not safe to eat, it's just not going to be out there for sale, but if it is determined that it should be allowed, that there be clear labeling allowed.

Dr. HAMBURG. I know time is limited. It's a complicated issue. I can assure you of a couple of things. One is that we have been taking a very, very systematic, science-based approach to the review of this application. It does represent the first in its class, so to speak, and so it's very, very important as a product in and of itself and also the pathway for review and approval.

We also undertook an environmental assessment, as I think you know, to address your concerns, vis-a-vis, the wild salmon populations. We published in December 2012 our preliminary findings and sought comment. Actually, we got—I think it was 33,000 or 35,000 comments, so this is a topic that people care a lot about.

We're going through those comments, taking them very seriously. And we will be moving forward in a deliberate, science-driven way, reflecting all of the important inputs, including, obviously, the perspectives that you've brought forward today and earlier, as we consider this product application.

Senator MURKOWSKI. Mr. Chairman, my time has expired.

But perhaps, Dr. Hamburg, you and I would have an opportunity to discuss further not only GE salmon, but progress that we're making in other areas.

I have some other questions that I will submit for the record, and I would ask that you pay particular attention to the level of inquiry about how we are doing with ALS research and the joint meetings that we have been having with stakeholders and how we can advance a cure for ALS.

Dr. HAMBURG. OK.

Senator MURKOWSKI. Thank you.

Thank you, Mr. Chairman.

Senator FRANKEN. Senator Murkowski, do any of the questions that you have for the record include reference to Frankenfish?

[Laughter.]

Senator MURKOWSKI. No, your——

Dr. HAMBURG. Do you want to screen those?

Senator FRANKEN. Well, we'll include them, then.

Senator MURKOWSKI. Thank you, Mr. Chairman.

Senator FRANKEN. Senator Hatch may be coming, but I'll take a round of questioning.

First of all, welcome.

Dr. HAMBURG. Thank you.

Senator FRANKEN. I want to start by thanking Chairman Harkin and Ranking Member Alexander for calling this important hearing and for the leadership that they've both shown regarding policy issues within the FDA's purview. It's been a pleasure working with both of them on reform of a number of FDA policies, most recently the pharmacy compounding legislation that passed into law in November, which I helped to develop with them and Senator Roberts.

I want to thank you, Dr. Hamburg, for working with us so closely on that. In your testimony, you noted your quick implementation of the laws allowing new companies to register as outsourcing facilities, what we call outsourcing facilities, already. This was a critical component of our bill. Can you tell the committee why this is so important? How does this new option improve public health and prevent new outbreaks?

Dr. HAMBURG. Well, this was targeted on high-risk products, sterile injectables, that we know can become contaminated, and when they do, there are very serious consequences for health. This will enable, for those companies that choose to register with us, a higher level of assurance in terms of good manufacturing practice and adherence with the kinds of manufacturing procedures that need to be undertaken to make these products safe.

So we think that this is hugely important. As I mentioned earlier, we certainly hope that companies will choose to go this pathway, and that, importantly, the marketplace will view this as an appropriate standard of care for the health, safety, and protection of their patients, and that healthcare systems will really seek out those that have not just registered—because that's the first step—but actually submitted applications and become outsourcing facilities with us and are part of our program of ongoing oversight, which would include regular inspections to ensure compliance with these important manufacturing procedures and safety protections.

Senator FRANKEN. Thank you for that answer. Dr. Hamburg, as you know, I'm proud to represent Minnesota, where we have a true culture of innovation, particularly in my State's medical device industry. I spend a lot of time with startup device companies, which serve as a major source of innovation within that industry and innovation for the next lifesaving therapies for patients.

These entrepreneurs and their investors are pretty tenacious, and they spend years doing R and D before they see a dime of profit in the hopes of creating a therapy that improves lives. I've been doing my part to fight for our device industry in Minnesota and around our country, the American device industry, and that's why I've been fighting the device tax since it was first proposed, and I'm working now to find a bipartisan solution to repeal the tax once and for all.

I want to do everything I can to help make sure our companies which face international competition are able to succeed. So in this vein, another area I've done a lot of work on is making sure that the process of review is streamlined as much as possible. And FDA—and I've seen this—FDA and the industry have different cultures. I've often seen the FDA and the device industry sort of talk past each other.

In Minnesota, we did something that I think is remarkable to bridge the difference between the cultures. The FDA and Minnesota's own LifeScience Alley, which happens to be the largest State-based life science trade association in the country, formed a partnership that I've worked hard to support. It's called the Medical Device Innovation Consortium, as you know. This public-private partnership is the first of its kind, and it's goal is to create efficiency and quality of regulation, and it studies regulatory science.

Can you tell me what progress has been made in advancing innovation and benefiting patients because of the creation of this organization?

Dr. HAMBURG. Well, thank you for the question. I actually felt badly that I forgot to mention it when I was responding to Senator Baldwin as an element of what exciting things are happening in the area of medical device innovation. It is a public-private partnership, as you mentioned, and I think it has gotten off to a very good start.

It was announced—I think we, together, launched it not too long ago, and it has doubled in size. I think there are 38 or so different members, and it spans device companies, consumer groups, patient groups, research organizations, and the FDA is part of it. I think what's exciting about it is that it has created a research agenda to

really focus on how we can advance the underlying science so that we can get the promise of science to people more quickly.

It is focused on a number of critical areas. One is new clinical trial designs so that we can ask and answer critical questions more efficiently and, hopefully, also encourage more device manufacturers to do their first human studies in the United States rather than overseas where it might be cheaper and less cumbersome. It's focused on patient-reported outcomes and how to actually integrate that into device development, which is so very important across all medical conditions and products, but devices, in particular.

Also, one of the things that excites me is developing computer simulations and models so that you could actually study some of these devices in that context instead of in animal models or in people in the early stages so that you can really, No. 1, manipulate things and play with it more, but also reduce cost and potential risks to patients, but still really get important information to, again, move things that have promise into the marketplace and making a difference in people's lives.

So I think it's a wonderful public-private partnership. Thank you for your leadership in helping to make it possible. We are very committed to working with it, and we are seeing benefits already, and we see, more importantly, the foundation for lots more progress.

Senator FRANKEN. Thank you for your role in that and for your excitement about it. I am, too.

Senator Enzi for a second round.

Senator ENZI. Thank you, Mr. Chairman.

I'd like to revisit the goals you immediately identified when you took the helm at the FDA in modernizing how the agency considers new therapies and closing the regulatory science gap. Those goals are ones we obviously all share.

That said, there is a continued level of frustration among patients and manufacturers that the FDA lags behind other countries in both timeliness and up-to-date understanding of critical responsibilities, including clinical trial design, valid end points for assessing the value of new therapies, and how the risk evaluation and mitigation strategies are tools to both protect patients and allow access to higher-risk products where patients are desperate for treatment.

In Senator Harkin's opening statement and questions, he mentioned a case where the committee voted against a product and then was overridden by the FDA. I'll talk about a little different situation, and that's dealing with multiple sclerosis.

FDA recently made a decision to break with an overwhelming advisory committee vote to support the safety and effectiveness of a novel therapy for multiple sclerosis, and then the agency chose not to approve the drug, despite it having been approved in 30 other jurisdictions based on the same data set. Can you explain the logic behind the agency's decisions? What did the FDA see that the advisory committee could not?

Dr. HAMBURG. First, let me address your broader question about us, in terms of—we are, I think, at the cutting edge in terms of review and approval of new products. If you look at drugs approved

in recent years, I think about three-quarters of them were approved in the United States first.

And on devices, apart from the highest risk devices, we are, I think, at par with comparable other countries in terms of review times, ET cetera. We do ask for more clinical data often on the higher risk devices. So I think there's some urban mythology about where we stand in comparison to review times and leadership there, and I would have to say the PDUFA, the user fee programs for both devices and drugs, have made a real difference in our ability to be as competitive as possible.

With respect to the role of advisory committees and the decision-making within the FDA, the advisory committees are a very important component of the review process, but they are not determinative, as you well know. We seek expert advice in many ways, including advisory committees. Advisory committees are not used with every product that is reviewed, of course.

But it's sometimes frustrating for me, I have to say, when people ask questions about a specific product and why we didn't approve it. That information is commercial confidential information that we're not allowed to share without permission of a company.

But I can assure you that the FDA review teams take their job very, very seriously, going through in a systematic way the data that is available to them, assessing safety and efficacy and overall risk-benefit and the benefit to patients. There often are things that are not obvious but that make a real difference in terms of a decision that's made.

Senator ENZI. And the advisory committee isn't——

Dr. HAMBURG. The advisory committee is a very important part of our input on a decision. I would say the majority of times, our ultimate decision aligns, but not always.

Senator ENZI. But you're saying they're lacking information that the people at FDA would have? So they're not getting the full story?

Dr. HAMBURG. I think that there are many components to the review, and the advisory committee is an important piece of it. But the advisory committee is not spending time with the patient level data that the review teams are, and there are, I think, aspects of the review that the advisory committee is not always engaged in. But we value their input. We take their input very seriously, and we do try to engage subject-matter experts to the greatest degree that we can.

Senator ENZI. The only reason this one came—that I noticed this one is that it had been approved in 30 other jurisdictions already, using the same data set. So those other jurisdictions are considered wrong, too. And that's a decision, I guess, that the FDA can make, and we do want you to keep us safe.

My time has run out.

Senator FRANKEN. Would you care to ask another question?

Senator ENZI. Well, it would be your turn.

Senator FRANKEN. I know, but go ahead.

Senator ENZI. I know that the FDA is underway in its implementation of the Generic Drug User Fee Act, and it's my understanding that not all first generic applications have been approved on the same day as the patent expiration. Is there a reason for that?

Dr. HAMBURG. Well, this is a program that, as I think you know, we've had serious backlogs in. That was a big part of why the user fee program was begun with the passage of FDASIA. We are moving forward in implementing that, hiring up, addressing the backlog in critical ways, and, also importantly, addressing the issues of expanding our inspectional capacity so that we can do those critical inspections, which increasingly are often overseas.

We're not where we need to be yet. But we're committed to moving forward, and we have made progress, but there's a lot more work to be done.

Senator ENZI. I'll submit some additional information that I'd like on that, like how many applications the agency has received for these first generic products and how many have missed the approval at the earliest possible date and what you're doing to ensure that the future generic applications are reviewed. So I'd be interested in some more detail on that.

Dr. HAMBURG. Of course.

Senator ENZI. Again, I thank you for being here today to answer our questions. We don't get this opportunity very often, and you've done an outstanding job. Thank you.

Dr. HAMBURG. Thank you.

Senator FRANKEN. Thank you, Senator Enzi.

When we did the reauthorization of the FDA user fees, I worked closely with you when you were ranking member of this committee and with Chairman Harkin to make sure that devices that are approved through the 510(k) process didn't have to go back to the agency every time an insignificant change was made to the device, such as the color of the label or the packaging was changed.

I know just recently, FDA sent the 510(k) modifications report to Congress, and I wanted to first congratulate you on that. I understand that FDA held a public meeting in advance of preparing the report and engaged in a healthy dialog with interested parties. I appreciate all that you did to work with the industry.

Again, this is about working with the industry, in this case, to develop the report. I think it's, again, another great example of FDA-industry collaboration and communication. What have you learned from the industry as a result of this collaboration? And as you prepare the draft guidance on this topic, which I understand to be the next step, do you anticipate that this sort of FDA-industry collaboration will continue?

Dr. HAMBURG. This kind of collaboration is key. I would add patients in as well, because I think at the end of the day, our goal is to provide the best medical devices for their needs. But I think it has been very valuable in helping us to better understand the way in which this industry works.

As you well know, it's not a one-size-fits-all industry in terms of the very small device companies and much larger device companies with very different needs and experience. And the range of device products is expanding rapidly and getting more and more complex. So we really do need to work together to be able to keep progress moving forward and, ultimately, to deliver what patients need.

But I wouldn't say that the interactions are always easy, but it's been very valuable to listen and learn. We've tried to be as responsive as possible, and I think it's making a difference.

Senator FRANKEN. No, they shouldn't necessarily always be easy.

Dr. HAMBURG. Right.

Senator FRANKEN. As part of FDASIA, I worked with Senator Alexander on a provision that created new incentives for medical device companies to develop products to treat rare conditions. In your written testimony, you noted that you have approved five new products under our provision. Thank you again for your work.

Can you explain why it is so important to reward innovators for developing products to treat rare conditions? In this case, it was rare conditions that adults had, if a treatment for pediatric use had already been approved. Can you talk about why it's important to have these incentives?

Dr. HAMBURG. I think it's very important that we have the right incentives to get companies to invest in developing technologies where there may not be a huge marketplace, where the return on investment will not necessarily be clear, but where there is essential medical need and where these products really will matter in addressing an individual's—either a pediatric patient or adult patients—medical needs and requirements.

So I think we see this on the device side, and we see it on the drug side, that you cannot always assume that these important healthcare and public health needs will be addressed without looking at what the opportunities are, what the barriers are, and are there incentives to help ensure that work goes on in these key, often under-addressed areas.

Senator FRANKEN. Well, I'm glad we've had success on these five new products.

Senator Enzi, any more questions?

[No verbal response.]

Senator FRANKEN. OK. Great.

Well, then, thank you, Dr. Hamburg, for your testimony and for your service.

This hearing is adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

DEPARTMENT OF HEALTH & HUMAN SERVICES,
FOOD AND DRUG ADMINISTRATION,
SILVER SPRING, MD 20993,
November 6, 2014.

