

**AGRICULTURE, RURAL DEVELOPMENT, FOOD
AND DRUG ADMINISTRATION, AND RE-
LATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2017**

WEDNESDAY, MARCH 2, 2016

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 1:58 p.m., in room SD-124, Dirksen Senate Office Building, Hon. Jerry Moran (chairman) presiding.
Present: Senators Moran, Daines, and Merkley.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

STATEMENT OF HON. DR. ROBERT CALIFF, M.D., M.A.C.C., COMMIS-
SIONER

ACCOMPANIED BY JAY TYLER, CHIEF FINANCIAL OFFICER

OPENING STATEMENT OF SENATOR JERRY MORAN

Senator MORAN. Good afternoon, everyone. We are having an abbreviated hearing today as a result of four votes being announced at 2:30.

Dr. Califf, congratulations on your confirmation. Welcome to the Food and Drug Administration (FDA). Senator Merkley and I have agreed to withhold our opening statements, which should be to the benefit of all in the audience.

[Laughter.]

Senator MORAN. And we will submit those for the record.

And we are going to start with your testimony, then we will have a round of questions for as long as we are able until the votes are called. We will go a little bit until that time.

So, Dr. Califf, we welcome your testimony as we begin the appropriations process for this year.

SUMMARY STATEMENT OF HON. DR. ROBERT CALIFF

Dr. CALIFF. Thank you, Chairman Moran and Ranking Member Merkley. I was advised that my testimony could be sidelined, too, but I am happy to give it if you would like. I know your time is limited.

Senator MORAN. We would welcome you perhaps highlighting the things you want to make certain we know, and perhaps if you can

do that rather than reading your statement, that is to all of our benefit.

Dr. CALIFF. Great. Well, I will try to do this in one minute instead of five, and I appreciate being here. I also want to acknowledge Dr. Ostroff sitting behind me, who has just finished his term as Acting Commissioner, and I think he has done a wonderful job. We all owe him a debt of gratitude for stepping in with such equanimity and grace.

You have got the budget in front of you. We think it is a very responsible budget, and several of the main priorities that I have in this, as you well know, are, first of all, the workforce at the FDA. Due to the increasing intensity of biological, agricultural, and engineering advances, we need a topnotch workforce, and much of our activity is devoted to that. And the second is shoring up the science base, which includes a heavy emphasis on quantitative analytics. One of our biggest priorities for this year is implementation of the Food Safety Modernization Act (FSMA).

At the core of that is a quality system, which you have all participated in helping us develop. We appreciate the funding increase that we got last year. It has made a big difference, but we still have work to do there. And at the core of it is a quality system built on high-level analytics so that we can deploy FDA forces in the most efficient and effective manner.

So at the core of it for me is that we are in a continuing evolution of the FDA as a science-based public health organization with a very broad scope of activities. There is an amazing array of details that we can talk about. They are specified in my testimony that we have submitted, and I look forward to taking your questions.

[The statement follows:]

PREPARED STATEMENT OF HON. DR. ROBERT CALIFF

I. INTRODUCTION

Good afternoon Chairman Moran, Ranking Member Merkley, and Members of the Subcommittee, I am Dr. Robert Califf, Commissioner of the Food and Drug Administration (FDA). Thank you for the opportunity to appear before you today to discuss the President's fiscal year (FY) 2017 Budget Request for FDA. I would like to thank the Subcommittee for its past investments in FDA, most recently for fiscal year 2016 funding, which have helped us meet the demands of our increasingly complex and diverse mission at home and abroad. For fiscal year 2017, FDA is requesting \$5.1 billion to support our essential functions and priority needs.

I am honored to have been chosen by the President and confirmed by Congress to lead the FDA. Thank you all for your willingness to share with me and my predecessor, Dr. Ostroff, your perspectives on ways the FDA can better serve the American people. My first priority as Commissioner is to strengthen and better support the FDA's talented and dedicated workforce. I will focus on the need to carry our critical priorities over the finish line. FDA's ambitious agenda currently includes implementation of the Food Safety Modernization Act, finalizing the Tobacco Deeming Rule, facilitating the development of medical counter measures, and making progress on the Combating Antibiotic Resistant Bacteria (CARB) initiative, and the Precision Medicine Initiative. I also want to further development of the FDA's science base that informs decisionmaking across drugs, medical devices, food safety, and more. FDA's work on the groundbreaking Sentinel system, supported by your mandate, demonstrates the power of the use of our new national digital infrastructure. We are increasingly able to rapidly develop evidence to inform FDA's decision-making, and giving us the ability to act quickly on safety issues, rather than having to wait for a new study every time a safety issue arises. I look forward to continued dialogue with you to gain support for FDA's important public health mission.

II. FDA PLAYS A CRITICAL ROLE IN AMERICA'S PUBLIC HEALTH SYSTEM

FDA is a science-based regulatory agency charged with an enormous and significant responsibility: to promote and protect public health. Our goal in carrying out our mission is to ensure the safety, effectiveness, and quality of human and veterinary drugs, biological products and medical devices; the safety of dietary supplements; as well as the safety and security of the vast majority of our nation's food supply. Additionally, the Agency regulates the manufacturing, marketing, and distribution of tobacco products, and seeks to reduce the use of tobacco products by minors and the detrimental effects of tobacco on the general population. FDA's relatively new authority to oversee tobacco products, as well as the Agency's heightened role in the food supply, has tremendously increased FDA's responsibilities and opportunities to promote and protect public health.

FDA plays a unique and vital role in facilitating the availability of safe and effective products and treatments, while also protecting people from products that are promoted using false claims or may cause harm. FDA works with a broad array of stakeholders including industry, other government agencies, and the public, in order to achieve the best possible outcomes.

Congress has recognized the dynamic role that FDA plays and the increasingly complex and inter-connected global environment in which we operate. As a result, FDA has been tasked with a multitude of new responsibilities and authorities in the public health arena, including the Drug Quality and Security Act (DQSA); the FDA Safety and Innovation Act (FDASIA); the FDA Food Safety Modernization Act (FSMA); and the Family Smoking Prevention and Tobacco Control Act (TCA). While FDA has stepped up to meet these essential public health responsibilities under current funding levels, successful implementation of these new authorities requires additional resources.

III. FDA Has a Proven Track Record of Success

FDA's accomplishments over the past year have been as substantial as any in the Agency's recent history. Across the areas of food safety and nutrition, medical product safety and innovation, tobacco control, and other areas of our work, our accomplishments demonstrate our ability to respond to evolving needs and opportunities—including the embrace of new approval pathways, innovative technologies, and cutting-edge science.

Moreover, given the importance of our work, FDA's budget is a bargain for American taxpayers. The products regulated by FDA account for more than 20 percent of every consumer dollar spent on products in the U.S.; individual Americans only pay about 2 cents per day to support oversight to help ensure that those products are safe and effective. This is a small price for life-saving medicines and treatments approved as fast as or faster than anywhere in the world, confidence in medical products that are relied on daily, and a food supply that is among the safest in the world.

IV. FDA'S INNOVATIONS IMPROVE AND PROTECT AMERICA'S FOOD SUPPLY

Food Safety Modernization. Congress enacted FSMA in response to dramatic changes over the last 25 years in the global food system and in our understanding of foodborne illness and its consequences, including the realization that foodborne illness is a significant public health problem, is preventable, and is costly. FDA is modernizing our food-safety system, using quality systems and analytics to prevent foodborne illness before it occurs. These food system changes and the new FSMA mandates require transformative change in how FDA does its work.

FDA published seven major proposed rules in 2013 and, after much stakeholder input, five of those became final in 2015: the preventive controls rules for human and animal food, the produce safety rule, the foreign supplier verification program rule and the third-party accreditation rule. These groundbreaking final rules will help food manufacturers, produce farmers, and food importers take steps to prevent food safety problems. The produce safety and foreign supplier verification rules, for the first time, establish enforceable science-based safety standards for the growing and harvesting of produce and make importers accountable for conducting risk-based verification to determine that imported food meets U.S. safety standards. In addition, as part of these rulemakings we are establishing a program for the accreditation of third-party certification bodies to conduct food safety audits of foreign food facilities.

Nutrition. Americans eat and drink about one-third of their calories away from home. To this end, on December 1, 2014, FDA carried out a congressional mandate to publish rules requiring that calorie information be listed on menus and menu boards in chain restaurants and similar retail food establishments, and on signs for vending machines. In 2015, FDA issued two guidances to help affected industries

implement the menu labeling rule, one aimed at small businesses, and the second providing more detailed advice on how the rule works in the context of a diverse industry. FDA also listened to stakeholders and extended the compliance date for menu labeling.

V. PROMOTING INNOVATIVE MEDICAL PRODUCT DEVELOPMENT

Medical Product Application Review. This year, through application of our efficient and flexible approval process, we again were able to approve a broad range of innovative medical products and treatments with the potential to make a positive difference in the lives of patients. These products included a new generation of targeted therapies that will be used to treat or prevent diseases that affect only a few individuals and additional products that will be used to treat diseases that affect large portions of the population. They involve novel approaches to therapy developed from the rapidly accelerating science of genomics and even new product categories, such as our approval of the first biosimilar biological product.

We also enhanced engagement of patients in the development, approval and evaluation process. And we continued to make progress in our application of some of the most cutting edge areas of science and technology, such as precision medicine, which is helping us to advance biomedical understanding and provide targeted therapies that will allow us to better treat individual patients and diseases.

FDA's rapid drug reviews and use of expedited programs for certain categories of drugs have helped provide meaningful new products to U.S. patients quickly without compromising our safety and efficacy standards. In 2015, FDA approved 56 novel new drugs. These approvals included four new treatments for patients with multiple myeloma, two new drugs for patients with heart failure, and another robust year of approvals of drugs for rare or "orphan" diseases.