Hon. TOM HARKIN, *Chairman*,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR MR. CHAIRMAN: Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the March 13, 2014, hearing entitled "Protecting the Public Health: Examining FDA's Initiatives and Priorities," before the Committee on Health, Education, Labor, and Pensions. This letter is a partial response for the record to foods and veterinary medicine questions posed by several members of the committee.

If you have further questions, please let us know.

Sincerely,

THOMAS A. KRAUS,
Associate Commissioner for Legislation.

RESPONSE BY THE FOOD & DRUG ADMINISTRATION TO QUESTIONS OF SENATOR HARKIN, SENATOR MURRAY, SENATOR SANDERS, SENATOR CASEY, SENATOR BENNET, SENATOR BALDWIN, SENATOR WARREN, SENATOR ALEXANDER, SENATOR BURR, SENATOR ISAKSON, SENATOR ENZI, SENATOR MURKOWSKI, SENATOR HATCH, SENATOR KIRK AND SENATOR ROBERTS

SENATOR HARKIN

DELAYED TOBACCO AND MENU LABELING REGULATIONS

I understand that both the menu labeling final rule, called for in the Affordable Care Act, and the proposed tobacco deeming rule, called for in the Family Smoking Prevention and Tobacco Control Act are under review by OMB. In both cases, regulatory action has been significantly delayed despite the fact that timely regulation has the potential to have a significant positive impact on public health. In regards to menu labeling, a final rule that covers chain restaurants and the full range of similar retail establishments, including movie theaters, grocery stores, and convenience stores—as I intended as the author of this provision—will ensure that Americans have access to the information they need to make healthy decisions for themselves and their families. When it comes to the tobacco deeming rule, coverage of novel tobacco products—such as e-cigarettes and liquid nicotine—will protect Americans from unregulated products and help prevent a new generation from becoming addicted to nicotine.

Question 1. Can you explain some of the obstacles that have prevented FDA from acting more quickly in both of these instances? And, going forward, if FDA were to assert their authority over e-cigarettes through the deeming rule, can you tell me what the timeline would be for actually regulating these products?

Answer 1. With respect to menu labeling, some of the issues in implementing this provision proved to be complex as we engaged in the rulemaking process. An example of this is the need to determine which entities are covered by the term "restaurants and similar retail food establishments." Since the proposed rule was published in April 2011, FDA has reviewed approximately 900 comments that were submitted and considered a number of issues raised, including the menu labeling rule's applicability to various establishments. Please be assured that we are working diligently to complete the final rules as quickly as possible.

Regarding tobacco, on April 25, 2014, FDA published a proposed rule to extend the Federal Food, Drug, and Cosmetic Act (FD&C Act) tobacco product authorities to cover additional products that meet the statutory definition of "tobacco product," such as electronic cigarettes (e-cigarettes). This proposed rule is the first step toward establishing an appropriate regulatory framework for these products.

The development and clearance of the proposed deeming rule involved a large number of complex issues, including addressing the broad array of products that would be covered by the scope of this proposed rulemaking. FDA and other Federal agencies involved in this regulatory process required ample time to fully review and analyze these issues. FDA cannot speculate on the timeframe for completing a final

deeming rule, which will largely depend upon the number and complexity of comments that FDA receives regarding the proposed rule.

SODIUM

Question 2. Upwards of 100,000 lives could be saved annually if sodium levels in packaged and restaurant foods were cut in half—which is why nearly 4 years ago the Institute of Medicine recommended FDA initiate a process to set national standards for the sodium content of foods. What has the agency been doing to address sodium consumption?

Answer 2. Since the release of the Institute of Medicine (IOM) report outlining strategies to reduce sodium intake, FDA has been carefully considering the challenges involved in sodium reduction. In 2011, we jointly published a notice in the *Federal Register*, with the U.S. Department of Agriculture's (USDA) Food Safety and Inspection Service, inviting comment on a number of issues related to sodium reduction, including issues identified in the IOM report, to help us better understand current challenges and opportunities. We also co-sponsored a public meeting with other Federal agencies to promote discussion of these issues. FDA is working with industry and other stakeholders to promote gradual, achievable, and sustainable reductions of sodium over time. We believe these efforts have built a strong foundation for future action. FDA is looking for ways to further encourage sodium reduction and has been working on the technical research and assessments for the development of draft voluntary targets for sodium reduction in foods.

As part of FDA's recently proposed revision of the Nutrition Facts Label, we recommended a daily value of 2,300 mg for sodium based on the tolerable upper intake level for sodium established in 2005 by the IOM and current sodium recommendations from other consensus reports. The current daily value is 2,400 mg. A daily value of 2,300 mg is much lower than the average daily consumption in the United States today which is 3,400 mg/day, based on data from the National Health and Nutrition Examination Survey (NHANES). While FDA is proposing a daily value of 2,300 mg, it is asking for comment on whether a daily value of 1,500 mg would be more appropriate and alternative approaches for selecting a dietary value for sodium. The comment period was originally scheduled to close on June 2, 2014, but was extended until August 1, 2014.

TRANS FAT

Question 3. Last November, FDA issued a critical preliminary determination to withdraw "Generally Recognized as Safe" (GRAS) status for partially hydrogenated oil, a critical first step toward phasing dangerous trans fat out of the food supply. How long do you anticipate it will take to issue and implement a final rule on the GRAS status of partially hydrogenated oil?

Answer 3. On November 8, 2013, FDA published a notice in the *Federal Register* announcing its tentative determination that partially hydrogenated oils (PHOs) are not generally recognized as safe (GRAS) for any use in food. In the notice, FDA requested comments on its tentative determination as well as other issues associated with the tentative determination. The initial 60-day comment period was extended an additional 60 days and closed on March 8, 2014. FDA received over 1,500 comments in response. After a complete evaluation of the comments received and other available information, FDA will issue any final determination regarding the use of PHOs in food.

DIETARY SUPPLEMENTS

Question 4. Senator Hatch and I met with you in 2012 to discuss our concerns with the FDA's "New Dietary Ingredient Notifications and Related Issues" draft guidance for dietary supplements issued on July 5, 2011. Would you please provide us an update on the status of FDA's work to develop and issue a new draft guidance that addresses our concerns?

Answer 4. As you know, FDA announced in June 2012 that it would revise and reissue the draft guidance on new dietary ingredient notifications and related issues (the NDI guidance). The purpose of issuing a revised draft guidance is to clarify matters that were not clear in the original draft of the NDI guidance and that were subject to misinterpretation. The revised draft is currently undergoing Agency clearance.

In order to understand and respond to the various issues raised about the original draft guidance, FDA has had a number of meetings with industry to discuss their concerns. Some of the key issues that will be addressed in the revised draft are (1) the development of a process to identify and document the universe of "pre-DSHEA" ingredients that are exempt from NDI notification requirements (grand fathered list

of ingredients); (2) what constitutes "chemical alteration" of an existing ingredient, such that it becomes a new dietary ingredient that requires an NDI submission; and (3) the treatment of synthetic copies of botanical ingredients. These are difficult issues to resolve, but FDA is committed to issuing revised draft guidance as soon as possible, which will provide stakeholders an additional opportunity to comment on these matters.

FSMA

In writing the Food Safety Modernization Act, Congress emphasized the importance of creating new regulations that worked with existing environmental and conservation efforts underway at Federal agencies. We included this provision because after an outbreak of E. coli in spinach in 2006, many buyers required farmers to remove existing conservation practices, damaging the landscape and throwing away the Federal investment in stewarding our natural resources.

Given this experience, I was glad to see strong statements about the importance of conservation priorities in the preamble of the proposed produce regulations, but I was concerned that that same language was not included in the regulatory text. Without additional protections for conservation in the regulations, we risk repeating events of the past.

Question 5. Can you please discuss how the agency plans to strengthen the produce safety regulations so that they more fully protect conservation practices and address the co-management of conservation and food safety?

Answer 5. FDA received several comments to the docket recommending that language related to conservation priorities, most notably language aimed at clarifying FDA's intent with regard to threatened and endangered species, be included in the final codified text. On September 19, 2014, FDA released proposed revisions to the proposed rule on produce safety. In response to concerns that the produce safety regulation may inadvertently promote practices that may adversely affect wildlife and animal habitat, including impacts on threatened or endangered species, we are proposing to include a new provision (§ 112.84) to explicitly state that the standards for the growing, harvesting, packing, and holding of produce for human consumption would not authorize or require covered farms to take actions that would constitute the "taking" of threatened or endangered species in violation of the Endangered Species Act, or require covered farms to take measures to exclude animals from outdoor growing areas, or destroy animal habitat or otherwise clear farm borders around outdoor growing areas or drainages. FDA consulted with USDA's National Resources Conservation Service and the U.S. Fish and Wildlife Service to inform our current thinking on this issue. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014.

FDA also is exploring the possibility of developing joint guidance documents that would involve other Federal agencies that have a significant role in food safety and conservation. Our efforts will be much more focused on guidance development after the publication of the final rule in 2015.

I am glad to see that the agency is undertaking an environmental review of the produce safety regulations. There are a number of potential environmental impacts with the proposed regulations, and it is important to balance new regulatory requirements with environmental considerations. Recently the agency extended the comment period on the scoping process for the Environmental Impact Statement in order to seek further public input.

Question 6. Can you please describe the agency's process for developing an EIS, seeking public comment on the EIS, and incorporating environmental considerations into the final regulations?

Answer 6. FDA's goal is to implement the FDA Food Safety Modernization Act (FSMA) in a way that improves public health protections while minimizing undue burden on farmers and other food producers. In August 2013, FDA announced its intent to prepare an Environmental Impact Statement (EIS) to evaluate the potential environmental effects of the proposed produce safety rule and also announced the beginning of the scoping process. During the scoping process, FDA solicits public comments to identify issues to be analyzed in the EIS.

The scope of the EIS includes consideration of alternatives to a range of actions. To facilitate public input during the scoping process, FDA identified a number of issues and a range of potential alternatives to be considered in the EIS. Alternatives were identified for provisions of the proposed produce rule that, if finalized, may significantly affect the quality of the human environment. Alternatives were identified for the following key provisions: (1) microbial standard for agricultural water used during growing activities for covered produce (other than sprouts) using a direct

water application method, (2) minimum application intervals for biological soil amendments of animal origin, (3) measures related to animal grazing and animal intrusion, and (4) scope of proposed rule and implications to land use and land management. FDA invited comment on whether there are other issues it should consider for in-depth analysis in the EIS and any alternatives related to these issues. FDA also held a public meeting in April 2014 as part of its ongoing efforts to seek public input on the issues and alternatives that the Agency should consider when preparing the EIS.

The public scoping period was extended twice, ultimately to April 18, 2014. FDA is now in the process of reviewing all comments received. The Agency will consider these comments in preparing a draft EIS. FDA will consider any potential significant environmental impacts identified during the scoping phase in the draft EIS, and then will consider public comments received on the draft EIS in the preparation of the final EIS and the final rule. This includes determining whether mitigation steps are needed for environmental impacts, and, if so, what those steps will involve.

SENATOR MURRAY

FOOD SAFETY

Question 1. Under the Food Safety Modernization Act, FDA investigators and inspectors will need to be well-trained in proper auditing of food safety systems. Until now, investigators have primarily inspected food facilities for physical evidence of hazards. Inspectors and investigators will need to take a more proactive approach when carrying out these activities under the Food Safety Modernization Act. They will need to be able to understand and evaluate the efficacy of a facility's food safety system and analyze whether the facility is complying with that system.

Can you provide a timeline for the implementation of a comprehensive training program for FDA inspectors, including State and local partners?

Answer 1. FDA recognizes the need to establish training programs for Federal and State regulators who will oversee compliance with the new FSMA regulations, when finalized, to ensure consistency in the performance and quality of inspections regardless of the regulatory entity that performs such inspections. To implement FSMA, FDA will need to work closely with State agencies and other partners to oversee compliance with the new requirements. FDA has funded the creation of three private-public university-based alliances—the Produce Safety Alliance (PSA), the Food Safety Preventive Controls Alliance (FSPCA), and the Sprouts Safety Alliance (SSA). These alliances are responsible for providing standardized curricula and establishing mechanisms to train industry and regulators on the requirements of the produce safety and preventive controls rules for human and animal food. This will help promote widespread industry compliance with the rules and provide for consistent regulatory inspections by State and Federal officials. More information about the Alliances is available on the Internet at *http://www.fda.gov/Food/GuidanceRegulation/FSMA/ucm293423.htm*.

Further, we expect to collaborate with State regulatory partners under the Partnership for Food Protection (PFP) umbrella, which includes representatives from the Association of Food and Drug Officials (AFDO) and the National Association of State Departments of Agriculture (NASDA), to develop training and tools targeted for use by regulators when performing inspections and other types of oversight activities to ensure industry compliance with the new prevention-oriented standards.

Finally, FDA's Office of Regulatory Affairs University (ORAU) offers an extensive course catalog of instruction, both traditional in-classroom and distance-learning formats. We envision collaborating with our State regulatory partners to develop and deliver FSMA-related training targeted specifically for regulators by using the alliances' standardized curricula and ORAU regulator training. We also envision that Federal and State regulators will be trained together using qualified trainers to ultimately establish a cadre of investigators who will conduct inspections to assess compliance with FSMA rules on the farm and in food facilities. We expect the Alliances and others to begin conducting training before the compliance dates of the final regulations.