In 2015, we also approved several important vaccines, including one for serogroup B meningococcal disease, the first seasonal influenza vaccine to contain an adjuvant (intended for people 65 years and older), and a new indication for anthrax vaccine to prevent disease following exposure to anthrax—the first vaccine to receive an approved indication based on the Animal Rule, which allows efficacy data generated in animal models to serve as the basis for the approval of medical countermeasures against chemical, biological, radiological or nuclear threats when human efficacy studies aren't ethical or feasible. We also saw the approval of several innovative devices that will make a positive difference in the lives of patients, including a device that extends the survival time of patients with brain cancer, and a transcatheter pulmonary valve that can be placed in certain patients with congenital heart disease, without requiring open heart surgery.

We have also seen important progress in our device review program. Our average time to reach decisions on premarket approvals (PMAs) has dropped 36 percent since 2009. And in 2015, FDA approved 79 novel devices, the most since the start of the Medical Device User Fee Program. Most importantly, enhanced flexibility and an efficient approval process have come without lowering our standards for safety and efficacy.

An important component of all of the medical product reviews is the use of interaction between product developers and our expert staff at FDA at critical points in product development. Our expert review teams "see it all" and therefore play an important role in providing guidance and feedback to companies that is enabling more effective product development. The enhanced communication and growing expertise within FDA promotes earlier exit of products that will not pass muster and a much higher rate of approval on first review for products that do meet our rigorous criteria for safety and efficacy. The success of this approach highlights the need for talented people at the FDA—as medical products become more sophisticated the need for talented reviewers at FDA will grow.

Opioid Medications. Prescription opioid analgesics are an important part of modern pain management; however, misuse and abuse of these products contribute to a serious and growing public health epidemic. After extensive internal review, the Agency has issued a detailed action plan that includes a new framework for considering the consequences of addiction, abuse and misuse not only on the individuals for whom the treatment is intended, but also upon the larger society that is affected by abuse and misuse. Additional post-market requirements for studies have been added. FDA continues to support development of antidotes to treat overdose, abuse deterrent formulations, non-addictive pain relievers, and medication-assisted treatments for dependence.

Biosimilars. FDA has been developing its biosimilar program, an effort which led to the approval of the first biosimilar biological product in March 2015. And there are more applications in the pipeline. To prepare, FDA has produced a variety of

guidances in this area. FDA remains committed to strengthening the biosimilars pathway by continuing to work diligently to provide development phase advice to sponsors and evaluate applications submitted under this abbreviated pathway, and issue additional guidance as needed to provide clarity to stakeholders.

Next Generation Sequencing and Precision Medicine. Our strengthened focus on regulatory science is helping to drive innovation. One illuminating example is our growing ability to apply the sophisticated technologies of next generation sequencing and precision medicine. FDA today is better prepared for and more engaged than ever in facilitating the development of these new technologies (as well as new uses for older technologies), with reasonable assurance of safety and effectiveness. These efforts help to achieve more precise diagnosis or treatment, through the development and review of state of the art diagnostics and drugs that are targeted to an individual's genetic blueprint. We continue to move forward on the White House's Precision Medicine Initiative to advance biomedical understanding by leveraging genomic advances, health information technologies, and new methods of analyzing large volumes of data. Recently, we launched FDA's precisionFDA web platform, a cloud-based portal that has already succeeded in enabling scientists from industry, academia, government and other partners to come together to foster innovation and develop the science behind next-generation sequencing. PrecisionFDA provides a clear example of regulatory science stimulating innovation.

We are also working to refine clinical trial design and statistical methods of analysis to create more efficient studies that take advantage of advances in genomics and information technology to provide more rapid, less expensive and more reliable answers about medical products. For instance, we continue to support collaborative efforts in clinical trials, such as the NIH's Lung-MAP protocol for lung cancer.

Drug Quality and Security Act. FDA is implementing the DQSA and working diligently to reduce the risks of compounded drug products in the U.S. Since enactment of the DQSA, FDA has conducted over 230 inspections of compounders, many in response to reports of serious adverse events, product quality problems, or other complaints. FDA continues to identify serious problems during these inspections, including contamination in purportedly sterile drugs and in the sterile compounding environment, and other insanitary conditions that put patients at risk. FDA has also investigated serious adverse events associated with non-sterile drugs that were superpotent, as much as 1000 times the labeled strength. As a result of these inspections, FDA has taken aggressive action to protect the American public from compounded drugs that could cause harm. Since enactment of the DQSA, FDA has issued over 75 warning letters to compounders and has worked closely with the Department of Justice on civil and criminal enforcement actions. Many compounders have recalled all of their sterile drugs and ceased sterile operations at FDA's recommendation. FDA has also been working diligently to implement sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (as added by DQSA) by publishing draft and final policy documents while taking into consideration stakeholder input. FDA has issued 12 draft guidance documents, five of which were finalized, a proposed rule, and a draft memorandum of understanding related to interstate distribution of drugs compounded by state-licensed pharmacies and Federal facilities. FDA has consulted with the Pharmacy Compounding Advisory Committee, convened three intergovernmental working meetings with state representatives, and has actively engaged with more than 50 stakeholder groups during listening sessions. FDA will continue to work diligently on draft and final policy documents to implement the DQSA, and to engage with stakeholders on our proposed policies. We have also put out a draft guidance on the appropriate use of compounded products for animals. Even though not specifically included in the legislation, stakeholders have asked us to clarify our policy on animal drug compounding for years, which we are now doing.

VI. FDA WORKS TO REDUCE THE IMPACT OF TOBACCO ON THE PUBLIC HEALTH

Family Smoking Prevention and Tobacco Control Act.

FDA closely monitors retailers' compliance with restrictions on tobacco product marketing and sales to youth—and takes strong corrective action when violations occur. In late 2015, FDA issued its first ever no-tobacco-sale-orders to retailers who continually violate the law. In addition, the Agency launched a second major public education campaign, "Fresh Empire," targeting multicultural youth with powerful messaging about the dangers of tobacco products, all as part of the effort to reduce the number of young people who use tobacco products.

Also for the first time, in 2015, FDA authorized the marketing of eight new tobacco products under the premarket tobacco application pathway. We have made significant progress and have taken many steps to improve timeframes in reviewing

marketing applications. Our actions include increasing scientific staffing; providing feedback to industry; issuing multiple guidance documents; holding meetings with industry; hosting webinars; sending letters and other communications to clarify expectations for industry; and, finally, establishing performance goals that include timeframes for review of Substantial Equivalence (SE) reports for products that are not on the market.

VII. FDA TACKLES EMERGING, UNIQUE, AND COMPLEX CHALLENGES

Combating Antibiotic-Resistant Bacteria (CARB). FDA has made progress on each of the five goals of the President’s National Action Plan for CARB. These goals are to slow the emergence of resistant bacteria and prevent the spread of infections caused by resistant bacteria; strengthen national one-health surveillance efforts to combat resistance; advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines; and improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development.

On June 2, 2015, both human and animal health stakeholders came together in support of a one-health antibiotic stewardship forum hosted by the White House. Additionally, CDC and FDA launched the antimicrobial-resistant isolate bank of over 160 isolates composed of collections of carbapenem-resistant Enterobacteriaceae and other multi-drug resistant bacteria of antibiotics that are approved for use in food-producing animals. FDA also is working closely with CDC and USDA on a data collection plan to verify the changes in on-farm antibiotic use that are expected to result from FDA’s initiative to eliminate animal production uses (e.g., growth promotion) of medically important antibiotics in food-producing animals and to require veterinary oversight for therapeutic uses of these drugs for the treatment, control or prevention of a specifically-identified disease. In support of this effort, FDA finalized changes to the Veterinary Feed Directive (VFD) regulation in June 2015 which took effect in October 2015. FDA also published a proposed rule in May 2015 that includes additional reporting requirements regarding the sale and distribution of antibiotics that are approved for use in food-producing animals.

Responding to Ebola. In a world where disease knows no borders, FDA’s response to the Ebola outbreak in West Africa demonstrated how we used our scientific expertise and regulatory authorities to the fullest extent possible to address a tragic public health crisis of global impact. Our response involved collaborating with partners across government, pharmaceutical and diagnostic companies, international organizations like the World Health Organization, and our international regulatory counterparts. We played a key role in encouraging the appropriate study of and expediting the availability of diagnostic tests, investigational therapeutics, and vaccines, as well as investigating fraudulent products marketed to diagnose, prevent and treat Ebola. And many FDA commissioned corps officers of the U.S. Public Health Service served on the front lines, deployed in a humanitarian mission to provide care to patients at the Monrovia Medical Unit in Liberia, one of the West African nations that were hard hit by the outbreak.

Medical Countermeasures. FDA’s Medical Countermeasures mission is to promote national health and security by facilitating the development and availability of medical countermeasures (MCMs) such as drugs, biologics, vaccines, devices, and diagnostic tests. These products are used to diagnose, prevent, or treat conditions stemming from an attack with a chemical, biological, radiological, or nuclear material, or a naturally occurring emerging infectious disease, such as Ebola or the most recent outbreak of Zika virus in the Americas. Sixteen diagnostic tests have been authorized under FDA’s Emergency Use Authorization authority in response to emerging infectious disease threats. MCMs have been approved for anthrax, plague, botulism, Acute Radiation Syndrome, and pandemic influenza, and several others are on an accelerated development track. FDA finalized the guidance “Product Development Under the Animal Rule”; to date, eleven drug and biologic products have been approved under this regulation. We also established a publicly available microbial DNA reference database to help advance diagnostic test development.

VIII. FDA’S FISCAL YEAR 2017 PRESIDENT’S BUDGET REQUEST

The fiscal year 2017 Budget Request for FDA is \$5.1 billion, an increase of 8 percent or \$358.3 million compared to the fiscal year 2016 enacted level. The budget includes \$2.7 billion for budget authority—an increase of one-half of 1 percent or

\$14.6 million compared to fiscal year 2016; \$2.3 billion for user fees¹ an increase of twelve percent or \$268.7 million compared to fiscal year 2016. Mindful of the larger pressures on the Federal budget, we have focused our request on the most urgent needs for fiscal year 2017.

Food Safety. The fiscal year 2017 Budget provides \$1.5 billion for food safety, an increase of \$211.6 million above the fiscal year 2016 level. The budget includes \$1.3 billion for budget authority—an increase of 1 percent or \$18.4 million compared to the fiscal year 2016 Enacted budget—and \$209.8 million for user fees—an increase of \$193.2 million compared to the fiscal year 2016 Enacted budget. The budget includes an increase of \$25.3 million to improve food and feed safety through continued FSMA implementation.

FDA's fiscal year 2017 budget will build on the fiscal year 2016 investments and focus on two strategic areas of investment that are essential to the success of FSMA: state capacity to partner with FDA and the safety of imported food. The fiscal year 2017 budget request for state capacity building will be used primarily to fund state cooperative agreements and grants that support the essential state role in implementing FSMA's new produce safety rule requirements.

Additionally, the fiscal year 2017 request will enable FDA to continue progress toward implementing the multifaceted new import safety system mandated by Congress, including the Foreign Supplier Verification Program (FSVP) rule, foreign food facility and produce inspections, and partnerships with foreign governments. Under the FSVP rule, importers must verify that imported food has been produced in a manner consistent with FSMA's new standards for produce safety and preventive controls.

The user fee request for food safety includes \$105.3 million in new resources to support the new import safety system and \$61.3 million in new resources to further modernize the FDA inspection program.

Medical Product Safety and Innovation. The fiscal year 2017 Budget request for FDA for Medical Product Safety and Availability is \$2.8 billion, an increase of \$116.2 million above the fiscal year 2016 Enacted level. The request includes \$1.3 billion for budget authority—an increase of 0.2 percent or \$3.2 million compared to the fiscal year 2016 Enacted level, \$1.4 billion for user fees—an increase of 3 percent or \$38.0 million compared to the fiscal year 2016 Enacted level, and \$75.0 million in new mandatory funding for the Vice President's Cancer Moonshot. With this request, FDA will improve medical product safety and innovation in five key areas: evaluating Precision Medicine-based diagnostics, improving the safety of compounded drugs, combating antibiotic resistant bacteria, supporting animal drug and medical device review, and improving cancer diagnostics and treatments.

FDA requests \$4 million in fiscal year 2017, an increase of \$2.0 million above fiscal year 2016 for Precision Medicine. With the majority of the increase, FDA will help advance Precision Medicine by establishing the National Medical Device Evaluation System (NMDES) to identify patients who benefit most or do not benefit from specific types of devices. FDA will also continue to invest in precisionFDA, which provides a crowd-sourced, cloud-based platform to advance regulatory science around NGS-based analytical tools and datasets.

FDA requests \$18 million, an increase of \$1 million above fiscal year 2016, to enhance oversight of human drug compounding through increased inspection and enforcement activities, policy development and implementation, and state collaboration and coordination.

For CARB, FDA requests \$42 million to support continued work to address public health concerns associated with antimicrobial drug use in animals and to better protect antibiotic effectiveness for both human and animal populations. FDA will work in collaboration with USDA to support efforts to monitor antimicrobial drug use in food-producing animals.

FDA requests an additional \$2.9 million to support ongoing activities within the Animal Drugs Review Program and the Devices Program to achieve enhanced and predictable review performance that meets industry, congressional, and public expectations. The increased funding requested will enable FDA to continue to meet premarket animal drug review requirements by having the necessary review staff to carry out these activities. The request will also support ongoing review activities in the Devices Program to meet statutory requirements for the review of medical device applications.

In fiscal year 2017, FDA requests \$75.0 million in mandatory resources as part of the Vice President's Cancer Moonshot in order to accelerate progress in cancer—

¹ Includes proposed Food Facility Registration and Inspection, Food Import, International Courier, Cosmetics, and Food Contact Substance Notification fees and proposed increase to the Export Certification fee.

to reduce the number of people who develop cancer and to improve the outcome for those who do. In order to support the dramatic increase in the number, complexity, and strength of cancer diagnostics and therapeutics, FDA will establish an Oncology Center of Excellence to streamline collaboration across FDA's Human Drugs, Biologics, and Devices and Radiological Health Programs and to interface more effectively with the NIH and the clinical environment. A highly effective interface will be needed to deal with the proliferation of highly effective but complex combinations of targeted drug and biological therapies and immunotherapy, driven by sophisticated diagnostic testing and monitoring devices. There is hope that many forms of cancer will be cured or changed to chronic diseases.

Infrastructure, Rent and Facilities. The fiscal year 2017 Budget Request provides an increase of \$3 million over the fiscal year 2016 Enacted level, for a total of \$12 million, for urgent facility investments that will provide functioning offices and labs across the country to ensure FDA can execute its Food Safety and Medical Product Safety mission. This \$3.0 million increase will be used to address repairs, improvements and mission support needs at FDA's owned laboratories and other critical owned facilities across the U.S.

IX. CONCLUSION

FDA's public-health mission is indispensable to the health and well-being of every American. We carry out our broad and expanding public health responsibilities effectively and with relatively few taxpayer dollars, despite dramatic expansions in our responsibilities as a result of new legislation, scientific and technological advances, and a globalized marketplace. The fiscal year 2017 Budget Request plans for efficient spending on programs that are essential to providing Americans with the safe foods and safe and effective medical products they expect. We look forward to answering your questions today and to working with you in the coming year.

Senator MORAN. Commissioner, thank you very much. Let me, first of all, agree with you and express my appreciation for the relationship and the work by Dr. Ostroff at FDA. I very much value his service to the Agency and to the American people, who, in my view, are safer because of his work. And so, thank you for that service, and we look forward to it continuing.

Let me start with a complaint, however.

[Laughter.]

Senator MORAN. And one of the things that I have, at least in my view when I became chairman of this committee, we have worked at developing a relationship with FDA, and I appreciate that we have that. But I am concerned that the FDA is often slow in communicating with us and with our staff, that many times, in fact today was a perfect example. I would guess that many questions will be submitted to the FDA in writing for the record. A timely response is not always the case, and specificity of answering those questions is often lacking.

And so, in an attempt to suit you up today on your first hearing before this subcommittee, Dr. Califf, I would ask if you would assure me that you will do everything as the commissioner to see that our subcommittee, its members, get appropriate, full, complete, and timely responses to inquiries we make to the FDA.

Dr. CALIFF. In my consideration of joining the FDA and taking this job, outspokenness was one of the criteria that was said about me, and it is the case that I do think the FDA can do a better job of explaining what it is doing and of communicating. I have also had a hard lesson coming to the FDA in learning about issues with regard to trade secrets, and I will just call them social mores that exist about how things roll out that you are well aware of.

But taking all that into account, we are going to step up our communications. I can promise you that we will do that. I am an old intensive care unit doctor. I carry a cell phone. I am used to being

called 24 by 7, and if you feel that communication is slow, just call me. I am here.

ARSENIC IN RICE

Senator MORAN. Thank you very much. Let me ask a specific question about rice and arsenic. Last week during the budget meeting in the House, Dr. Ostroff noted that the FDA was making the risk assessment for arsenic in rice a priority. When do you plan to move, and what exactly are you planning to release in that regard?

Dr. CALIFF. Well, as you well know, the issue here is estimating the risk associated with arsenic that is in rice, and estimating the benefits of rice, which has been a staple of the American diet. My ancestors down between Charleston and Hilton Head actually farmed rice for a living, so I have a little history here.

The assessment is complicated because the data are imperfect. It is in a multiagency review. I think you are well aware of that. It is a very high priority for us to get this out. We know that people are waiting. I am not able to give you the specifics of what will be in it, but we are working on it very hard with other Federal agencies.

Senator MORAN. This decision potentially has significant consequence to a lot of people, from producers to consumers, and I would ask that you initiate a broad discussion among those affected by this decision before a conclusion is reached. Is that something you intend to do?

Dr. CALIFF. Yes, I would say there has already been a good bit of discussion, but there certainly will be a lot of discussion about it.

Senator MORAN. Are there other foods that are involved in this topic besides rice?

Dr. CALIFF. This particular decision is a rice decision, which, of course, comes in many preparations, including infant formulas and nutritional aspects, so, you know, it is an important decision. We are well aware of that. It will affect people, and we want to make sure we take that into account.

Senator MORAN. Thank you very much. Let me now turn to the ranking member, Senator Merkley.

TOBACCO RELATED ISSUES

Senator MERKLEY. Thank you, Mr. Chairman, and congratulations, Dr. Califf. There are plenty of fascinating and really important issues that the FDA deals with, and the one I wanted to start off with is related to the tobacco deeming regulation. That regulation has now been in the Office of Management and Budget (OMB) since October 2015. The basic rules are that it is not supposed to be there more than 90 days with one 30-day extension. That would be 120 days. As of today we are at 134 and counting.

So it has been a mystery year after year after year that this deeming regulation has not been finished because while essentially we have been not acting, the addiction rate for e-cigarettes has increased dramatically. They are targeted at kids with all kinds of flavors—Scooby Doo, Double Dutch Chocolate. You name it, you can find it. And to have a product targeted to children that is that effective is troublesome since it means the likelihood of a lifetime

of nicotine addiction with related health consequences, and certainly a lot of expenses for our healthcare system as well.

So what is going on? Is this ever going to emerge from OMB?

Dr. CALIFF. I can assure that it will emerge, and just—as I think you know, I am a cardiologist. I had a very busy clinical practice and intensive care units, so I have probably seen as many people die or have strokes, or heart attacks, or renal failure due to tobacco-related issues as almost anyone on earth at this point. So I am strongly committed to get this out. You are also well aware of the complexity. We had 135,000 comments. There are many views about the details that were aired that we have been working through.

But I do not think you will find anybody more committed to getting this out than I am. I have seen the consequences of tobacco-related illnesses, and we need to take care of this.

Senator MERKLEY. Well, I do appreciate that your personal background gives you that direct insight because some type of special change is needed here because for 2011, 2012, 2013, 2014, 2015, now we are in 2016, very responsible individuals who have said they care a lot about this issue, that they care a lot about kids, they care a lot about people, say we are doing everything we can, we will have it in a short period of time. And it just never happens. So I am hoping the new energy you bring and your perspective can say let us get this done.