ANTIBIOTICS IN ANIMALS

The use of antibiotics in food animals is an issue of concern for many people at home in Washington State. According to the Centers for Disease Control and Prevention, the widespread use of antibiotics in food-producing animals contributes to the emergence of antibiotic-resistant bacteria in these animals and is linked to the occurrence of antibiotic-resistant infections in humans. I was pleased to see FDA

take steps to address the use of antibiotics in food animals by announcing Industry Guidance 213 and the Veterinary Feed Directive proposed rule in December 2013.

As you know, Guidance 213 defines the appropriate uses of antibiotics in food animals as only for "the treatment, control, and prevention of specific diseases . . . necessary for assuring the health of food-producing animals." It calls on pharmaceutical companies to change product labels on antibiotics so that they are not allowed to be used for growth promotion or other production purposes. This is a good first step to curb the use of antibiotics in animal feed for growth promotion purposes, but more clarification is needed on FDA's intent to address the use of antibiotics for disease prevention purposes. I have heard concerns that this guidance may not address existing inappropriate uses of antibiotics for disease prevention purposes.

Question 2. What steps will you take to ensure the appropriate use of antibiotics for disease prevention? Will you encourage pharmaceutical companies to tighten existing antibiotic approvals so that only legitimate disease prevention is allowed?

Answer 2. FDA agrees that it is important to ensure that the use of medically important antimicrobial drugs for prevention purposes is judicious and appropriately targeted to address specifically identified animal health risks. FDA has developed a "judicious use" strategy aimed at phasing out the use of medically important antimicrobial drugs for non-therapeutic purposes (e.g., feed efficiency and growth promotion) and providing for veterinary oversight over the remaining therapeutic uses of such drugs, as established in Guidance for Industry #209 (GFI #209) in April 2012. The Agency finalized Guidance for Industry #213 (GFI #213) in December 2013, which outlined a voluntary process for the animal pharmaceutical industry to align their affected products with the recommendations in GFI #209. In December 2013, we also issued a proposed rule intended to revise the Agency's Veterinary Feed Directive (VFD) regulation to improve the efficiency of the VFD program and facilitate the process of bringing the use of medically important antimicrobials in animal feed under the oversight of licensed veterinarians.

Once production uses are removed from affected medicated feed products, such products can only legally be used for prevention purposes if the labeling of the product includes an FDA-approved prevention indication. If a medicated feed product were to be used for an unapproved disease prevention purpose, FDA could initiate action on the grounds that such use caused the drug to be unsafe under section 512(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 360b(a) and adulterated within the meaning of section 501(a)(5) of the FD&C Act, 21 U.S.C. § 351(a)(5).

In addition, acknowledging the importance of this concept, GFI #213 outlines several important factors that veterinarians should consider when determining the appropriateness of a preventive use. These factors include whether: (a) there is evidence of effectiveness, (b) such a preventive use is consistent with accepted veterinary practice, (c) the use is linked to a specific etiologic agent, (d) the use is appropriately targeted to animals at risk of developing a specific disease, and (e) no reasonable alternatives for intervention exist.

The Agency believes veterinary oversight of these products is a critical element for ensuring that the above factors are considered in determining the specific situations where prevention use is necessary and appropriate. FDA intends to work with veterinary and animal producer organizations to reinforce the importance of these principles.

Question 3. How does FDA plan to collect, analyze, and provide to Congress and the public comprehensive data on the implementation of Guidance 213 and its effect on the amount of antibiotics used in food animals?

Answer 3. FDA is committed to updating the public on the progress that drug sponsors have made in aligning their products with GFI #213, including through notifying the public of changes to approvals, updating the list of affected applications on CVM's Web site, and providing periodic progress reports on a 6-month basis. The Agency issued its first progress report on June 30, 2014. FDA's progress reports will summarize current and pending actions taken by sponsors to align with the guidance, including the type of action (e.g., withdrawal, change in marketing status) and, when possible without revealing confidential business information, the type of animal for which the drug is approved for use and the type of application (pioneer, generic, combination).

FDA has received confirmation in writing from all 26 affected sponsors of their commitment to implement the changes. In addition to the summary information FDA has already released concerning the affected drug sponsors' responses, the Agency will continue to monitor the progress of GFI #213 implementation and provide further updates. FDA intends to notify the public of completed changes to affected products that are implemented through approvals of supplemental new ani-

mal drug applications. Some sponsors may opt to voluntarily withdraw their approved applications for certain animal drugs, and the Agency is also currently notifying the public of these withdrawal actions.

In addition to tracking completion of the changes, FDA recognizes that it is important to identify ways to assess the effect of these measures over time. FDA is currently enhancing data sources in a number of ways to help monitor the effect of GFI #213. Currently, the Agency collects data on antimicrobial resistance among foodborne pathogens as part of the National Antimicrobial Resistance Monitoring System (NARMS), as well as data on the sale and distribution of antimicrobial drugs intended for use in food-producing animals, which FDA collects and reports annually under section 105 of the 2008 Animal Drug User Fee Amendments (ADUFA 105). The U.S. Department of Agriculture (USDA) also periodically collects antimicrobial use data on livestock and poultry operations as part of the National Animal Health Monitoring System.

Recent enhancements to the NARMS program make the data more useful for measuring the effect of GFI #213, particularly a new USDA Food Safety Inspection Service slaughter sampling program, launched in March 2013, which increases national representativeness of the animal samples. In addition, FDA is working with four State partners to perform whole-genome sequencing on NARMS samples. The data will provide unprecedented details on changes in resistance genes from animals and animal-derived foods.

Based on broad public input, FDA has enhanced the format of the ADUFA 105 annual summary reports to better describe data on the annual sales and distribution of antimicrobials intended for use in food-producing animals using a more detailed format that will allow the public to better understand the changes that occur as GFI #213 is implemented. On October 2, 2014, FDA released the summary report for 2012, using this new format, and provided updated annual reports from previous years to include the new data tables. The changes expanded the format of reporting sales and distribution data by antimicrobial class to include information on the importance of the drug in human medicine. These changes also provide aggregate data on the approved route of administration of antimicrobial drugs sold or distributed for use in food-producing animals, whether such drugs are available over the counter or require veterinary oversight, and whether they are approved for therapeutic indications, or both therapeutic and production indications.

You may be interested to know that the Agency is also developing a proposed regulation to enhance the existing requirements related to the collection of antimicrobial drug sales and distribution data for antimicrobial drugs intended for use in food-producing animals. New requirements being considered include the collection of additional drug sales and distribution data, including reporting sales and distribution data by species.

FDA is working with USDA and the Centers for Disease Control and Prevention (CDC) to identify possible approaches for further enhancing current data collection efforts, focused on actual use (exposure) on the farm. This will help identify meaningful metrics for assessing the effectiveness of GFI #213 in reducing the public health risk of antibiotic resistance. The Agency intends to seek further public input on this issue in early 2015.

In addition, as part of this collaborative effort it was determined that there is currently no appropriate method to analyze associations between changes in antimicrobial use and shifts in resistance patterns on a national level, as is needed to assess the public health impact of interventions such as GFI #213. Therefore, FDA and USDA are collaborating with a Cornell University researcher and submitted a National Institute of Mathematical and Biological Synthesis (NIMBioS) proposal to create a working group to develop a new mathematical modeling methodology that would inform the approach to monitoring and assessing the impacts of GFI #213. This will allow the collaborating Federal agencies to efficiently allocate limited resources by targeting data which are most valuable. The proposal was accepted and the first meeting of the working group occurred in September 2014.

CATFISH INSPECTION

The Health, Education, Labor, and Pensions Committee has overseen the FDA for decades, including FDA's inspection and regulation responsibilities for seafood. My home State of Washington is home to thousands who make a living in the fishing industry, from recreational guides, to salesmen, to reel manufacturers, commercial fishermen, processors, and more. In fact, 2009 data from the National Oceanic and Atmospheric Administration shows that the seafood industry, including commercial harvesters, primary dealers and processors, secondary seafood wholesalers and

distributers, grocers, and restaurants) had a sales impact of more than $7.3 billion and supported more than 57,000 jobs in Washington alone.

As you may know, the 2008 and 2014 Farm bills included provisions regarding catfish inspection, and the USDA is currently engaged in a rulemaking process to begin their statutorily required catfish inspection. I have been a strong supporter of repealing the USDA catfish inspection program because it could have a negative impact on the vibrant seafood economy in Washington, and because the Government Accountability Office identified the USDA catfish inspection office as duplicative and a waste of taxpayer dollars. The USDA, the agency now tasked with inspecting only one of many seafood products inspected by the U.S. Government each year, has identified catfish as a low-risk food.

Question 4. Can you explain where catfish ranks in terms of risk to human health?

Answer 4. Seafood in general carries some unique risks, and that is why FDA established the Hazard Analysis and Critical Control Points (HACCP) program in 1997. We also have import alerts in place that provide for increased review and testing of imported seafood that may pose particular risks. Those programs have been very successful in mitigating the safety issues inherent in seafood production.

It is also fair to say that, generally speaking, catfish are generally less risky than certain other types of fish. Catfish are generally not eaten raw or packaged in ready to eat form.

Question 5. Can you explain how the FDA regulates seafood under its current regime?

Answer 5. FDA operates a mandatory safety program for all fish and fishery products under the provisions of the FD&C Act, the Public Health Service Act, and related regulations. The FDA program includes research, inspection, compliance, enforcement, outreach, and the development of regulations and industry guidance.

All seafood processors are required to adhere to HACCP regulations. Under HACCP, processers of fish and fishery products must identify hazards that are reasonably likely to occur for their products and formulate control strategies. Seafood HACCP requirements have been in place for years and serve as the foundation of the proposed hazard analysis and risk-based preventive control requirements found in FSMA proposed rules for all food products.

FDA regularly conducts inspections of domestic and foreign food facilities in an effort to ensure that seafood processors are adhering to seafood HACCP regulations. FDA screens all import entries electronically prior to the products' entering the country, and a subset of those are physically inspected at varying rates depending on the potential risk associated with them. The Agency has implemented an automated screening system, the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) system, which significantly improves FDA's risk-based targeting of imported food.

When there are concerns about a particular product, including fish, being imported into the United States, FDA may place foreign processors who manufacture products that appear to be adulterated or misbranded on import alert, which notifies FDA field personnel that FDA has sufficient evidence to refuse admission of future shipments of the products. To obtain entry of such product, the importer would need to provide sufficient evidence to FDA that the product is not adulterated and/or misbranded. The Agency has a number of import alerts for seafood products for various reasons, including the appearance of the foreign processors not being in compliance with seafood HACCP, the presence of unapproved new drugs, the presence of methyl mercury at unsafe levels, and the products not being labeled correctly or being misbranded.

FDA has also invested in significant technical improvements to enhance its ability to identify seafood species using state-of-the-art DNA sequencing. DNA sequencing has greatly improved FDA's ability to identify misbranded seafood products in interstate commerce.

In addition, FDA can use the new enforcement tools provided by FSMA to keep unsafe seafood from reaching consumers. For example, under certain circumstances the Agency can administratively detain seafood, order a mandatory recall, and refuse entry into the United States of imported seafood if the facility refuses to allow an inspection.

SENATOR SANDERS

Question. During its consideration of the Food Safety Modernization Act, Congress emphasized the importance of a regulatory framework that worked for the broad diversity of farming systems in America. Congress specifically required the Food and

Drug Administration not to include any requirements that conflict with or duplicate the requirements of the National Organic Program for certified organic production. Despite this mandate, the proposed produce safety rule released last year contained requirements around the use of biological soil amendments of animal origin that conflicted with the use of manure and compost on certified organic farms and that are part of sustainable production. I have heard from many farmers in Vermont that the intervals between application and harvest were too long. This would severely restrict the use of manure, impede the use of compost on their farms, disrupt management practices and increase costs of production. How does the agency intend to address these issues in the rulemaking process?

Answer. FDA's intent in developing the proposed produce safety rule is to reduce risk associated with the consumption of produce. We received many comments on our proposed 9-month, pre-harvest interval for raw manure that may contact the produce after application, which differs from the 120-day interval required by the U.S. Department of Agriculture's (USDA) National Organic Program (NOP) standards for organic certification. FDA's proposed interval was based on the best available science and FDA's judgment at the time of the proposal regarding an interval that would be sufficient to protect food safety in a wide range of growing conditions across the country.

On September 19, 2014, FDA released proposed revisions to the proposed rule on produce safety that are more flexible and less burdensome in key areas. Specifically, FDA is removing the 9-month proposed minimum-time interval between the application of untreated biological soil amendments of animal origin (including raw manure) and crop harvesting. The Agency is deferring its decision on an appropriate time interval until it pursues certain actions. These include conducting a risk assessment and extensive research to strengthen scientific support for any future proposal, working with USDA and other stakeholders. In addition, at this time, FDA does not intend to take exception to farmers complying with the USDA's NOP standards, which call for a 120-day interval between the application of raw manure for crops in contact with the soil and 90 days for crops not in contact with the soil.

The Agency is also proposing to eliminate the previously proposed 45-day minimum application interval for compost (also known as humus), including composted manures. Properly treated and handled compost is safer than raw manure from a public health standpoint and this change to the proposal would help facilitate its use while still providing an appropriate level of public health protection.