Let me just note that between 2013 and 2014, e-cigarette use tripled among middle and high school students in 1 year. And so, obviously the targeting of children is very effective, and it is hurting a lot of people, and this is something where we can actually make a difference for the good. So I do hope you take your personal experiences and pry this out into the public space, and hopefully it will include a ban on all of these kid targeting flavors, and hopefully it will include caps that are difficult for children to take off so that we do not have as many poison cases as we have had with children. That is my hope, my hope and my prayer.

Dr. CALIFF. Well, I mean, as you know, we are instructed by law to take care of the children with the Tobacco Act, and we plan to do it. Chairman Upton this morning in a meeting—I was with him—pointed out that we can all understand the FDA better if we think about our own families. And I have a son, a brilliant rocket scientist son, who became addicted to nicotine at age 12 in North Carolina, so this is not a matter of intelligence or willpower. It is something that we need to protect children from. And 400,000 people a year are dying from tobacco-related illnesses even now, so we have work to do here.

Senator MERKLEY. Thank you, doctor.

AGRICULTURE AND BIOTECHNOLOGY

Senator MORAN. The Senator from Montana.

Senator DAINES. Thank you, Mr. Chairman. Thank you for the efficiency with which you run this committee. I greatly appreciate it.

Dr. Califf, congratulations to you as well on your recent confirmation, and thank you for coming before this committee.

As you know, the United States is a world leader in food production, in food safety, and the FDA plays a critical role in maintaining our global leadership in those fields. In my home State of Montana, agriculture is our number one industry, and our farmers, our ranchers, whether they produce wheat, cattle, sugar, beets, pulse crops, or other products, play a critical role in not only feeding the United States, but also the world.

And one important way Montana is able to do that is by having a world-class research facility at the land grant university, Montana State University (MSU). In fact, I was particularly proud when I heard that MSU was able to endow its first Montana plant sciences chair who is a world leader in cereal genetics and started earlier this year.

Moving forward, it is critical that Washington not get in the way and push policies that have the potential to hinder or even discriminate against ag research and technology that has proven to be effective, proven to be safe, and proven to be productive. In particular, the prospects for biotechnology continue to be bright. Whether it is enhancing production by increasing crop yields or helping protect the environment by requiring fewer pesticides, or reducing demand for water, for example, or even lower food costs for families, I view biotech as essential to the future of our food supply.

So with that as background, my question is, there was a decision made in November of 2015 by the FDA to deny a petition to require mandatory labeling of biotech in food products. Do you agree with that decision?

Dr. CALIFF. Well, this is a decision that was really mandated by law in the opinion of the FDA because in order for the FDA to mandate a label, it would be required that there be a material difference, for example, as measured by a change in the nutritional composition of what you eat for a genetically engineered product versus a non-genetically engineered product. And we have been unable to detect such differences at this point, which explains our decision.

Senator DAINES. So as a food safety agency, it sounds like you would believe, and I do not want to put words in your mouth, but do you believe the FDA should make its decisions based on sound science rather than unsubstantiated claims that might not be supported by evidence?

Dr. CALIFF. We are firmly committed at the FDA to base our decisions and policies on the best science that we can possibly get.

Senator DAINES. Yeah, it is good to have a doctor running it. Thank you, and I agree with you. And to bring this issue home, for example, in Montana on the eastern side of our State, sugar beets are a major crop. They are an economic driver for our State, and, in fact, the source of hundreds of jobs, and most sugar beets are grown utilizing biotechnology. But the sugar that results from the processing of a conventional sugar beet versus a biotech sugar beet is identical in both nutritional value and composition, I think to the point that were just describing there.

If a biotech food product, like sugar beets in the example provided, is deemed by the FDA to be safe for human consumption, meet the same quality standards as a non-biotech, and is nutrition-

ally and essentially the same as a non-biotech counterpart, should it be regulated by the FDA any differently?

Dr. CALIFF. Well, the law tells us it should not be labeled specifically for that if the quality is as you described. But I also want to take the chance here to stress something that you said. This is vitally dependent on a robust agricultural, biomedical research enterprise, which is not predominantly located at the FDA. We have great people, and Susan Main is here today who leads that.

But it is very important to have first-rate universities that are doing the kind of research that you described where you are. In my previous career at Duke University, we had great biology and botany, but NC State, you know, is world class in the broader agricultural sciences, and I had the chance to do a lot of work with those folks. So what we are really dependent on is a first-rate research enterprise that delivers the science that we need to make good decisions, so any decision would depend on the specifics of what was measured about the plant that you are discussing.

Senator DAINES. Well, I am out of time, but I want to thank you, Commissioner Califf, for the thoughtful remarks. And moving forward, I do believe it is important that the FDA remains focused on its mission to helping ensure the United States has a safe food supply and abstains from marketing or labeling mandates that would have no bearing on food safety. So thanks for your remarks.

Dr. CALIFF. I would like to add, Senator, that we did issue a guidance on voluntary labeling so those who wish to do so have a specified way to do that for those. Who think it should be labeled as such.

Senator DAINES. Thank you.

FOOD SAFETY MODERIZATION ACT CFSMA

Senator MORAN. Thank you, Senator. Commissioner, let me turn my attention, our attention, to FSMA and the topic of guidance documents. How many guidance documents is FDA working on, and does FDA anticipate releasing—how many do they intend to release in regard to FSMA implementation?

Dr. CALIFF. Well, Senator Moran, this has been a fascinating issue for me because essentially thanks to Congress, we are implementing an entire new structure to prevent food-borne illness and problems, rather than reacting to it. So this means an entire system is having to be put into place.

As you know, five out of the seven major rules have already been issued. We have two more rules to come out shortly, and then emanating from those rules will be a whole series of guidance documents. And what I have come to understand about this particular area that is really fascinating and of emblematic of where America should be, is a system that starts at the farm, works at the county, works at the State, and includes the Federal Government.

And as guidance documents are put out, and I cannot give you an exact number because it will depend somewhat on how things go. It is really the interpretation of the rules that gives people the information they need to for implementation. And since this is not the Federal Government saying here is exactly how you have to do it, it is really a discussion occurring among multiple parties. There has to be some flexibility in here so that we get it right.

And you might even imagine the exact way things are implemented could vary depending on the circumstances in particular regions or with particular issues. So we are committed to issuing the guidance documents that are needed so that this is done right and it prevents food-borne illness.

Senator MORAN. And something you just said is a reminder to me to remind you and FDA, when your inspectors are reviewing practices and making a determination whether compliance is occurring, the guidance documents are just guidance. And the entity being reviewed can perform compliance in a different way than the guidance documents. That is true?

Dr. CALIFF. Yes. So let me tell you why—I am actually excited about this topic. A lot of my career was built on doing multinational human clinical trials, and the first one we did was so big about 20 years ago, the FDA was not prepared for the inspection. So we ended up with meat inspectors looking at our electrocardiograms out in hospitals around the world, and it just was not ideal.

And so, you know, before I got here, wise people figured out that our inspectors need to be aligned with a particular center so that there is a continuity between the expertise and the center and what the inspectors are doing. And when you have that expertise, it gives you the flexibility for the inspectors to look at the built-in quality as opposed to just reading a document and saying you have to do it this way.

And, you know, I am really pleased to say this is well under way. It is a critical part of FSMA, so people inspecting farms and food places will have expertise in that area, and they will be connected to the center so that if there are issues rather than just relying on rote memory, they will be able to deal with it. Now, you know, whenever you have a complex system it is never perfect. People will need to let us know so we can adjust if there are problems.

Senator MORAN. You are making the point that I wanted to make sure was clear because even though a producer or a processor may not follow the guidelines, they still could be in compliance. And I want to make sure that your inspector would know that.

Dr. CALIFF. Yeah, so—

Senator MORAN. It is about the result. It is not about—I mean, FSMA is designed in a way to create safe food, not a regulatory checklist. And I think that is what you just told me that you agree with.

Dr. CALIFF. I agree with that, but I do want to pick a little finer point here—

Senator MORAN. Okay.

Dr. CALIFF. [continuing]. Because in general, I can speak to this from hospital quality which has similar issues. The process typically is closely related to the outcome that you want. So when you deviate from a standard process that has been proven to be effective, then you need to have a good reason for doing it, and there often are good reasons. And I have been on the other side of the inspection, so I feel like I understand when a good reason may be in play.

But I would not want anybody to believe that we can throw the process out the window here. I mean, the whole reason to have FSMA is so that we can share knowledge, and people on the farms

and in the food processing places can know what the best standard for quality is. And our inspectors should know that quite well, too, because if we did not have that, we would have total chaos and no standard.

So we are going to be flexible, but, you know, we have got to have people understand that process leads to the quality. Does that make sense?

Senator MORAN. It does. Related topic, what is the status of the personnel necessary to pursue compliance of FSMA? Are you in hiring mode?

Dr. CALIFF. We have done a lot of hiring. We are still in hiring mode, and again, thanks for the funding because it is has made a huge difference. We are having to increase the workforce and the realignment. Remember previously it was geographically organized. Now we are saying, you know, you have got a particular job to do with a particular industry. And so, it is not just hiring people. It is also a tremendous amount of team building, and the things that you would do if you are building a first rate in a company.

Senator MORAN. Education and training.

Dr. CALIFF. Yeah, and, you know it is a complex process. We have States and counties involved in doing a lot of the work. It is well underway, and I think it is going really well. We are excited about it.

Senator MORAN. Thank you, doctor. Senator Merkley.

OPIOIDS AND ADDICTION

Senator MERKLEY. I want to turn to the current Senate conversation about opioids and opioid addiction and the overdoses that are occurring. The FDA has come under criticism for not always using an advisory panel on opioids. With Zohydro approved back in 2013, the FDA did have an advisory panel. It recommended 12–2 against approval, but FDA approved it anyway. And then the following year the FDA approved two additional opioids, but decided not to convene an advisory panel. What was the reason? Was it that FDA did not want to hear about the concerns from medical professionals, or why would on such an important issue—with so many addiction-related issues, why would the FDA have wanted to trash their advisory panel system?

Dr. CALIFF. Well, let me be clear. There is no interest at the FDA in trashing the advisory panel system. As you know, we have recently taken a very deep look at opioids. It is right that people are upset. I know you are dealing with it today on the Senate floor. It is a national epidemic, more people dying from overdoses than from auto accidents, which is a startling statistic.

So we have a very deep eight-point plan that was just published in the New England Journal with everything from having advisory panels on almost everything to reframing the whole issue. You know, the question is how do you consider a situation where maybe half of opioids that are prescribed are actually diverted to someone for whom the prescription was not written. How do you consider the societal effects in addition to the effects on the person for whom the treatment is prescribed?

So this is a major point of emphasis. We are changing our tactic on this. And I guess the way I like to describe it is we are fighting

a battle here against a very tough opponent. I think the FDA has always tried to do the best job it could, but the opponents have gotten tough very quickly, and we are having to change our tact here. We are going to do that.

Senator MERKLEY. So I know you were not at the FDA last year when the FDA approved OxyContin for children without an advisory panel. It just kind of defies logic, and so I want to ask the question again. Why did the FDA decide to do away with advisory panels on these dangerous drugs?

Dr. CALIFF. Let me address the two that you brought up specifically, Zohydro and pediatric OxyContin. And it will take just a minute, if it is okay. I know we are pressed for time.

This Zohydro issue, it is true the panel took a vote that you have recited, but it also specified that there were criteria that might make it okay. Their problem was they were concerned about the post-market system that was in place. And I have learned there was a feeling at the FDA that the requirements of the advisory panel were met, so it was not felt that it was really disagreeing with the advisory panel. It was listening to the advisory panel and making the changes.

But on that one, we are in complete agreement. If had we to do it over again, we would have met with the advisory panel again and reviewed the issues.

And on the pediatric OxyContin, this is a very important one, and I think technically I do not think it is correct to simply call it an approval. OxyContin has been available for children. There are about 10,000 children a year, and if you have ever seen a child with sickle cell disease, for example, which is one of the serious illnesses for which chronic opioids are needed for very severe pain, or a child dying of cancer, the drugs are being prescribed, and we think for children, mostly appropriately so. Pediatricians would not use these drugs ad hoc.

So the only change that was made was to make proper dosing available in the label as opposed to changing fundamentally the way the drug was used. And it was associated with a very profound post-market commitment to make sure we are able to track what is done with OxyContin. Having said that, we learned a lot by seeing what happened, and I should note that I was at the FDA when this happened because I was at Medical Products and Tobacco. So I do not want to be shirking responsibility here.

But seeing the public reaction to this, we are going to have two consecutive pediatric advisory panels to review all of our approaches to opioids and children. They are already scheduled. They will be very intensive, and we will certainly listen to the advice.

Finally, if I could just note one other thing about this, we do have a letter that was recently in the Boston Globe from the American Academy of Pediatrics and from the chair of the Standing Pediatric Advisory Committee of the FDA saying that they thought our decision was the correct decision to give doctors dosing information so they would know the right doses to use when these drugs are indicated. But, you know, having said that, we are going to use advisory panels to review these things.

Senator MERKLEY. Mr. Chairman, could I ask one more question here?

Senator MORAN. Yes.

OPIOID LABELS

Senator MERKLEY. So I am glad to hear the commitment to advisory panels going forward. Did you require on the label warnings about the addiction properties? Is that on all the opioids now?

Dr. CALIFF. Yes.

Senator MERKLEY. And if not, is that something that can be done right away?

Dr. CALIFF. It is on all the opioids, but we are going to strengthen the labels, which is part of the plan that you see. And one thing that happened is there were a whole series of things done for long-acting opioids, so-called ER/LA, extended-release and long-acting. And we are just updating this information to put out sterner warnings.

So I think if you read what is in the label, it is pretty clear what the problems are, but we have learned that it has not gotten through, and we need to get to prescribers because the prescribing really needs to be brought under control.

Senator MERKLEY. Well, I can tell you it does not get through because just recently, for example, my daughter had her wisdom teeth extracted, and so when she came home and she had her prescription, I said to her, you know, we have to be very careful of these because of the dangers of addiction, and it was one of those, "oh, Dad" moments. Now, if the dentist had talked to her about the dangers of addiction that would have carried some weight, if the pharmacist had talked with her about the dangers of addiction.

But it was crazy to her. What is this crazy idea that she is hearing from her dad. And as I have talked to people, very few get any sort of education from their doctors about the substantial risks involved. And just think in Oregon, four million people last year, 100 million opioid pills prescribed. One hundred million.

Dr. CALIFF. Well, if I may, I feel qualified to talk about this because up until 10 months I was a pretty busy practicing doc. I started in intensive care, and then had an outpatient practice. So, you know, recently it was not so big because I had administrator responsibilities, but still saw it all.

The medical practice issue here is profound, and I know you all are going to be dealing with it actually today. It is our stated position in the New England Journal there should be mandatory education. And a really critical thing as you talk about this, to back up one second, we spent all day yesterday with our science board in a public meeting. One of your colleagues actually came out to the FDA to give some public testimony.

A really critical thing here is mandatory education, but not just about opioids because, you know, the pain that people have is real. There are 10 to 12 million Americans with severe chronic pain, and we also heard from them. And so, the doctors need to be trained about how to deal with pain and then how to deal with the opioid part of pain.

We have a voluntary program which is part of the RIMS commitment that companies have to pay for it, but independent CME providers do it. But one problem with voluntary education is that people most likely to volunteer to take it are the ones who probably

need it the least. So we are officially in favor of mandatory education, and we think it is one of the most important things that could be done.

Senator MERKLEY. Thank you.

CENTER FOR VETERINARY MEDICINE

Senator MORAN. Commissioner, I saw recently that the Director of the Center for Veterinary Medicine announced that she was leaving the agency. And I would ask you and encourage you to consider the appointment of a veterinary medicine practitioner, a doctor of veterinary medicine, to that position. Have you thought about what is next in this regard?

Dr. CALIFF. I have. We will do a national search, and, you know, by standard we need to have it open to all types of people who might apply. I will note that I have a proclivity towards veterinarians right now. My future daughter-in-law, we have a family wedding coming up in Colorado. She is actually a Wyoming native, has just graduated from the Cornell Veterinary School. So I have heard the veterinarians' perspective on this, and personally I have sort of a love of veterinarians because of that, but we have to open it up to everyone.

Being a medical doctor and now in charge of the FDA, I understand what you are saying, the concerns, the deep science concerns, you know. It would mean that someone from that background could be very helpful and someone with experience out in the field.

BIOSIMILARS

Senator MORAN. Thank you. Let me talk a moment about biosimilars and highlight language that was included in the omnibus spending bill directing the commission to respond, the FDA to respond. And what the language says is—first of all, I would preface this by saying there are lots of folks in the industry who would like to have input, understanding analysis as the biosimilar program is developed, naming labeling, interchangeability, and indication extrapolation. And our language in the appropriation bill that you are now operating under directed that the committee be provided with an estimated timeline by which the Agency will finalize all pending draft biosimilar guidance documents and regulations.

The committee expects to receive this report no later than 60 days after enactment. Enactment occurred in December, and we have not had a response to that directive. What is the status, and what can we expect?

Dr. CALIFF. Well, it sounds lame to say I am going to have to get back with you on the details of the timing, but we will get back with you. I will just point out, I was in charge of the clinical trial for the first biologic in cardiology, and ended up working a lot with biologics. So I am well aware of the issues. They are complex, but I think we are very close.

I will give a shout out to Janet Woodcock and her team who have been working on this. They are not only regulators. They are world authorities on the chemistry and biology of biologic drugs.

So we are going to get this as quickly as we can. I mean, after all, we have 59 compounds in the pipeline now for the biosimilar

program. So if we do not get this out soon, it is going to be difficult for people to navigate and know what they need to do.
So I hear you, and we will get back with you.
[The information follows:]

Report to the Committee on Appropriations

Draft Biosimilar Guidance

Report in Response to

Senate Report 114-82

And

Explanatory Statement Accompanying the

Consolidated Appropriations Act, 2016

Food and Drug Administration

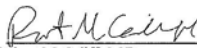

Robert M. Califf, M.D.
Commissioner of Food and Drugs

Table of Contents

I. Introduction	3
II. FDA Response.....	3

I. Introduction

This report is prepared in response to the following language:

A. Senate Report 114-82:

Biosimilars- The Committee is concerned that FDA has failed to provide the public adequate opportunity to review and comment on regulatory standards for the approval and oversight of biosimilar drugs. Therefore, FDA is directed to provide the Committee with an estimated timeline by which the agency will: finalize all pending draft biosimilars guidance documents, publish draft biosimilar guidance documents included in its 2015 regulatory agenda, and finalize those draft guidance documents. The Committee expects to receive this report no later than 2 weeks after the Committee reports this legislation.

B. Explanatory Statement accompanying the Consolidated Appropriations Act, 2016:

The agreement acknowledges some progress in FDA's effort to address issues with products that are biosimilar to and interchangeable with FDA-licensed biological drug products. In August of this year, the FDA issued draft guidance and a proposed rule regarding naming of these products. However, the agreement remains concerned that FDA needs to provide the public with a greater opportunity to review and comment on all regulatory standards for the approval and oversight of biosimilar drugs. Therefore, FDA is directed to provide the Committees with an estimated timeline by which the agency will finalize all pending draft biosimilars guidance documents and regulations. The Committees expect to receive this report no later than 60 days after enactment.

II. Food and Drug Administration Response

The Food and Drug Administration (FDA) has worked diligently to issue multiple guidances on biosimilar products since enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). While FDA will continue to work on drafting guidances, reviewing submitted comments, and finalizing guidances in fiscal year 2016, the release of guidances is dependent on factors such as ongoing work, competing priorities, and the timing of interagency clearance.

FDA anticipates issuing the following biosimilar final guidances in the next 12 months:

1. Final Guidance: Nonproprietary Naming of Biological Products
2. Final Guidance: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
3. Final Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
4. Final Guidance: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act

FDA anticipates issuing the following biosimilar draft guidances in the next 12 months:

1. Draft Guidance: Considerations in Demonstrating Interchangeability With a Reference Product

2. Draft Guidance: Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity

Please keep in mind that while these are our best estimates, they are subject to change and factors such as workload and a shift in priorities could influence the list.