You may be interested to know that FDA has provided approximately $1 million to sponsor research at USDA's Agricultural Research Service and to develop a produce safety rule research network at the Western Center for Food Safety at the University of California, Davis. We intend for these collaborative efforts to result in the collection of data that may help resolve questions that have arisen during the public comment period about the necessary time between application of raw manure, or water that does not meet the relevant quality standard, and safe harvest of produce in key agro-ecological growing conditions and for key crops. Our goal is for this research to result in suggested protocols that farms could follow in compliance with a final produce safety rule, and for this process to be duplicated for other crops and regions as further funding is secured. This FDA-sponsored research was initiated to demonstrate the commitment of Federal agencies to address the needs of farmers, to provide data to finalize study protocols for further research, and to attract matching funds from industry.

SENATOR CASEY

RESTAURANT MENU LABELING

Question 1. FDA may soon release a final rule on menu labeling requirements for chain restaurants. I think it's important for consumers to have nutrition information for what they're eating. But there are some differences between convenience stores and chain restaurants. I encourage FDA to consider excluding pre-packaged foods, which are already labeled, from revenues and include fuel sales in overall sales calculations. Will FDA make this consideration in its final rule for menu labeling?

Answer 1. Determining which entities are covered by the term "restaurants and similar retail food establishments" has proven to be complex, with strongly held opinions being expressed by those who advocate for either a more expansive or restrictive scope of coverage. Since the proposed rules were published in April 2011, FDA has reviewed approximately 900 comments that were submitted and considered a number of issues raised, including the menu labeling rule's applicability to

various establishments. Please be assured that we are working diligently to complete the final rules as quickly as possible.

FOOD SAFETY MODERNIZATION ACT

Question 2. One of the greatest concerns some Pennsylvania farmers have is about the frequency and character of on-farm inspections that will occur with FDA's new authority under the Food Safety Modernization Act. There have been several on-farm inspections occurring on Pennsylvania farms in the past year that have not gone well. I've been told some of these inspections include incidents of inspectors arguing with each other about why they were there at all, an inspector who forced a farmer to come home from vacation for an inspection and then missed the appointment himself, and a high-profile inspection that was described as a non-inspection, even in the inspection report that was later filed. I am concerned about the direction that these inspections have taken and that the focus of limited resources is shifting away from high-risk activities and facilities. Can you please discuss why the agency is conducting these inspections, how the agency plans to train inspectors so that they are familiar with farming systems, and how the agency intends to target limited inspection resources to high-risk operations once the regulations go into effect?

Answer 2. FDA is tasked with ensuring compliance with the provisions outlined in the produce safety proposed rule which would establish science-based minimum standards for the safe growing, harvesting, packing, and holding of produce on farms. To that end, the rule proposes new standards in the following major areas:

- Worker Training and Health and Hygiene
- Agricultural Water
- Biological Soil Amendments of Animal Origin
- Domesticated and Wild Animals
- Equipment, Tools, and Buildings
- Sprouts

While the Agency currently conducts a limited number of farm inspections under existing regulations and has existing training modules related to some farm activities and continues to leverage those activities internally and with our State counterparts, we are also assessing existing training and new training opportunities that can be leveraged moving forward with FSMA implementation. As new rules are finalized and implemented, FDA intends to work with State and industry partners in developing and delivering training prior to conducting farm inspections under the new FSMA authorities. Such training will focus on regulatory requirements, inspection procedures, and better understanding of the farming environment.

For example, the Produce Safety Alliance (PSA) is led by Cornell University, and involves FDA, the U.S. Department of Agriculture (USDA), State food and agriculture departments, and two national industry trade associations. The PSA will produce a standard on-farm training manual and curriculum and plans to offer courses to deliver the training. The PSA is developing a training protocol with State and Federal regulators to help ensure uniformity in inspections. It will also be a repository for up-to-date scientific and technical information, including a compendium of produce hazards. The training will be finalized shortly after the publication of the final rule on produce safety. The Alliance and others will conduct training that will begin during the period that precedes the compliance dates.

Further, we expect to collaborate with State regulatory partners under the Partnership for Food Protection (PFP) umbrella, which includes representatives from the Association of Food and Drug Officials (AFDO) and the National Association of State Departments of Agriculture (NASDA), to develop training and tools targeted for use by regulators when performing inspections and other types of oversight activities to ensure industry compliance with the new prevention-oriented standards.

We acknowledge there have been some instances of on-farm activities in which additional guidance would have been beneficial for both regulated industry and FDA staff. For example, some farms have registered unnecessarily with FDA as a facility when they did not need to do so. Farms are generally exempt from the registration requirement unless they are a mixed-type facility. A farm mixed-type facility is an establishment that grows and harvests crops or raises animals and may conduct other activities within the farm definition but also conducts activities that require the farm to be registered as a facility. Facilities required to register with FDA would be subject to the preventive controls for human food rule and are covered by FDA's FSMA inspection mandate for food facilities. FSMA requires facility inspections to be based on risk and the frequency of inspections of food facilities to increase. It calls for all high-risk domestic food facilities to be inspected within 5 years of the bill's signing and then at least once every 3 years after that. Further, all other do-

mestic food facilities are to be inspected within 7 years of the bill's signing and then at least once every 5 years thereafter.

We received many comments related to activities conducted on a farm that are considered part of farming by farmers yet trigger the requirement for a farm to register with FDA as a facility. On September 19, 2014, FDA released proposed revisions to the proposed rule on produce safety that are more flexible and less burdensome in key areas. The proposed revisions include the definition of "farm"—a farm would no longer be required to register as a food facility merely because it packs or holds raw agricultural commodities grown on another farm under a different ownership. FDA is proposing that such activities would be subject to the produce safety rule (as applicable) rather than the preventive controls rule for human food. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014.

The Agency is committed to developing a final rule on produce safety that prevents illnesses but is also practical and adaptable to a wide diversity of growing conditions and practices. We also are looking to working with our Federal and State counterparts who have worked with the produce community for many years to assist us in our efforts.

Question 3. Additionally, on the food manufacturer side, FDA inspectors and investigators will need to understand and evaluate the effectiveness of a facility's food system in order to properly audit food safety systems. Can you provide a timeline for FDA's implementation of a comprehensive training program for FDA inspectors, including State and local partners?

Answer 3. FDA recognizes the need to establish training programs for Federal and State regulators who will oversee compliance with the new FSMA regulations, when finalized, to ensure consistency in the performance and quality of inspections regardless of the regulatory entity that performs such inspections. To implement FSMA, FDA will need to work closely with State agencies and other partners to oversee compliance with the new requirements. FDA has funded the creation of three private-public university-based alliances—the Produce Safety Alliance (PSA), the Food Safety Preventive Controls Alliance (FSPCA), and the Sprouts Safety Alliance (SSA). These alliances are responsible for providing standardized curricula and establishing mechanisms to train industry and regulators on the requirements of the produce safety and preventive controls rules for human and animal food. This will help promote widespread industry compliance with the rules and provide for consistent regulatory inspections by State and Federal officials. More information about the alliances is available on the Internet at *http://www.fda.gov/Food/GuidanceRegulation/FSMA/ucm293423.htm*.

Further, we expect to collaborate with State regulatory partners under the Partnership for Food Protection (PFP) umbrella, which includes representatives from the Association of Food and Drug Officials (AFDO) and the National Association of State Departments of Agriculture (NASDA), to develop training and tools targeted for use by regulators when performing inspections and other types of oversight activities to ensure industry compliance with the new prevention-oriented standards.

Finally, FDA's Office of Regulatory Affairs University (ORAU) offers an extensive course catalog of instruction, both traditional in classroom and distance-learning formats. We envision collaborating with our State regulatory partners to develop and deliver FSMA-related training targeted specifically for regulators by using the alliances' standardized curricula and ORAU regulator training. We also envision that Federal and State regulators will be trained together using qualified trainers to ultimately establish a cadre of investigators who will conduct inspections to assess compliance with FSMA rules on the farm and in food facilities. We expect the Alliances and others to begin conducting training before the compliance dates of the final regulations.

Question 4. In Pennsylvania, we have many mid-sized family farms that are involved in dairy and other production. We also have a high and increasing demand for local, fresh fruits and vegetables. Many dairy and commodity farmers are responding to that market demand and diversifying their operations. This is especially true with younger generations getting started on well-established family farms. However, FDA's proposed regulations might discourage those operations from taking advantage of those market opportunities because those farmers will not be eligible for the less burdensome requirements due to their sales from other commodities, and will be faced with the full compliance costs of meeting the full set of requirements. This is due to the fact that eligibility for those modified requirements and the $25,000 *de minimus* exemption from the produce safety regulations is based on the value of "all food" and not just the value of regulated food. So in other words,

if the value of milk shipped to a processor is above $25,000 per year (almost all cases) or even $500,000 per year (most cases), the very first tomato grown and sold off the farm will have to meet the highest level of requirements contained in FSMA. Congress in FSMA gave FDA broad authority to develop scale-appropriate regulations applicable to different practices, sizes, and systems of production. Given this authority and the flexibility it provides, can you discuss how you intend to address this issue, especially in light of the "all food" definition?

Answer 4. FDA recognizes the tremendous diversity of the produce farming industry, not just in terms of the size of farming operations, but also in the types of commodities produced, crops grown, and growing methods used. The Agency shares your concern that the new safety standards must be flexible enough to account for this diversity. FSMA and the proposed produce safety rule provide various exemptions and limitations on the rule's coverage. For example, the proposed produce safety rule excludes certain produce commodities that constitute the lowest risk, with respect to biological hazards. The proposed produce safety rule also would not apply to produce for personal or on-farm consumption.

Regarding calculation of the gross dollar amount of food sold at a farm or facility, you indicate that the rules should specify that only food potentially subject to the new regulations ought to count toward the $25,000 threshold for coverage in the proposed produce safety rule and for the $500,000 annual gross sales limit for the modified requirements for a farm or facility in both rules. We are pleased to inform you that, on September 19, 2014, FDA released proposed revisions to the proposed rule on produce safety that are more flexible and less burdensome in key areas. Specifically, FDA is proposing that farms or farm mixed-type facilities with an average annual monetary value of produce sales of $25,000 or less will not be covered. The original proposed rule defined that monetary threshold in terms of all food sales. The Agency is also proposing corresponding changes to the definitions of "very small business" and "small business" to base those monetary thresholds on produce sales rather than food sales. The monetary threshold for the qualified exemption with modified requirements, however, would not change because that exemption is defined by statute. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014.

SENATOR BENNET

REGULATION OF BREWERS' SPENT GRAIN

Question. Dr. Hamburg, I have a question on the regulation of brewers' spent grain. I represent one of the leading beer producing States in the United States, with large and small craft brewers. If the FDA moves forward with its proposed rule, "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Food for Animals," some brewers have expressed concern that they may be unable to absorb the cost of compliance and may have no choice but to dispose of their spent grain in landfills, which could cost millions in landfill fees. Has the FDA conducted an environmental impact analysis on the implications of landfilling large quantities of spent grains into landfills? If so, when can we expect the analysis to be completed?

Answer. You express concerns that we also heard from many in the brewing community regarding the potential impact of the proposed rule on the long-standing practice of beer brewers providing the "spent grains," resulting from the brewing process, to farmers to use as animal food.

Breweries making products for human consumption are already subject to human food Current Good Manufacturing Practice (CGMP) regulations. FDA's current understanding is that the potential hazards associated with spent grains from brewers and distillers of human beverages are minimal, provided the food manufacturer takes common-sense steps, such as minimizing the possibility of physical or chemical hazards being inadvertently introduced into a container of spent grains. In addition, we agree that there are substantial efficiency and sustainability benefits from the recycling of human food by-products—such as spent grains—to animal food, and it is not our intention to disrupt this practice.

We are pleased to inform you that, on September 19, 2014, FDA proposed a number of revisions to its proposed rule on preventive controls for animal food that are more flexible and less burdensome in key areas. Specifically, the Agency has proposed that, in general, human food processors already subject to and complying with FDA human food safety requirements, such as brewers, would not need to implement additional preventive controls or CGMP regulations when supplying a by-product (e.g., wet spent grains, fruit or vegetable peels, liquid whey) for animal food, except for proposed CGMPs to prevent physical and chemical contamination when

holding and distributing the by-product (e.g., ensuring the by-product isn't co-mingled with garbage).

Please be assured that we are working to develop regulations that are responsive to the concerns expressed, practical for businesses, and that also help ensure that food for animals is safe and will not cause injury to animals or humans. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014. We hope to continue our active dialog with stakeholders, including the brewing community, about how we can achieve our food safety goals in the most practical way.

SENATOR BALDWIN

Question. In Wisconsin we have two proud beverage traditions: we produce a large volume of milk and also have many breweries across our State. These two industries come together in an interesting way related to animal feed, and have raised concerns with the FDA's proposed rule, "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Food for Animals."

Many breweries provide spent grains to our dairy and livestock farmers as a source of animal feed. Under the new rule, breweries could incur very large compliance costs, which would likely cause them to divert the grains away from this productive second use into a waste stream. It is unclear whether the compliance proposed in the rule addresses a substantial threat to human or animal health, or whether compliance would result in measureable improvements in safety.

Brewers' spent grains are an indispensable feed source for the dairy industry in Wisconsin. Can you please describe how the FDA will review this portion of the proposed rule, consider the input provided by industry voices that have expressed concern about this provision, and review options to update this section accordingly?

Answer. You express concerns that we also heard from many in the brewing community regarding the potential impact of the proposed rule on the long-standing practice of beer brewers providing the "spent grains," resulting from the brewing process, to farmers to use as animal food.