GAO REPORT ON FDA'S IT INFRASTRUCTURE

Senator MORAN. Let me highlight a Government Accountability Office (GAO) report that was released in December of 2015 on FDA's information technology infrastructure. That report made a recommendation that FDA define schedules and milestones for incorporating into its IT plan elements that align the Agency's mission and business strategies, and fully implement the plan.

I have gotten interested in IT. We have seen lots of problems in Federal agencies and their use of IT, and I would highlight the GAO report for your consideration and information, and encourage the FDA to take an active role in meeting the recommendations of

the GAO report. This matters a lot to efficiency and good government.

Dr. CALIFF. Well, let me just say it was an interesting experience to come from a major university with a lot of Federal funds and then to step inside of the Federal system on IT, so I appreciate your concerns. And what I would say is that in the past, the primary issue at the FDA has been considered to be protecting all of the highly protected trade secret information that is under constant attack, and that has gone well. We have done that well.

But I am pleased to say we hired a new CIO just as I came on board. He is a great guy. He has experience in the Federal Government and the private sector. We read the GAO report and we are complying with it. Not only that, we are working closely with the GAO to close the gaps.

And what it pointed out was there was a plan for IT inside the FDA, but not a marriage of the IT plan with the overall strategic plan of the organization. And I can assure you in a science-based organization, if you do not have good knowledge management infrastructure, and the way the FDA works it is a lot of transactions, a lot like a business. People put in applications, and they have to be dealt with. If you do not have those systems working, you have got a real deficit that is going to hurt you, so we are very focused on it. And I am confident we will comply.

Senator MORAN. We have just a few more minutes. The vote has been called, but let me ask Senator Merkley if he has any brief, short follow-up questions that he would like to make sure he asks.

OPIOIDS

Senator MERKLEY. Thank you, Mr. Chairman. I want to go back to the opioid situation, and I mentioned the number of pills in Oregon, the 100 million pills prescribed for the population in 1 year of 4 million. It seems like there must be ways to take this on. So many people say, hey, I needed eight pills, and I had 30 left over or whatever. And not only are they not getting from their doctors about the addiction risk, they are also not being told, and these represent a significant problem, these leftover pills, so this is what I want you to do. This is how you get rid of those pills. This is how you return them to me, or this is how you—

So is it worth thinking about a smaller number of prescribed initially? And the way, I was shocked to read that the number—the percent—that virtually everyone who suffered an opioid overdose—I think it was 90 percent of those who suffered an overdose, were able to go back and easily fulfill—get a prescription filled again even after their overdose. In other words, there is something—maybe we do not have a tracking database, people are getting prescriptions in various places.

What can we do? It is crazy, 100 million pills in the State of Oregon?

Dr. CALIFF. There is no doubt about this, and I should reveal that in my academic career just before coming to FDA, I was involved in the National Institute on Drug Abuse (NIDA) network to deal with opioid abuse, the National Institutes of Health (NIH)-funded network. We oversaw a project Kaiser was doing to organize its health system to offer alternative team-based approaches to

pain to reduce opioid prescription. And we had a grant from NIDA together with the CMS Innovation Center to develop electronic health record systems to identify and intervene people who were high risk in rural southern counties in West Virginia, Mississippi, and North Carolina. So I have done a lot of work on this topic.

You are fair to call it crazy, and if I could take 1 minute. I know you have got to go vote. Ten years ago there was a call for America's doctors to stamp out pain. It was a quality measure in hospitals. Doctors were taught that you had to get the pain level down to zero, and that was the goal. There obviously was an over-reaction. It is extreme. It has created a national epidemic. We have got to rein it in.

The FDA has a role. We are not going to shirk our responsibility. I believe our directions are currently clear, but if you talk to doctors, none of them read medical drug labels. I did not either. It is the derivative instructions that go to the doctor and the education.

So we are one of multiple Federal agencies, and the Congress, and the States that need to work together. Remember that medicine is regulated mostly at the State level. We are prohibited from regulating the practice of medicine. We are going to be very outspoken about this along with you, and we have got to put practical things in place.

One just quick comment about arbitrary restrictions on numbers of days. It is complicated because many of the people actually do need opioids for chronic pain. We had amazing testimony by someone from Walter Reed yesterday who was involved with tens of thousands of veterans that have had amputations. And many of them are in extended living facilities or other places where they cannot easily get back to the doctor to get their prescriptions refilled.

So I would urge against an arbitrary restriction, but we have got to work together to convince doctors that they need to exert the most care with the fewest possible pills prescribed. And there are clear instructions for disposal of the medication if you do not need everything that is in your bottle.

CONCLUSION

Senator MORAN. Dr. Califf, thank you very much. Thank you for your testimony today. I was impressed with your level of knowledge and expertise, and I wish you well as you lead the Food and Drug Administration. My intention, as I indicated when we visited in my office, that I would have expected to have a conversation today about Zika, about opioids, which Senator Merkley clearly was interested in, and about cancer—the cure of cancer, and the moonshot effort. I welcome those conversations to continue. We can do that one-on-one.

But my hope is that a few months into your job as we get through the appropriations process, that we would invite you back, that you would accept that invitation, and we would give not only Senator Merkley and I, but other members of this subcommittee the chance to have a more in-depth conversation about a variety of issues facing the FDA.

Dr. CALIFF. I would really appreciate that opportunity. As my testimony submitted for the record says, we need the interchange

and the guidance to get it right because we base everything we do on science, and we must insist that we get better and better at the science. But policy obviously involves an intersection of culture and science, and you are the intersection. So we look forward to working with you.

Senator MORAN. Thank you very much. And, Mr. Tyler, thank you for joining us. You have been very good at handing notes to the Commissioner.

[Laughter.]

ADDITIONAL COMMITTEE QUESTIONS

Senator MORAN. I would take the opportunity to formally conclude this hearing as soon as I find the magic words.

For members of the subcommittee, any questions that you would like to submit for the record should be turned into the subcommittee staff within 1 week, which is Wednesday, March the 9th. We would appreciate if we could have responses from the FDA within 4 weeks of that time.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

CANCER MOONSHOT

Question. The budget requests \$755 million in mandatory funds for new cancer-related research activities, of which \$75 million would be transferred from NIH to FDA to develop a virtual Oncology Center of Excellence.

It is my understanding that the \$75 million in mandatory funding for the Cancer Moonshot would be available for 5 years. How does that work? Would this funding only be used for infrastructure/IT, or would it be used for staffing? Would the mandatory funding need to be reauthorized, or is it a one-time cost?

Answer. FDA is conducting a needs assessment to ensure a successful implementation of the Oncology Center of Excellence. Until business and systems requirements are fully documented, funding should be distributed equally across all 5 years, allocating \$15 million per year.

Preliminary budget estimates for fiscal year 2017 include a mix of:

- IT funding to support system enhancements and innovation for oncology related activities and improve analytic capabilities in CBER, CDER and CDRH (each Center has multiple IT systems that may need major or minor enhancements to support oncology efforts)
- Funding for executive recruitment search efforts to hire a dedicated Oncology Center of Excellence Program Director and senior staff
- Funding for FTEs to support oncology activities across medical product areas: drugs, biologics, and devices
- Funding for FTEs to document business and systems requirements: business project managers, information technology specialists, systems engineers and other support disciplines.

After the first 5 years, FDA will assess whether additional funding is necessary for the Oncology Center of Excellence.

Question. Should Congress not move forward with the mandatory funding for the Cancer Moonshot, how much money would you need in fiscal year 17 to begin moving forward with the virtual Oncology Center of Excellence?

Answer. Mandates such as the Oncology Center of Excellence can be challenging to implement without appropriate funding. Based on the magnitude of establishing a new structure to support the Oncology Center of Excellence, the minimum funding needed in fiscal year 2017 would be \$15million in budget authority, consistent with the distribution methodology over 5 years as described above. FDA regulates multiple product areas for drugs, biologics and devices, in addition to building, enhancing and maintaining various IT systems needed to automate the regulatory review processes.

FSMA—PRODUCE

Question. The produce industry has expressed concerns about the possibility of having some of their packinghouses subject to the preventive controls rule while other packinghouses would be subject to the produce rule. The produce industry has worked closely with FDA to ensure that there are commodity specific, risk based standards put in place under the produce rule.

Would you agree that it makes no sense for produce facilities, because of ownership structure, to not be handled under the produce rule and instead under the preventive controls rule?

Answer. In September, 2015 FDA launched a FSMA Technical Assistance Network (TAN) to provide technical assistance to industry, regulators, academia, consumers and others regarding FSMA implementation. FDA is using information specialists and subject matter experts to respond to questions related to the FSMA rules and programs. These questions are being tracked and trended to assist FDA in prioritizing FSMA guidance and training. FDA is also establishing a technical assistance network to support FDA food safety staff (FDA and State) performing inspections and compliance activities. FDA is identifying a cadre of experts to be available to assist inspectors and compliance staff with technical and policy questions including queries about regulation requirements and applicability.

Question. Don't you think this would create added complexity, confusion, and cost when the real focus should be on food safety?

Answer. Under FSMA, farms packing and holding covered produce are subject to the produce safety rule, and facilities required to register are subject to the preventive controls for human food rule. Our preventive controls and produce safety regulations adhere to the statutory framework. Accordingly, produce packing houses that fall under the new farm definition and pack covered produce are covered by the produce safety rule. Produce packing houses that do not fall under the new farm definition are facilities covered by the preventive controls for human food rule.

We acknowledge the circumstances that result from the framework and have used our authority to minimize the practical effect of this dichotomy to the extent possible. First, we expanded our definition of "farm" to include more packinghouses than before. However, it was important to us for the definition to reflect what farms are in the real world. As a result, we did not include all packinghouses, such as those businesses with a limited relationship to a farm, within that definition.