Breweries making products for human consumption are already subject to human food Current Good Manufacturing Practice (CGMP) regulations. FDA's current understanding is that the potential hazards associated with spent grains from brewers and distillers of human beverages are minimal, provided the food manufacturer takes common-sense steps, such as minimizing the possibility of physical or chemical hazards being inadvertently introduced into a container of spent grains. In addition, we agree that there are substantial efficiency and sustainability benefits from the recycling of human food by-products—such as spent grains—to animal food, and it is not our intention to disrupt this practice.

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SENATOR WARREN

Recently the FDA released two guidance documents, GFI #209 and #213, and a proposed rule for Veterinary Feed Directives. These measures will make the use of all antibiotics in animal feed subject to VFD and eventually eliminate the use of antibiotics for production purposes. The FDA hopes that these measures will curb the overuse of antibiotics in animal agriculture.

Question 1a. How do you intend to measure whether the non-judicious use of antibiotics in animal agriculture declines, or simply stays the same but under the guise of disease prevention?

Answer 1a. Regarding the concern that medically antimicrobial drugs will continue to be used under the guise of disease prevention, once production uses are removed from affected medicated feed products, such products can only legally be used for prevention purposes if the labeling of the product includes an FDA-approved prevention indication. If a medicated feed product were to be used for an unapproved disease prevention purpose, FDA could initiate action on the grounds that such use caused the drug to be unsafe under section 512(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 360b(a) and adulterated within the meaning of section 501(a)(5) of the FD&C Act, 21 U.S.C. § 351(a)(5).

In addition, acknowledging the importance of this concept, GFI #213 outlines several important factors that veterinarians should consider when determining the appropriateness of a preventive use. These factors include whether: (a) there is evidence of effectiveness, (b) such a preventive use is consistent with accepted veterinary practice, (c) the use is linked to a specific etiologic agent, (d) the use is appropriately targeted to animals at risk of developing a specific disease, and (e) no reasonable alternatives for intervention exist.

The Agency believes veterinary oversight of these products is a critical element for ensuring that the above factors are considered in determining the specific situations where prevention use is necessary and appropriate. FDA intends to work with veterinary and animal producer organizations to reinforce the importance of these principles.

The Agency recognizes that it is important to identify ways to assess the effect of these measures over time. FDA is currently enhancing data sources in a number of ways to help monitor the effect of GFI #213. Currently, the Agency collects data on antimicrobial resistance among foodborne pathogens as part of the National Antimicrobial Resistance Monitoring System (NARMS), as well as data on the sale and distribution of antimicrobial drugs intended for use in food-producing animals, which FDA collects and reports annually under section 105 of the 2008 Animal Drug User Fee Amendments (ADUFA 105). The U.S. Department of Agriculture (USDA) also periodically collects antimicrobial use data on livestock and poultry operations as part of the National Animal Health Monitoring System.

Recent enhancements to the NARMS program make the data more useful for measuring the effect of GFI #213, particularly a new USDA Food Safety Inspection Service slaughter sampling program, launched in March 2013, which increases national representativeness of the animal samples. In addition, FDA is working with four State partners to perform whole-genome sequencing on NARMS samples. The data will provide unprecedented details on changes in resistance genes from animals and animal-derived foods.

Based on broad public input, FDA has enhanced the format of the ADUFA 105 annual summary reports to better describe data on the annual sales and distribution of antimicrobials intended for use in food-producing animals using a more detailed format that will allow the public to better understand the changes that occur as GFI #213 is implemented. On October 2, 2014, FDA released the summary report for 2012, using this new format, and provided updated annual reports from previous years to include the new data tables. The changes expanded the format of reporting sales and distribution data by antimicrobial class to include information on the importance of the drug in human medicine. These changes also provide aggregate data on the approved route of administration of antimicrobial drugs sold or distributed for use in food-producing animals, whether such drugs are available over the counter or require veterinary oversight, and whether they are approved for therapeutic indications, or both therapeutic and production indications.

You may be interested to know that the Agency is also developing a proposed regulation to enhance the existing requirements related to the collection of antimicrobial drug sales and distribution data for antimicrobial drugs intended for use in food-producing animals. New requirements being considered include the collection of additional drug sales and distribution data, including reporting sales and distribution data by species.

FDA is working with USDA and the Centers for Disease Control and Prevention (CDC) to identify possible approaches for further enhancing current data collection efforts, focused on actual use (exposure) on the farm. This will help identify meaningful metrics for assessing the effectiveness of GFI #213 in reducing the public health risk of antibiotic resistance. The Agency intends to seek further public input on this issue in early 2015.

In addition, as part of this collaborative effort it was determined that there is currently no appropriate method to analyze associations between changes in antimicrobial use and shifts in resistance patterns on a national level, as is needed to assess the public health impact of interventions such as GFI #213. Therefore, FDA and USDA are collaborating with a Cornell University researcher and submitted a

National Institute of Mathematical and Biological Synthesis (NIMBioS) proposal to create a working group to develop a new mathematical modeling methodology that would inform the approach to monitoring and assessing the impacts of GFI #213. This will allow the collaborating Federal agencies to efficiently allocate limited resources by targeting data which are most valuable. The proposal was accepted and the first meeting of the working group occurred in September 2014.

Under the *Veterinary Feed Directive proposed rule*, all of the Nation's 1,366 medicated feed distributors will have two largely expanded roles—making sure that medicated feed is sold only with a valid veterinary feed directive and that the feed labeling reflects appropriate uses. This presents an important opportunity to obtain more data on what's going on. Right now, our understanding of how these drugs are used is basically a black box—we know what antibiotics are being used and how much they are being used, but we don't have a clear picture of what animals they are going into, how they are being administered, or for what purpose.

Question 1b. Does the FDA currently have the authority and capacity not only to inspect the facilities to make sure that VFDs are complete and being used appropriately, but also to collect data from the VFDs about how antibiotics are being used in animal agriculture?

Answer 1b. FDA believes that the VFD regulation, when finalized, will establish a clear set of requirements governing the sale or distribution of VFD drugs. This includes specifying the type of information that veterinarians must include on the VFD authorizations they issue as well as the type of records that need to be maintained. Veterinarians, feed mills, and producers are required to maintain copies of VFDs and to make them available to FDA upon request during inspections or other investigations.

FDA currently has the authority to collect data from VFDs during inspection. We anticipate, as part of the implementation of GFI #213, a large number of over-the-counter products transitioning to a new VFD status when the VFD proposed rule is finalized. FDA intends to continue to conduct inspections in order to ensure that veterinarians, feed mills, and producers understand the new VFD requirements, once established, and are in compliance with them.

Question 1c. If not, what resources and authority do you need to capture the information?

Answer 1c. As noted above, FDA has the authority to collect data from VFDs during inspection.

Question 1d. If the FDA was able to compile the data associated with veterinary feed directives, would the agency be able to better track how exactly antibiotics are being used in different types of food animals?

Answer 1d. FDA does not consider VFDs to be a comprehensive source of drug use information because they are limited to medicated feeds and do not capture all antibiotics, such as those for use in water and injectable products. In addition, VFDs do not necessarily accurately represent the amount that is actually administered by the end-user. However, the Agency is considering all options for collecting additional data that would enhance our assessment of the impacts of our efforts to address antimicrobial resistance.

As noted in the response to question 1(a) above, the Agency is currently developing a proposed regulation to enhance the existing requirements related to the collection of antimicrobial drug sales and distribution data for antimicrobial drugs intended for use in food-producing animals.

In addition, as we explain in greater detail above, FDA is working with USDA and CDC to identify possible approaches for further enhancing current data collection efforts, focused on actual use (exposure) on the farm, which will help identify meaningful metrics for assessing the effectiveness of GFI #213 in reducing the public health risk of antibiotic resistance.

SENATOR ALEXANDER

In the Food Safety and Modernization Act, Congress directed FDA to concentrate produce safety rulemaking on commodities or commodity groups with the highest risk profile. However, FDA appears to have rejected that approach.

Question 1a. Why did FDA choose to broadly regulate commodities that have not been associated with human foodborne illness, when the law specifically asked the FDA to focus on highest risk produce?

Answer 1a. The law directed FDA to "establish science-based minimum standards for the safe production and harvesting of those types of fruits and vegetables . . . for which the Secretary has determined that such standards minimize the risk of

serious adverse health consequences or death" (Federal Food, Drug, and Cosmetic Act (FD&C Act) § 419(a)(1)(A)). We specifically solicited comment on our approach in the proposed produce rule and will be considering those comments carefully as we move forward to finalize the rule. FDA initially considered covering only those produce commodities or commodity groups that had been associated with foodborne illness outbreaks. However, because only a small percentage of outbreaks are both reported and attributed to a specific food vehicle, outbreak data may not provide a complete picture of the commodities upon which we need to focus to minimize current and future risk of illness. The food vehicle responsible for an outbreak is not identified in about half of all outbreaks. Identifying the vehicle of an outbreak in which the vehicle is contained in a multi-ingredient food (e.g., salsa, salads) is particularly challenging. As our ability to detect outbreaks and to identify food vehicles responsible for an outbreak improves, it is likely that previously unrecognized outbreak vehicles will be identified. A further complication to the use of outbreak data as an indication of commodity risk is that, until a food is identified as a vehicle in an outbreak, public health officials may not be likely to include questions about that commodity when investigating an outbreak, making the attribution of outbreaks to commodities with no outbreak history more difficult.

In addition, as discussed in the draft Qualitative Assessment of Risk that the Agency issued along with the proposed rule, our data show that the patterns of outbreaks associated with produce commodities change over time. On the one hand, some commodities, such as tomatoes and leafy greens, have a continuing and repeated pattern of association with outbreaks, over multiple years. On the other hand, occasionally a produce commodity is associated with an outbreak that had not been previously linked to foodborne illness. For example, papayas had not been associated with outbreaks prior to an outbreak that occurred in 2011. Therefore, a regulatory approach that relied on a static list of commodities prepared solely from a history of outbreaks would not be able to prevent future outbreaks in commodities not previously associated with an outbreak.

FDA tentatively elected not to take a commodity-specific approach, in part, because we do not believe that the past history of outbreaks can be fully predictive of future outbreaks. We also reviewed the relative risk of different commodities using other data sources, such as commodity characteristics and pathogen surveillance data. Our analysis shows that each data source presents certain gaps that make it challenging to develop a commodity-specific approach that would adequately minimize the risk of serious adverse health consequences or death. [Please note that the only commodity-specific requirements proposed in this rule are those designated for sprouts, which have unique growing procedures (i.e., warm, moist nutrient-rich environment for an extended period of time that supports pathogen growth in addition to sprouting) and, therefore, present a unique risk profile. For this reason, we tentatively concluded that a specific set of safety standards for this produce commodity is warranted.] However, as we mentioned earlier, we have specifically solicited comment on this determination and on whether there are commodity-specific approaches that would adequately minimize the risk of serious adverse health consequences or death and whether such approaches would sufficiently move us toward the prevention-based food safety system envisioned by FSMA.

Question 1b. Did FDA consider the risks and benefits associated with regulating individual commodities? How were those cost-benefit results different for leafy grains as compared to citrus, for example?

Answer 1b. FDA did explore the option of excluding commodities not associated with any recorded outbreaks in Option 2, under Section D. Regulatory Options (found on page 43 of the preliminary regulatory impact analysis). However, for the numerous reasons listed there and in Section IV.C of the proposed rule, we tentatively concluded that this was not the most appropriate option. We specifically solicited comment on this topic in the preliminary regulatory impact analysis and will be considering those comments carefully as we move forward to finalize the rule.

We tentatively concluded that an integrated approach that focuses on the likelihood of contamination of produce posed by the agricultural practices applied to the crop, while exempting the lowest-risk produce, would provide the most appropriate balance between public health protection, flexibility, and appropriate management of different levels of risk. We also tentatively concluded that we should use a regulatory framework based on practices, procedures, and processes associated with growing, harvesting, packing, and holding of all covered produce. We considered and tentatively rejected the option to develop a framework that (based solely on a history of outbreaks or illnesses associated with the commodity) would be applicable to individual commodities or classes of commodities. Procedures, processes, and practices in each of the on-farm routes of contamination outlined in the proposed

rule have the potential to introduce biological hazards into or onto any covered produce.

Question 2. Do you commit to providing a flexible approach to getting consumers the nutrition information that they need without unnecessarily adding cost and complexity without scientific evidence it will produce a benefit?

Answer 2. FDA's recently proposed update to the Nutrition Facts label reflects the latest scientific information, including the link between diet and chronic diseases such as obesity and heart disease. FDA is proposing to replace out-of-date serving size requirements to better align with how much people really eat and require labels that feature a fresh design to highlight key parts of the label such as calories and serving sizes. These changes would provide information to help consumers make better-informed food choices to support a healthy diet.

The estimated benefits of these changes would far outweigh the costs. FDA is proposing that manufacturers have 2 years after the effective date of the final rule to comply with any new requirements.

SENATOR BURR

Question 1. I have heard concerns from my constituents that the final rule may establish costly testing requirements that divert resources away from the most critical food safety activities. The Food Safety Modernization Act was intentionally designed to be flexible and risk-based, based on the circumstances of products and manufacturing operations. FDA was not supposed to impose a one-size-fits-all approach to food safety. Do you agree that pathogen testing should be based on the risk of the product, process, and hygienic status of the production environment, as well as the risk information provided from verification activities?

Answer 1. In our proposed rule, "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food," we did not include specific requirements for environmental monitoring but we acknowledged that such programs, when implemented appropriately in particular facilities, could be used to verify the effectiveness of preventive controls when contamination of food with an environmental pathogen is reasonably likely to occur. On September 19, 2014, FDA released proposed revisions to its proposed rule on preventive controls for human food that are more flexible and less burdensome in key areas. With regard to product testing and environmental monitoring, the Agency is now providing an opportunity for input on specific language and seeking comment on whether to include it in the final rule. Specifically, FDA is seeking comment on whether the preventive controls for human food should require a facility, as appropriate to the facility, the food, and the nature of the preventive control, to conduct product testing or environmental monitoring to verify implementation and effectiveness of preventive controls if contamination of a ready-to-eat food with an environmental pathogen is a significant hazard. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014.

Question 2. Why has the agency failed to amend the definition of "retail food establishment" as required by the Food Safety Modernization Act to clarify that the sale of food directly to consumers includes the sale of food through community-supported agriculture programs, farmers markets, and other direct-consumer venues? Without this required clarification, these entities could be subject to regulation that is not consistent with congressional intent. Does the agency plan to include this important clarification in the re-proposal of the regulations later this year? If not, please explain the agency's path forward for carrying this statutory clarification.

Answer 2. We learned a great deal during our conversations with farmers, including information about the diversity of these operations, and through other outreach engagements, in addition to numerous comments received to the docket. FDA recognizes the importance of crafting food safety standards that are practical to implement for the diverse industry. Section 102 of FSMA requires that FDA clarify the definition of "retail food establishment" relative to certain direct-to-consumer platforms. FDA intends to address this clarification in an upcoming rulemaking that addresses this issue and other provisions of FSMA Section 102.

Question 3. Why has the agency proposed significantly increasing the types of studies and clinical research for certain foods through IND submissions? Is the intent of this final guidance to make certain foods adhere to pharmaceutical drug standards?

Answer 3. This question refers to final guidance issued by FDA on September 10, 2013, entitled "Guidance for Industry: Investigational New Drug Applications

(INDs)—Determining Whether Human Research Studies can be Conducted without an IND." The guidance was initially published in draft for public comment in 2010. Although largely addressing pharmaceutical issues, both the 2010 draft and the 2013 final guidance also addressed circumstances when dietary supplements are studied for drug uses and therefore the study requires an IND. Because several comments on the draft guidance recommended that the dietary supplement section should be expanded and clarified and that other categories of foods should also be discussed, the final guidance included a more detailed section on dietary supplements and added a section on conventional foods. At both the draft and final stages, the guidance as it relates to dietary supplements and other foods was intended to clarify when an IND is required under the Federal Food, Drug, and Cosmetic Act. Because the final guidance generated significantly more interest and concern from industry than did the 2010 draft, FDA reopened the comment period on the portion of the final guidance relating to foods, as well as the portion relating to cosmetics. That additional comment period has closed, and FDA is in the process of reviewing the comments.

SENATOR BURR AND SENATOR ISAKSON

Question. It is essential that FDA have a good working relationship with the Agricultural Community as the agency proceeds with implementation of FSMA. Therefore, it is particularly concerning to hear that the relationship between farms and the FDA is strained due to the manner in which the agency has engaged in inspection and compliance activities. Please outline how the FDA plans to ensure a good working relationship with the Agricultural Community moving forward, including ensuring inspectors are consistently complying with the agency's compliance standards and strategies? How will the agency ensure that regulated entities, including product growers, are afforded due process in the issuance, revision, appeal, and adjudication of 483s, including with respect to disagreement over "significant findings," in order to ensure adequate resolution of 483s in the future?

Answer. FDA appreciates and takes very seriously the extensive input we have received from produce farmers and others in the agricultural sector on the proposed FSMA rules on produce safety and preventive controls for human food. Our discussions with farmers have reiterated the importance of taking a collaborative approach to implementing the rules. This entails working with our State, territorial, and tribal partners; extension services; and industry to provide education, training, and technical assistance to help farmers and facilities comply with the rules, once finalized, and move toward the shared goals of food safety and consumer confidence in the safety of the food supply.

FDA is developing outreach materials in cooperation with State, industry, and consumer groups to ensure there is uniformity in the information and education activities related to the new requirements under FSMA. In addition, FDA will be providing training programs for inspectors to ensure that inspections to determine compliance with the new requirements will be uniform. The Produce Safety Alliance (PSA) is led by Cornell University, and involves FDA, the U.S. Department of Agriculture (USDA), State food and agriculture departments, and two national industry trade associations. The PSA will produce a standard on-farm training manual and curriculum and plans to offer courses to deliver the training. It will develop and disseminate science- and risk-based training and education programs to provide produce farms with fundamental food safety knowledge, starting in advance of the proposed produce safety rule and continuing after the final rule is promulgated. In addition, the PSA is developing a training protocol with State and Federal regulators to help ensure uniformity in inspections. It will also be a repository for up-to-date scientific and technical information, including a compendium of produce hazards. The training will be finalized shortly after the publication of the final rule on produce safety. The Alliance and others will conduct training that will begin during the period that precedes the compliance dates.

Regarding potential disagreements in the future between the Agency and regulated entities, FDA's Office of Regulatory Affairs (ORA) has analyzed the need and is initiating the process to establish an Ombudsman position and associated processes, whereby issues or establishment concerns raised in these inspectional communications may be escalated by the establishment or by FDA in a manner consistent with how disputes are processed by other FDA centers and offices. As part of the FSMA implementation effort, FDA and ORA have acknowledged industry's request to consider dispute resolution processes that provide for confidentiality as well as for enhanced consistency across all regions and commodities and an improved global approach in light of the increased formal foreign presence. The possible ORA Om-

budsman would address these goals as well as offer a process for resolving issues that arise outside of an inspection.

SENATOR BURR, SENATOR ENZI, AND SENATOR ISAKSON

Question. The Food Safety Modernization Act adopted a "reasonably foreseeable" standard with respect to preventive controls. In legislating FSMA Congress debated whether to follow the HACCP model, but definitively decided not to use HACCP in the bill, instead establishing preventive controls with a different standard. Why is FDA proposing a standard different than what was enacted in FSMA in the proposed regulations?

Answer. In the proposed rule, "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food," we proposed that the application of preventive controls would be required in cases where facilities determine that hazards are reasonably likely to occur. We received many comments related to the use of the term "reasonably likely to occur." Comments expressed concern that if we use this term as the basis for determining the need for preventive controls, then either all preventive controls will need critical control points (CCPs) or people will be confused by the term being different in this rule from the seafood and juice Hazard Analysis and Critical Control Points (HACCP) rules. In the proposed revisions to the proposed rule on preventive controls for human food that we released on September 19, 2014, we indicated that we are proposing to eliminate the term "hazard reasonably likely to occur" throughout the proposed requirements to reduce the potential for a misinterpretation that all necessary preventive controls must be established at CCPs. The revised regulations would use a new term ("significant hazard") in its place. The defined term "significant hazard" would be linked to the facility's hazard analysis, which addresses risk (i.e., both the severity of a potential hazard and the probability that the hazard will occur). Thus, this term would reflect the risk-based nature of the requirements. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014.

SENATOR ENZI

Question 1. I have heard concerns from rural veterinarians and livestock producers about the onerous burdens placed on the livestock industry by the FDA's food animal antibiotic use guidance and proposed Veterinary Feed Directive. Many rural areas, including most parts of Wyoming, are underserved by large animal veterinarians and it is already difficult for these professionals to service remote areas where livestock are raised. Could you please tell me how FDA provided accommodations in its proposal for the concerns these individuals raised in the rulemaking process?

Answer 1. With the publication of GFI #213 on December 12, 2013, FDA began the 3-year implementation of its strategy to promote the judicious use of medically important antimicrobial drugs in food-producing animals. The goal of the strategy is to work with animal drug sponsors to voluntarily phaseout the use of medically important antimicrobials in food animals for production purposes (e.g., to enhance growth or improve feed efficiency) and to bring the therapeutic uses of such drugs (e.g., to treat, control, or prevent specific diseases) under the oversight of licensed veterinarians. In order to help phase in veterinary oversight of those drugs covered by the guidance that are intended for medically appropriate uses in feed, FDA also issued a proposed rule to update the existing regulations relating to VFD drugs.

Because of the complex scientific and regulatory issues involved and the potential impact that changes to the VFD regulations may have on stakeholders, FDA sought stakeholder input via multiple opportunities for public comment, including an advance notice of proposed rulemaking (ANPRM) (75 FR 15387, March 29, 2010) and draft text of proposed amendments to the current VFD regulations (77 FR 22247, April 13, 2012). FDA also announced its plans for a series of five meetings (78 FR 14801, March 7, 2013) which were held around the country in 2013 to provide the public with opportunities to discuss and provide critical feedback on the challenges faced by livestock producers and veterinarians as FDA phases in veterinary oversight of the therapeutic use of certain medically important antimicrobials. The meetings were jointly sponsored by FDA and the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service and were intended to provide a forum to discuss potential challenges faced by animal producers in areas of the country that may lack access to adequate veterinary services and to explore possible options for minimizing adverse impacts.

Based on the input the Agency received, the proposed VFD regulation includes several provisions that could allow veterinarians to more effectively provide services to food animal producers in remote geographical areas where veterinary professional resources are limited and distances are great. For example, one major proposed

change is to replace the explicit veterinary-client-patient relationship (VCPR) provision with the requirement that veterinarians ordering the use of VFD drugs do so only "in animals under his or her supervision or oversight in the course of his or her professional practice, and in compliance with all applicable veterinary licensing and practice requirements." The purpose of this revision is to defer to the individual States and the veterinary profession for the specific criteria for acceptable veterinary professional conduct, rather than relying on a more rigid, one-size-fits-all, Federal standard. From a practical standpoint, this enables the veterinary profession and individual States to adjust the specific criteria for a VCPR to appropriately align with current veterinary practice standards, technological and medical advances, and other regional considerations.

Other examples that are intended to help accommodate concerns regarding veterinary access are connected to a number of proposed changes to the information required on a VFD order. These include establishing a "default" maximum expiration date of 6 months, allowing veterinarians to estimate the approximate number of animals instead of the exact quantity of feed, and allowing veterinarians the option to identify premises where the animals are located instead of more detailed individual animal identification. While the existing process requires VFD orders to be written for a specific amount of medicated feed to be delivered to specifically identified animals, these proposed revisions would allow veterinarians to opt for this level of specificity or to exercise their professional judgment to issue a broader "standing order" for up to 6 months and for a specified approximate number of animals.

FDA has worked with many stakeholder groups and USDA to develop a strategy that it believes will be successful in reducing antimicrobial resistance while minimizing adverse impacts on animal health and disruption to the animal agricultural industry. In order to help minimize these impacts while still ensuring that VFD drugs are used in a manner that affords adequate protection for human and animal health, FDA has proposed amendments to the existing VFD regulations to improve the efficiency of the VFD program. The comment period for the proposed VFD regulation closed March 12, 2014, and the Agency is currently reviewing all comments received. As part of the effort to finalize and implement updated VFD regulations, FDA will continue to work with affected stakeholders in the veterinary and livestock industries to ensure the needed outreach and education is provided to support the implementation of these significant changes to how antimicrobials are used in food-producing animals.

Question 2. What is the status of implementation of the "Tester Amendment" to the Food Safety Modernization Act (FSMA) which provides specific accommodations to the preventive controls in the law for small farmers and producers?

Answer 2. FDA has included provisions implementing the "Tester Amendment" in its proposed rules implementing sections 103 (preventive controls) and 105 (produce safety) of FSMA.

Question 3. Despite last year's sequester, FDA received from Congress an increase of $96 million over the amount provided in fiscal year 2013 and $3 million above the agency's budget request. In the most recent FSMA implementation progress report, you announced that you are doing more inspections and working hard to meet court ordered deadlines to release pending regulations. This has been done with appropriated funds, and without the imposition of new regulatory taxes. Could you explain then why FDA needs these user fees? Have you hired or trained new inspectors, retrained current inspectors? How have you done so in the absence of final regulations?

Answer 3. FDA is committed to fully implementing FSMA and is working diligently to prioritize new and existing resources toward this effort. We have adequate resources to issue the required regulations and conduct the mandated number of domestic inspections, and we will continue efforts to make the best use of the resources we have. However, FDA cannot fully implement FSMA and achieve the benefits of a safer food supply without a significant increase in resources.

As you know, the President's fiscal year 2015 budget request affirms the need for additional resources to implement FSMA by requesting that Congress provide $253 million in additional funding via a combination of added appropriations and new user fees. These resources are needed to adequately implement FSMA, including resources needed to retrain FDA and State inspectors, provide grants to States to build the capacity to conduct inspections and coordinate with FDA, and implement the new import safety system mandated by Congress.

The urgency of receiving adequate funding in 2015 and 2016 is that FDA is under court-ordered deadlines to issue key final rules in late 2015 and early 2016, which means FDA must be equipped to begin sound inspection and other oversight activi-

ties to ensure smooth and effective implementation in late 2016 and 2017. Without immediate investment in the advance preparation that is essential for sound implementation of the FSMA rules, implementation will be disrupted and delayed to the detriment of public health, consumers, and the food industry.