Second, we expect that the specific steps necessary to ensure the safety of produce would generally be the same for on-farm and off-farm produce packing houses. For example, several of the CGMP requirements in the preventive controls rule that would apply to an off-farm produce packing facility (like provisions for employee health and hygiene, the plant and its grounds, sanitary operations and facilities, and equipment and utensils) have analogous counterparts in the produce safety rule. In addition, although an off-farm produce packing facility would be required to establish and implement a food safety plan and establish preventive controls food safety management components, we expect that, in general, off-farm produce packing houses can look toward the produce safety rule for guidance. We expect that an off-farm produce packing facility's food safety plan would focus on a few key preventive controls, which reflect similar measures in the produce safety rule. For example, we expect that the food safety plan for an off-farm produce packing facility would include preventive controls such as maintaining and monitoring the temperature of water used during packing. We also expect that an off-farm produce packing facility would establish sanitation controls to address the cleanliness of food-contact surfaces (including food-contact surfaces of utensils and equipment) and the prevention of cross-contamination from insanitary objects and from personnel to food, food packaging material, and other food-contact surfaces. These preventive controls are also reflected in the produce safety rule.

FSMA—SUPPLIER VERIFICATION

Question. There is a great deal of concern and confusion regarding the provisions in the final rule for Human Consumption dealing with situations when a facility is not required to implement a preventive control specifically with respect to the requirement for written assurances from customers.

Does FDA intend to issue additional guidance on this section and if so when? With the final rule effective in close to 6 months, would FDA exercise enforcement discretion for this provision?

Answer. FDA understands there is some concern about written assurances from customers required under certain provisions of the regulations on preventive controls for human and animal food as well as the regulation on foreign supplier verification programs, and we continue to have dialogue with industry to better un-

derstand their concerns and identify areas of confusion. We are considering guidance in this area, as well as other options for addressing the written assurance provisions before the first facilities have to comply with the preventive controls regulations on September 19, 2016.

FSMA—TECHNICAL ASSISTANCE NETWORK

Question. FDA has developed a Technical Assistance Network (TAN) to share information among consumers, industry, regulators and other stakeholders working to implement FSMA.

Are the questions and answers submitted to TAN made public? If not, what is FDA's rationale for not making the questions and answers public?

Answer. The individual questions and answers submitted to FDA's Technical Assistance Network (TAN) are not currently posted on FDA's web site. The TAN process is intended to address questions from individuals and firms. The posting of questions and answers FDA provides through the TAN process is not a substitute for FDA following the good guidance practice requirements (21 USC 371(h); 21 CFR 10.115) for communicating its current thinking on regulatory issues to a wider audience. In addition, FDA is in the process of developing answers to frequently asked questions for posting on the web site. Further, FDA is developing guidance documents that are being informed by the questions received through TAN. FDA will be better able to provide comprehensive, organized information through guidance documents to a broad audience while using a process that includes public input.

The Department of Agriculture Food Safety Inspection Service (FSIS) has a similar system called "AskFSIS" which functions very well as a way to share information with industry and provide answers in a timely fashion. It's a helpful, searchable tool, and the content is public so everyone has access to the same answers. This also provides efficiencies so that the same questions aren't asked again and again.

Question. Have you engaged in any discussions with FSIS to learn from their experience?

Answer. Yes, FDA engaged in lengthy and productive discussions with FSIS from May through September 2015 before launching the FDA FSMA Technical Assistance Network in September 2015. Representatives from FDA visited the FSIS Technical Service Center in Omaha, Nebraska in May 2015 to learn about their system and processes. The following features of the AskFSIS system and processes were adopted by FDA: the staffing structure including administrators and Subject Matter Experts to answer questions; the use of an IT platform (Knowledge Management System) that provides an internal searchable database of questions and answers to promote consistency in responses and tracking of responses; and trending responses to identify those that are frequently occurring so as to inform FDA's guidance documents. The FDA TAN has been well-received by our stakeholders, and we believe that our early engagement with FSIS helped us build a solid foundation for our success.

FSMA—INSPECTION PROCESS

Question. Under FSMA FDA is tasked to develop and implement a comprehensive program to train investigators on a wide range of issues including what the regulations require and how inspections should be conducted. It is essential that regulations are enforced consistently from one region to another, and by both Federal and state officials.

Given the breadth of the new FSMA rules, what specific resources will inspectors have at their disposal during facility inspections when technical questions arise?

Answer. For Preventive Controls inspection and compliance work, FDA is developing an electronic resource library that will include the following resource tools to aid FDA's food safety staff (including state employees performing inspections on FDA's behalf) before, during, and after inspections: special instructions and assignments; FDA guidance documents; links to commodity specific processing videos; fact sheets describing commodity specific processes and potential hazards and controls; and a contact list identifying subject matter experts by area of expertise.

For issues relating to sprouts, FDA also plans to have a resource library that would include resources such as the Produce Safety Rule, FDA guidance, Sprout Safety Alliance training materials and resources, and subject matter expert contacts lists to provide technical and policy support to regulators inspecting sprout operations for compliance with the Produce Safety Rule and the Federal Food, Drug and Cosmetic Act.

For Produce Safety, FDA is establishing a network of regionally-based FDA personnel who will coordinate with state and other partners to fully implement and foster industry compliance with the Produce Safety Rule. This network will provide scientific and technical support to regulators performing inspections.

Question. Has the FDA considered creating a hotline or phone number for inspectors to contact FDA experts?

Answer. In September 2015, FDA launched a FSMA Technical Assistance Network (TAN) to provide technical assistance to industry, regulators, academia, consumers and others regarding FSMA implementation. FDA is using information specialists and subject matter experts to respond to questions related to FSMA rules and programs. FDA is tracking and trending these questions to assist FDA in prioritizing FSMA guidance and training. FDA is also establishing a technical assistance network to support FDA food safety staff (FDA and State) performing inspections and compliance activities. FDA is identifying a cadre of experts that will be readily available to assist inspectors and compliance staff with technical and policy questions including queries about regulation requirements and applicability.

Question. It is foreseeable that a facility may disagree with an inspector's conclusions and/or interpretation of the rules.

How will these differences be resolved?

Answer. If a facility disagrees with the interpretations of the rules and conclusions reported during an inspection, the first step in the process should be contacting the District Office or state if applicable. Technical experts in the relevant Center (i.e., Center for Food Safety and Applied Nutrition or Center for Veterinary Medicine) would be engaged in questions regarding rule interpretation and application.

If the facility does not believe the District Office or state has been responsive, or they do not understand the process for how to proceed next, then the facility should contact the ORA Ombudsman's office. The facility also may contact the ORA Ombudsman's office (or the FDA Ombudsman's office) for matters it believes are appropriate to raise in a different venue.

Question. When a facility disagrees with an observation reported on a FDA Form 483 (Notice of Inspectional Observations), how should it appeal that decision?

Answer. If a facility disagrees with an observation reported on a FDA Form 483, it would be able to appeal that decision using the same mechanisms utilized for all other inspections. As stated in the previous response, the first step in the process should be contacting the District Office or state if applicable. If that does not resolve the matter, for an FDA decision, a firm can file a formal request for review. FDA regulations (21 CFR 10.75) provide a mechanism for any interested person to obtain formal review of any FDA decision by raising the matter with the supervisor of the employee who made the decision.

Question. Will the FDA provide a centralized, timely mechanism for companies/facilities to appeal an FDA enforcement action?

Answer. If a facility disagrees with an observation reported on a FDA Form 483, it would be able to appeal that decision using the same mechanisms utilized for all other inspections. First, the firm can contact the issuing district office, as stated in the previous response. If that does not resolve the matter, the firm can file a formal request for review. FDA regulations (21 CFR 10.75) provide a mechanism for any interested person to obtain formal review of any FDA decision by raising the matter with the supervisor of the employee who made the decision.

Question. Do you agree that a formal appeals process would also help identify areas where additional inspector training would be helpful?

Answer. See our responses to previous questions describing the review process. FDA agrees that if a state, District Office, or ORA Ombudsman Office have been routinely contacted by regulated entities challenging inspectors' conclusions and/or interpretation of the rules for similar reasons it would potentially help identify areas for improvement. FDA could then consider this information when designing and administering subsequent inspector trainings to help prevent similar future disputes.

FSMA—DEFICIENCY LETTERS

Question. On May 2, 2014, FDA released its Operational Strategy for Implementing the FDA Food Safety Modernization Act, and that document contained a list of administrative compliance tools including "voluntary correction achieved at the district level through deficiency letters . . . to document significant safety-related deficiencies and request corrective action within a specified period of time."

What is a "deficiency letter"? Please explain why this new enforcement tool is necessary and provide specific examples of situations that would lead to a deficiency letter?

Answer. A deficiency letter is a potential new tool that FDA is considering using to inform a firm of observed violations that appear to pose a significant public health concern and FDA's expectations regarding a timely and effective response to

address the identified concern. The deficiency letter would be issued within a relatively short time period after FDA made observations of non-compliance which, if not corrected quickly, could affect public health. Further, a deficiency letter would describe the enforcement tools available to FDA if, after Agency review, the firm has not adequately corrected the violation(s) and FDA continues to have the same level of concern.

As contemplated, the intent of the deficiency letter would be to immediately, and in a formal way, advise the firm of the situation and to seek expedited compliance for those violations that present a significant public health concern. If the firm does not resolve the deficiency promptly, and further review within FDA supports the seriousness of the violation, FDA would determine what additional Agency action is necessary.

The deficiency letter would have the potential to expedite FDA actions to protect public health. We believe the deficiency letters could enhance FDA's existing tools which include the Form FDA-483, Advisory Letters, and other enforcement tools, potentially decreasing the need for their use, but not replacing them.

Our current thinking is that FDA would issue a deficiency letter only when the likely outcome of the observed violation would have significant public health implications. The specific criteria that would trigger a deficiency letter are still under development.

Question. Please explain in detail the process FDA will be using for issuing deficiency letters including the following: who will issue them, who will review them, under what circumstances will they be issued, how much time will a facility be given to respond, will they be publicly available?"

Answer. FDA is still considering whether to use deficiency letters as a possible compliance tool. If we decide to use deficiency letters, we will establish written standards for determining when to use deficiency letters, including the level of substantiation needed to support issuance. We also would establish written procedures for issuing and responding to deficiency letters.