For example, with regard to your question about inspectors, FDA inspectors are currently trained to inspect food manufacturers using a compliance model focused on finding evidence of hazards. The new food safety paradigm will be focused on preventing food contamination through a system-based approach and on ensuring consistency among all inspections. This new paradigm involves a major reorientation and retraining of almost 1,700 inspectors, compliance officers, and other staff involved in food safety activities in fundamentally different approaches to food safety inspection and compliance. To accomplish this in time, training in the new prevention and systems approach must begin in 2015, with further technical training continuing into 2016 and beyond after the FSMA rules are finalized.

In addition, the States are projected to conduct over half of the domestic facility inspections required by FSMA. Building State capacity to coordinate effectively with FDA is a central tenet of FSMA and is needed to ensure that States are prepared to conduct these inspections using the same standards and methodologies as FDA inspectors. States will need inspector training, greater information sharing capacity with FDA and other States, State laboratory coordination, and inspector certification programs. Like FDA's own retraining effort, those processes, which will be carried out mostly via FDA grants to 40 or more States, must begin in 2015 if the States are to be prepared when industry becomes obligated to comply with the new prevention standards starting in 2016.

Question 4. It is my understanding that not all FSMA rules have been issued. As a result, we do not yet know the entire cost of implementation. Will you be asking for more and more fees to regulate these businesses as these rules come out?

Answer 4. FDA does not currently anticipate proposing new user fees to support FSMA implementation beyond those identified in the fiscal year 2015 request.

Question 5. What research have you done in relation to alternatives to the use of partially hydrogenated oils (PHOs) in food production, such as saturated fat or palm oil? What are the potential consequences to using these alternatives, which are the only options available at this time? Was a cost-benefit analysis conducted prior to the FDA rule banning trans fats?

Answer 5. Since FDA's trans fat labeling rule took effect in 2006, FDA has observed that the food industry has significantly reduced the amount of partially hydrogenated oils (PHOs) used in their products. We have also observed that in all product categories the food industry now offers at least some products that do not contain PHOs. To reduce the risk of coronary heart disease, ideally PHOs should be replaced with healthier oils (e.g., polyunsaturated or monounsaturated oils) rather than oils high in saturated fat. While PHOs may be replaced with oils high in saturated fats for some products, a 2010 review article showed that major brand-name reformulations generally reduced the trans fat content substantially without making equivalent increases in saturated fat. The notice FDA issued about PHOs in 2013 was not a rule banning trans fats; rather, it was a tentative determination that PHOs are not generally recognized as safe (GRAS) for any use in food. In response to this notice, FDA has received a number of comments about alternatives to PHOs, including comments from the soybean industry that they have developed high oleic soybean varieties (a healthier alternative to PHOs) which may be used as an alternative to PHOs.

In 2013, FDA conducted an estimate of the potential costs and benefits associated with removing PHOs from the food supply. FDA estimates that monetizing the lives saved, along with the value of the nonfatal illnesses and medical expenses prevented, yields an estimated 20-year value of benefits from this proposal of about $117 billion. The estimated cost of removing PHOs from the food supply over 20 years (at a 7 percent discount rate) is $12 billion.

Question 6. There is bipartisan support to eliminate duplicative programs and reduce government waste. The Government Accountability Office (GAO) has concluded on numerous occasions that the USDA catfish program would duplicate FDA's seafood Hazard Analysis Critical Control Points (HACCP) program. The most recent GAO report in April 2013 concluded that repealing the USDA catfish program "would avoid duplication of Federal programs and could save taxpayers millions of dollars annually without affecting the safety of catfish intended for human consumption." FDA has the government's preeminent seafood experts and if implemented the USDA catfish program would require two separate seafood regulators with two very different regulatory frameworks depending on the species of fish.

Based on FDA's evaluation of the science, is there any food safety basis that would justify duplicative regulation of seafood products by USDA treating catfish any differently than any other seafood that FDA regulates?

Answer 6. FDA operates a mandatory safety program for all fish and fishery products under the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Public Health Service Act, and related regulations. The FDA program includes research, inspection, compliance, enforcement, outreach, and the development of regulations and industry guidance.

Seafood in general carries some unique risks, and that is why FDA established the Hazard Analysis and Critical Control Points (HACCP) program in 1997. Currently, all seafood processors are required to adhere to HACCP regulations. Under HACCP, processers of fish and fishery products must identify hazards that are reasonably likely to occur for their products and formulate control strategies. Seafood HACCP requirements have been in place for years and serve as the foundation of the proposed hazard analysis and risk-based preventive control requirements found in the FSMA proposed rules for all food products.

FDA also has import alerts in place that provide for increased review and testing of imported seafood that may pose particular risks. These programs have been very successful in mitigating the safety issues inherent in seafood production.

With regard to catfish specifically, catfish are generally less risky than some other types of fish. Catfish are generally not eaten raw or packaged in ready to eat form.

Question 7. Section 12106 of the 2014 Farm bill, the Agriculture Act of 2014, includes new language that was inserted for the first time during the Farm bill conference process that requires USDA to issue a final rulemaking taking jurisdiction of "catfish" from FDA. Unless Congress acts to repeal the USDA catfish program, this would mean FDA would maintain primary jurisdiction over all seafood except "catfish," which USDA would regulate. Under Section 12106(b)(4) of the Agriculture Act, FDA and USDA are directed to enter into a memorandum of understanding (MOU) regarding the inspection of seafood. Given that FDA has primary jurisdiction over seafood and employs the government's seafood experts, can you confirm that in any MOU signed by FDA in relation to the USDA catfish program, FDA will insist that FDA inspectors will have primary jurisdiction over seafood other than catfish even if USDA is in the same facility to inspect catfish?

Answer 7. On April 30, 2014, FDA and USDA signed an MOU to address fish of the order Siluriformes, which includes catfish, as required by the Agriculture Act of 2014. The MOU reflects FDA's intention to continue to exercise its current regulatory oversight over seafood other than Siluriformes.

SENATOR MURKOWSKI

Question 1. I continue to strongly oppose FDA approval of genetically engineered salmon. I do not believe that FDA has adequately studied the environmental effects, the economic impacts on wild salmon and seafood markets that would result from approval, let alone the potential human health impacts. Given these concerns Commissioner Hamburg, can you assure me that FDA is prepared to deny approval of the sale of GE salmon to consumers if your agency determines that it cannot guarantee that it is safe to eat?

Answer 1. FDA will not approve the application related to AquAdvantage Salmon unless it determines that food derived from AquAdvantage Salmon meets the standard of a "reasonable certainty of no harm." FDA regulates genetically engineered (GE) animals under the new animal drug review provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The recombinant DNA (rDNA) construct used to introduce the fast growing trait into AquAdvantage Salmon meets the definition of a drug because it is intended to affect the structure or function of the animal. The new animal drug approval process provides the most rigorous review for such products that the U.S. Government has in place. This regulatory pathway prohibits the introduction of AquAdvantage Salmon, or food derived from AquAdvantage Salmon, into U.S. commerce without a specific FDA approval, which would include an evaluation of food safety. The Agency will not approve the application related to AquAdvantage Salmon until it has completed its science-based review of animal health and food safety, determined that the rDNA construct is safe to the animal, that food derived from AquAdvantage is safe to eat, and met its requirements under the National Environmental Policy Act.

Question 2. If FDA were to approve GE salmon for sale to consumers, what steps will the agency take to require clear labeling to ensure consumers know what they are buying?

Answer 2. FDA regulates the labeling of food derived from GE animals under the FD&C Act. Under the FD&C Act, FDA may require special labeling for a GE food when the food differs materially from other foods, for example, where the food differs in nutritional profile or functionality. The Agency is looking carefully at this issue with respect to food derived from AquAdvantage Salmon. We recognize that many consumers are interested in knowing whether the foods they purchase are produced using genetic engineering. Currently, food manufacturers may indicate through voluntary labeling whether foods have or have not been developed through genetic engineering, provided that such labeling is truthful and not misleading. FDA is supportive of such voluntary labeling. The Agency has issued draft guidance for industry on voluntary labeling of plant-based foods to indicate whether such foods have or have not been derived from GE plants to assist firms that wish to provide such labeling. We are working to finalize this guidance.

Question 3. Does FDA have existing authority to require labeling of GE salmon?

Answer 3. FDA regulates the labeling of food derived from GE animals under the FD&C Act. The FD&C Act prohibits food labeling that is false or misleading, and provides, in relevant part, that labeling is misleading if it fails to reveal "material" facts. Accordingly, and as interpreted by Federal courts, the Agency may require special labeling for a GE food when the genetic change results in a "material" difference in the food, such as a difference in nutritional content or functionality. However, the fact that a food comes from a GE source is normally not a material fact within the meaning of the FD&C Act, and thereby does not, by itself, trigger required labeling. These courts have further held that consumer desire to know alone is not sufficient to require such labeling.

Question 4. I am very concerned about the lack of progress to either lift the ongoing Chinese ban of all shellfish imports from the West Coast of the United States, or to at least narrow the restrictions to smaller regions. When I met recently with constituents in Ketchikan, they shared with me their frustrations with the slow pace of discussions with the Chinese. These are mostly small, family businesses that are being hit hard by the ban, with the region losing hundreds of thousands of dollars a week throughout the winter season. What specific actions is FDA taking to expedite the resolution of the ban?

Answer 4. As you know, on May 23, 2014, Chinese food safety officials advised the National Oceanic and Atmospheric Administration (NOAA) that they were lifting their ban on imports of live shellfish, including geoduck clams from Alaska and Washington. We understand the economic impact such a suspension has on local businesses and are pleased that China has lifted the ban.

In December 2013, near the beginning of the suspension, officials from FDA's Center for Food Safety and Applied Nutrition and ORA met with food safety officials in China about this issue. FDA reviewed evidence from Washington and Alaska health officials and NOAA that demonstrated the safety of geoduck clams. Based on this evidence, FDA was confident that geoduck clams, as well as other species of bivalve molluscan shellfish, were in compliance with State and Federal regulations and met the rigorous public health standards necessary to control the safety of shellfish intended for human consumption. FDA relayed its safety assessment to China's General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ).

As part of its trade facilitation mission, NOAA's Seafood Inspection Program issues health certificates for U.S. exporters for certain commodities, such as the geoducks in question. In this role, NOAA has coordinated the communication with AQSIQ on this issue. FDA, as the regulatory authority for seafood, works with NOAA when there are safety questions. FDA contributed significantly to all of NOAA's written correspondence to AQSIQ on the issue. Contributions included providing scientific and technical details on paralytic shellfish poisoning toxins and arsenic as hazards in seafood and information on methodologies for detecting these hazards and the National Shellfish Sanitation Program. FDA staff also engaged in extensive technical discussions with the NOAA delegation team as they prepared for a meeting with AQSIQ held on March 21, 2014, in China. FDA was available to NOAA during the meeting to address any scientific, technical, or regulatory issues.

FDA will work diligently with NOAA and other U.S. partners on any followup needed to ensure the continued export of shellfish to China.

SENATOR HATCH

Question. While further reduction of trans fat in the food supply is important, I am concerned about the specific course FDA utilized to meet its goal by tentatively determining PHOs as no longer generally recognized as safe (GRAS). This appears

to be a significant change in how the GRAS process has been utilized in the past. I understand you have some data to support this decision, but I am questioning how you decided to address PHOs through the GRAS process rather than through other means.

Given the importance of GRAS to the entire industry, including my constituents in the dietary supplement industry, I am concerned that this change will have significant effect without adequate discussion. Can you provide me with assurance that you won't move forward with such changes in the GRAS process without thorough and adequate discussion with the industry?

Answer. As you know, on November 8, 2013, FDA announced in the *Federal Register* that the Agency has tentatively determined that partially hydrogenated oils (PHOs), the primary dietary source of industrially produced trans fatty acids (trans fat), are not generally recognized as safe (GRAS) for any use in food based on current scientific evidence establishing the health risks associated with the consumption of trans fat, and therefore PHOs are food additives. If finalized, this would mean that PHOs could not be used in food without prior FDA approval for use as a food additive.

FDA addressed the status of PHOs through this tentative determination because the uses of these substances by the food industry have been based on their GRAS status for use in food. For example, partially hydrogenated soybean oil, cottonseed oil, coconut oil, and palm oil are considered GRAS based on a history of use prior to 1958, while the partially hydrogenated versions of low erucic acid rapeseed oil and menhaden oil, although not commonly used, are affirmed by regulation as GRAS for use in food.

A substance is GRAS if it is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures to be safe under the conditions of its intended use (or, in the case of a substance used in food prior to 1958, through either scientific procedures or experience based on common use in food). However, the GRAS status of a specific use of a particular substance in food is time-dependent. That is, as new scientific data and information develop about a substance or the understanding of the consequences of consumption of a substance evolves, expert opinion regarding the safety of a substance for a particular use may change such that there is no longer a consensus that the specific use is safe. The fact that the status of a substance may evolve over time is the underlying basis for FDA's regulation at 21 CFR § 170.38, which provides in part that FDA may, on its own initiative, propose to determine that a substance is not GRAS.

FDA will certainly consider the views of industry and work with them to implement, with minimal disruption, any final determination the Agency may make. FDA extended, until March 8, 2014, the comment period for the November 2013 *Federal Register* notice, due to multiple requests for a 60-day extension. If FDA makes a final determination that PHOs are not GRAS, the Agency intends to provide adequate time for producers to reformulate any products as necessary and that would minimize market disruption. To help address this concern in an appropriate manner, the *Federal Register* notice calls for comment on how long it would take the food industry to phaseout its use of PHOs. Further, we requested comment specifically on the costs of such a decision to small businesses and any special considerations that might be made in order to minimize the burden on these entities.

SENATOR ISAKSON

Obesity is a serious public health problem in our country. I believe there are basically two approaches we can take to confronting this challenge. One is to educate and empower people to make healthier diet and exercise choices for themselves and their families, which I believe is the better and more effective approach. The other alternative is to tax and regulate and try to use the power of the government to stop people from making choices that are viewed as unhealthy, and it seems to me that FDA's decision to issue a "tentative determination" that trans fats and partially hydrogenated oils are unsafe falls into this category. It is my understanding that the food industry has already been in the process of phasing out the use of trans fats, but this heavy-handed regulatory approach threatens to disrupt that process. I am also concerned that by issuing a tentative determination rather than going through the formal regulatory process, FDA is avoiding the requirements to respond to public comments and to estimate the economic impact of this decision.

Question 1. Could you explain why your agency decided to use a tentative determination notice as opposed to a rulemaking for this decision? Also, could you clarify what you believe to be the scope of FDA's existing authority to regulate food prod-

ucts based on concerns that their long-term use may be one of multiple factors contributing to obesity, heart disease, or other health problems?

Answer 1. As you know, on November 8, 2013, FDA announced in the *Federal Register* that the Agency has tentatively determined that partially hydrogenated oils (PHOs), the primary dietary source of industrially produced trans fatty acids (trans fat), are not generally recognized as safe (GRAS) for any use in food based on current scientific evidence establishing the health risks associated with the consumption of trans fat, therefore that PHOs are food additives. If finalized, this would mean that PHOs could not be used in food without prior FDA approval for use as a food additive.

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FDA will consider the views of industry and work with them to implement, with minimal disruption, any final determination the Agency may make. If FDA makes a final determination that PHOs are not GRAS, the Agency intends to provide adequate time for producers to reformulate any products as necessary and that would minimize market disruption. To help address this concern in an appropriate manner, the *Federal Register* notice calls for comment on how long it would take the food industry to phaseout its use of PHOs. Further, we requested comment specifically on the costs of such a decision to small businesses and any special considerations that might be made in order to minimize the burden on these entities.

Question 2. As you are aware, this committee has expressed concern about illegal animal drug compounding and has requested a GAO report to further investigate this issue. I have received reports of entities characterizing themselves as "compounding pharmacies" that are essentially copying FDA-approved products and mass-marketing them as a cheaper alternative that is not subject to the safety requirements and quality controls with which manufacturers must comply. What steps is your agency currently taking, using existing resources and statutory authority, to address the problem of entities mass-producing copies of FDA-approved animal drug products? Additionally, please outline any efforts FDA has undertaken to work with State pharmacy boards with respect to animal drug compounding oversight.

Answer 2. FDA is also very concerned about illegal animal drug compounding, particularly the production of drug products that are essentially copies of FDA-approved products. Animal drugs were included in the Agency's inspection initiative last year that targeted high-risk compounding firms, and followup actions are currently being evaluated. In addition, FDA continues to collect evidence including product samples and adverse event reports from various sources and will target firms whose practices, if deficient, would pose the highest risk to public health. To aid in this endeavor, FDA has been working closely with the State boards of pharmacy to identify firms engaged in deficient or inappropriate practices and, when appropriate, we plan to take action, including enforcement action, to protect public health. FDA is also working closely with veterinary associations to ensure that practitioners have the information they need to distinguish between approved and unapproved animal drug products to allow them to make informed decisions when choosing a product for their client.

SENATOR ISAKSON AND SENATOR ENZI

Question. As you know, the Food Safety Modernization Act explicitly exempts alcohol production from FDA regulation. I am troubled that the FDA has indicated an intention to regulate brewers' spent grain through the proposed rule on animal feed. The premium, high food-grade barley used to produce beer is the same grain that results in brewers' spent grain. It makes no sense to us to exclude the handling and distribution of those grains while the brewery is using it to produce beer, yet deny that brewery the benefit of the exemption once the grain is spent. We believe Congress intended to exempt the entire process of manufacturing beverage alcohol products, including by-products or residue of that alcohol manufacturing process, even if the by-products or residue have separate value or potential use as food for animals. Will you reconsider this issue prior to finalizing the FSMA rules?

Answer. Yes. You express concerns that we also heard from many in the brewing community regarding the potential impact of the proposed rule on the long-standing practice of beer brewers providing the "spent grains," resulting from the brewing process, to farmers to use as animal food.

Breweries making products for human consumption are already subject to human food Current Good Manufacturing Practice (CGMP) regulations. FDA's current understanding is that the potential hazards associated with spent grains from brewers and distillers of human beverages are minimal, provided the food manufacturer takes common-sense steps, such as minimizing the possibility of physical or chemical hazards being inadvertently introduced into a container of spent grains. In addition, we agree that there are substantial efficiency and sustainability benefits from the recycling of human food by-products—such as spent grains—to animal food, and it is not our intention to disrupt this practice.

We are pleased to inform you that, on September 19, 2014, FDA proposed a number of revisions to its proposed rule on preventive controls for animal food that are more flexible and less burdensome in key areas. Specifically, the Agency has proposed that, in general, human food processors already subject to and complying with FDA human food safety requirements, such as brewers, would not need to implement additional preventive controls or CGMP regulations when supplying a by-product (e.g., wet spent grains, fruit or vegetable peels, liquid whey) for animal food, except for proposed CGMPs to prevent physical and chemical contamination when holding and distributing the by-product (e.g., ensuring the by-product isn't co-mingled with garbage).

Please be assured that we are working to develop regulations that are responsive to the concerns expressed, practical for businesses, and that also help ensure that food for animals is safe and will not cause injury to animals or humans. FDA is seeking comment on the supplemental notice of proposed rulemaking until December 15, 2014. We hope to continue our active dialog with stakeholders, including the brewing community, about how we can achieve our food safety goals in the most practical way.

SENATOR KIRK

Question 1. Data is critical to understanding the use of antibiotics in animal agriculture. I was glad to see that in September 2013, the FDA proposed improvements to current antibiotic data reporting under the Animal Drug User Fee Act. However, in order to properly implement Guidance 213, additional data would help industry target specific areas where improvement is needed. Dispensing status, route of administration, drug class and indication would not only provide better insight, but it would make the process more efficient. When will the FDA issue the 2012 data report in the proposed new format? Will the agency followup on the July 2012 ANPR by proposing a rule to collect additional data?

Answer 1. As you know, FDA sought additional public input in September 2013 (78 FR 58308 (September 26, 2013)), on proposed additions to FDA's annual Summary Report of Antimicrobials Sold or Distributed for Use in Food-producing Animals (ADUFA 105 annual summary report). Based on broad public input, FDA has enhanced the format of the ADUFA 105 annual summary reports to better describe data on the annual sales and distribution of antimicrobials intended for use in food-producing animals using a more detailed format that will allow the public to better understand the changes that occur as GFI #213 is implemented. On October 2, 2014, FDA released the summary report for 2012, using this new format, and provided updated annual reports from previous years to include the new data tables. The changes expanded the format of reporting sales and distribution data by antimicrobial class to include information on the importance of the drug in human medicine. These changes also provide aggregate data on the approved route of administration of antimicrobial drugs sold or distributed for use in food-producing animals,

whether such drugs are available over the counter or require veterinary oversight, and whether they are approved for therapeutic indications, or both therapeutic and production indications.

The Agency is also developing a proposed regulation to enhance the existing requirements related to the collection of antimicrobial drug sales and distribution data for antimicrobial drugs intended for use in food-producing animals. New requirements being considered include the collection of additional drug sales and distribution data, including reporting sales and distribution data by species.

FDA is working with the U.S. Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC) to identify possible approaches for further enhancing current data collection efforts, focused on actual use (exposure) on the farm. This will help identify meaningful metrics for assessing the effectiveness of GFI #213 in reducing the public health risk of antibiotic resistance. The Agency intends to seek further public input on this issue in early 2015.

In addition, as part of this collaborative effort it was determined that there is currently no appropriate method to analyze associations between changes in antimicrobial use and shifts in resistance patterns on a national level, as is needed to assess the public health impact of interventions such as GFI #213. Therefore, FDA and USDA are collaborating with a Cornell University researcher and submitted a National Institute of Mathematical and Biological Synthesis (NIMBioS) proposal to create a working group to develop a new mathematical modeling methodology that would inform the approach to monitoring and assessing the impacts of GFI #213. This will allow the collaborating Federal agencies to efficiently allocate limited resources by targeting data which are most valuable. The proposal was accepted and the first meeting of the working group occurred in September 2014.

Question 2. The Agency recently published guidance seeking to clarify what constitutes a "medical food", and what conditions might need the use of medical foods. Specifically, the agency is seeking to clarify the use of certain medical claims on labels, and the guidance states that diabetes and pregnancy are two types of conditions that do not warrant the use of medical foods, because they can be treated through "diet alone".

This point of "treating diabetes through diet alone" goes beyond the statutory definition of a "medical food", as outlined in the original Orphan Drug Act. Treating diabetes is not as simple as monitoring food intake. By disallowing the use of clear labeling to notify patients of what is contained in certain medical foods, this guidance has the potential to further negative health outcomes associated with the disease, increase patient confusion, and limit patient choice. Does the Commissioner have any comment on the diabetes portion of the medical foods guidance, which is now through its draft stage?

Answer 2. FDA recognizes and appreciates the difficulties associated with managing diabetes. We received a number of comments during the comment period regarding the diabetes portion of the medical foods draft guidance and are considering them as we determine how to proceed with the draft guidance.

SENATOR ROBERTS

Question 1. I have heard quite a bit of conversation from our industry leaders about the implementation of the Food Safety and Modernization Act. More recently I have been hearing concerns related to the Preventive Controls for Human Food proposed rule that I believe is still open for comment. I am specifically hearing feedback that the proposed rule mentions testing and supplier verification requirements in the preamble but does not provide the specific requirements in the rule. I also understand that a version of the rule that was more prescriptive on these requirements was released but not published. Can you assure me that you will not finalize the rule with these more prescriptive testing and supplier verification requirements unless they go through a full notice and comment period regulatory process, including the revised economic analysis? Can you also assure me that this rule will not be issued as an interim final rule?

Answer 1. In our proposed rule, "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food," we did not include specific requirements for product testing, environmental monitoring, and supplier controls, but we acknowledged that such programs, when implemented appropriately in particular facilities, could be used to verify the effectiveness of preventive controls. On September 19, 2014, FDA released proposed revisions to its proposed rule on preventive controls for human food that are more flexible and less burdensome in key areas. With regard to product testing, environmental monitoring, and

supplier controls, the Agency is now providing an opportunity for input on specific language and seeking comment on whether to include it in the final rule.

Specifically, FDA is seeking comment on whether the preventive controls for human food should require a facility, as appropriate to the facility, the food, and the nature of the preventive control, to conduct product testing to verify implementation and effectiveness of preventive controls. FDA is also seeking comment on whether the preventive controls for human food should require a facility, as appropriate to the facility, the food, and the nature of the preventive control, to conduct environmental monitoring to verify implementation and effectiveness of preventive controls if contamination of a ready-to-eat food with an environmental pathogen is a significant hazard.

The potential provisions would require supplier controls when the receiving facility's hazard analysis identifies a significant hazard for a raw material or ingredient and that hazard is controlled before the facility receives the raw material or ingredient from a supplier. We have indicated that if these provisions were to be included, the facility would have flexibility to determine the appropriate verification activity (such as onsite audit, sampling, and testing) unless there is a reasonable probability that exposure to the hazard will result in serious adverse health consequences or death to humans. In that instance, an annual onsite audit of the supplier would be required unless the facility can show that other verification activities and/or less frequent onsite auditing of the supplier provide adequate assurance that the hazards are controlled.

FDA is seeking comment on this new language until December 15, 2014.

Question 2. The economic impact analyses accompanying the proposed Produce Rule and proposed Preventive Controls Rule estimated very high compliance costs for farmers and food facilities. In the analyses, FDA sought comment on a number of issues and failed to adequately account for certain costs and realities on farm, including length of growing season. Given that FDA will be re-proposing major sections of the rules, including sections that determine scope and impact of the rules, can you please discuss whether the agency plans to release revised economic impact analyses for public comment?

Answer 2. The economic analyses for the proposed rules on produce safety and preventive controls for human food that accompanied the original proposed rules contain estimates that were based on the best data available to FDA at the time of publication. We understand that, due to the limited amount of data, and because the estimates reflect average costs over broad size categories, the estimates may not perfectly reflect reality for every individual farm or facility. Wherever possible, we attempted to capture the variability across size and category and the uncertainty inherent in this type of estimation.

On September 19, 2014, FDA released proposed revisions to its proposed rule on preventive controls for human food and its proposed rule on produce safety that are more flexible and less burdensome in key areas. The Agency performed additional analyses to examine the impacts of the amended and new proposed provisions, which can be found in the corresponding dockets as references to the *Federal Register* supplemental notices for the preventive controls for human food proposed rule and the produce safety proposed rule, and can also be found on FDA's Web site.[1] FDA is seeking comment on the new language, including the additional economic analyses, until December 15, 2014.

[Whereupon, at 11:10 a.m., the hearing was adjourned.]

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[1] *http://wwwfda.gov/downloads/Food/GuidanceRegulation/FSMA/UCM415041.pdf*; *http://www.fda.gov/downloads/Food/GuidanceRegulation/FSMA/UCM415037.pdf*.