Question. How will deficiency letters fit into FDA's current administrative process?

Answer. As contemplated, the intent of the deficiency letter would be to achieve expedited compliance for those violations that present the most significant public health concern. Thus, deficiency letters, if employed, would be a more targeted tool than warning letters. If a firm does not expeditiously correct the violation, FDA would be prepared to take further administrative or enforcement action to protect public health.

Question. What is the implication/consequence of getting a deficiency letter?

Answer. As deficiency letters are currently contemplated, a firm receiving a deficiency letter would be informed of any violations that pose the most significant public health concern. The deficiency letter would inform the firm that it should address such a violation in an expeditious manner. If the firm does not correct the violation in an appropriate timeframe, the firm would likely be subject to further administrative or enforcement action.

FSMA—SPENT GRAIN

Question. The Committee understands that FDA is working on clarifying guidance on its dried Distiller's Grains rules. The Committee took action last year on delaying the implementation of the new rule while distillers awaited this guidance.

Please inform the Committee when this guidance will be completed, provide response to what it would contain, and if the intent of the limitation contained in Sec. 750 will be complied with.

Answer. Animal food, including distillers grains used for animal food, must be safe for its intended use and not adulterated. In September 2015, FDA finalized the Preventive Controls for Animal Food (PCAF) rule that established new regulations for current good manufacturing practices (CGMPs) and hazard analysis and risk-based preventive controls for animal food. This rule addressed a range of animal food, including byproducts of human food production used as animal food. Distillers grains from the alcoholic beverage industry are considered human food byproducts.

FDA is currently developing guidance for industry to assist implementation of the rule. In the coming months, we are planning to issue draft guidance on compliance with the CGMPs and draft guidance for human food producers with byproducts going to animal food. Other guidance documents, including a draft guidance document on the hazard analysis and risk-based preventive controls requirements, will follow. We intend to issue these draft guidances before the applicable compliance dates for the PCAF rule. The guidance documents are part of a broader effort to foster and support compliance that also includes education, training, and FDA's

Technical Assistance Network (through which firms can get answers to how the rule applies to their particular operation).

FDA also assures the Committee that as we move forward with implementation of the PCAF rule, we will comply with the requirements of Sec. 750.

LISTERIA

Question. Did FDA's 2013 quantitative risk assessment study include data regarding the risk of Listeriosis associated with consumption of frozen vegetables and frozen food entrees?

Answer. No. The 2013 quantitative risk assessment, issued jointly with the USDA Food Safety and Inspection Service, focused on deli foods and did not include data on frozen vegetables or frozen food entrees. The "Interagency Risk Assessment: Listeria monocytogenes in Retail Delicatessens" may be viewed at <http://www.fda.gov/downloads/food/foodscienceresearch/risksafetyassessment/ucm370243.pdf>.

Question. What relative risk of Listeria monocytogenes related illnesses does FDA believe frozen foods such as frozen vegetables and frozen food entrees pose compared to other foods historically known to be associated with Listeria monocytogenes?

Answer. The quantitative risk assessments on Listeria monocytogenes that FDA has conducted to date have addressed frozen foods such as ice cream and other frozen dairy products, but have not addressed other frozen foods such as frozen vegetables and frozen food entrees.

Question. Will FDA continue to distinguish between frozen ready-to-eat foods (RTE) and frozen not ready-to-eat (NRTE) foods when frozen NRTE foods bear validated cooking instructions?

Answer. FDA evaluates each situation in which a hazard, such as Listeria monocytogenes or Salmonella, is detected in a frozen food on a case-by-case basis. Where cooking instructions are present on the label of a frozen food, FDA will consider such factors as whether it is reasonable that a consumer or food service facility would thaw the frozen food for consumption without following package cooking instructions, or whether a consumer would follow recipes in which a frozen food would be thawed and included as an ingredient in a fresh, uncooked food such as salsa or a dip.

Question. Will FDA align with global regulatory policy and treat the presence of Listeria monocytogenes in RTE foods on the basis of whether the RTE food does or does not support the growth of Listeria monocytogenes?

Answer. FDA currently is discussing international standards on Listeria monocytogenes in RTE foods that vary based on whether the RTE food does or does not support the growth of Listeria monocytogenes. To further internal dialogue, in December 2015, FDA convened a meeting of the CFSAN Food Advisory Committee (FAC) to consider, among other things, whether FDA should treat the presence of Listeria monocytogenes differently in RTE foods, depending on whether the food supports the growth of Listeria monocytogenes. A majority of the FAC voting members (7 of 11 voting members) recommended that FDA should not treat the presence of Listeria monocytogenes differently in RTE foods, depending on whether the food supports the growth of Listeria monocytogenes. FDA intends to take the recommendations of the FAC into account in its internal deliberations.

More information about the December 2015 FAC meeting, including the agenda, presentations, background information, transcripts and final FAC recommendations, can be found at: <http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/foodadvisorycommittee/ucm471769.htm>.

Question. Will FDA align its testing guidance to reflect current USDA practice? Specifically, will FDA change its recommendation on when a firm should speciate Listeria and encourage food manufacturers to follow up on a single finding of Listeria spp. on a food contact surface with corrective actions followed by additional testing?

Answer. FDA currently is internally discussing better alignment of FDA's 2008 draft testing guidance to current USDA practices. To inform those discussions, in December 2015, FDA convened a meeting of the CFSAN Food Advisory Committee (FAC) to consider, among other things, whether FDA should change its recommendations on speciation of Listeria and appropriate follow up to a positive finding of Listeria species (spp.) on a food contact surface. The FAC recommended that "FDA should follow the Food Safety and Inspection Service (FSIS) approach for Listeria spp. detected on a food-contact surface, if it tests positive then corrective action should be taken." FDA intends to take the recommendations of the FAC into account in its internal deliberations.

ZIKA

Question. It is my understanding that several vaccine platform technologies have been developed over the last several years and could now be called upon to try to quickly develop vaccines for medical countermeasures, as well as emerging infectious diseases, like Zika.

Can you explain FDA's role working with other agencies and companies to advance vaccine candidates for emerging infectious diseases?

Answer. FDA works closely with other components of the Department of Health and Human Services—including the Office of the Assistant Secretary for Preparedness and Response (ASPR) and its Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC)—as well as with medical product developers, counterpart national regulatory authorities, and other international organizations (e.g., World Health Organization (WHO)) to advance the development and availability of medical products (including drugs, vaccines, and diagnostic tests) to respond to emerging infectious disease outbreaks as quickly and effectively as possible.

FDA's efforts include providing scientific and regulatory advice to product developers and U.S. government agencies that support medical product development to help speed development programs. Specific activities include clarifying regulatory requirements through agency guidance and meetings, reviewing and providing input on pre-clinical and clinical trial designs, and expediting the regulatory review of data as they are received from product developers. As needed, FDA expedites the review of Investigational New Drug (IND) applications and related amendments, which are required for FDA-regulated clinical trials of drugs and vaccines to proceed. In addition, FDA collaborates with WHO and international regulatory counterparts—including the European Medicines Agency, Health Canada, and many others—under confidentiality agreements to provide technical support and scientific advice and to exchange information about investigational products in support of international product development efforts.

Question. What resources are needed to respond quickly and nimbly to emerging infectious diseases and other potential threats to our public health security?

Answer. Emerging infectious diseases and other threats to our public health security—such as the deliberate use of chemical, biological, radiological/nuclear agents—may occur without warning. Responding quickly and effectively to such no-notice events has required resources beyond what base resources can support. For example, to support the response to the Ebola epidemic in West Africa, Congress authorized \$5.4 billion in supplemental funding in fiscal year 2015, which included \$25 million for FDA. FDA is using this supplemental funding to support ongoing Ebola response activities, including:

- Working closely with interagency partners, product developers, the World Health Organization (WHO) and international regulatory counterparts to encourage and facilitate the development and assessment of vaccines, drugs and diagnostic tests;
- Collaborating with West African health authorities to facilitate access to investigational products as necessary (e.g., for flare-ups) through appropriate mechanisms until approved products are available;
- Maintaining the availability of diagnostic tests under FDA's Emergency Use Authorization authority; and
- Supporting regulatory science to help facilitate Ebola medical product development and review.

To support response to the Zika virus outbreak, the Administration has requested approximately \$1.9 billion in supplemental funding including \$10 million for FDA. If appropriated, FDA will use the \$10 million supplemental Zika funding to support highly targeted regulatory science research required to enhance the efficient development and regulatory review of medical products and blood screening assays for Zika virus; collaboration with and technical support to international partners' response efforts; and FDA staff to support the development, review, regulation, and surveillance of vaccines, diagnostics and therapies.¹

TOBACCO

Question. Public Health England, the English version of the U.S. Center for Disease Control and Prevention, stated that e-cigarettes are 95 percent less harmful than a combustible cigarette. Moreover, England's government health plan, the Na-

¹ https://www.whitehouse.gov/sites/default/files/omb/assets/budget_amendments/emergency_supplemental_2-22-16_zika.pdf

tional Health Service states that, “There is evidence that e-cigarettes can help people stop smoking.” And it is reported that the National Health Service will likely begin prescribing e-cigarettes as a cessation tool in 2016.

Do you share the view of Public Health England and the National Health Service related to reducing the harm associated with combustible tobacco through e-cigarettes?

Answer. Specific to individual health risk, the Public Health England Report’s estimate of 95 percent lower risk of e-cigarettes compared to tobacco cigarettes relied upon evidence from a prior paper (Nutt, D. J., L. D. Phillips, D. Balfour, et al., “Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach,” *European Addiction Research*, 20(5):218–225, 2014) to assess the relative harm of electronic nicotine delivery systems (ENDS) products. The Nutt et al (2014) paper employed an analysis model that quantified the relative health harms of 12 tobacco products using a series of 14 harm criteria. The expert panel determined that while cigarettes scored 100 percent in their assessment of maximum relative harm, ENDS products were rated to have only 4 percent maximum relative harm, which contributed to Public Health England’s assessment that ENDS are around 95 percent safer than smoking combusted cigarettes. The Report’s use of the Nutt et al (2014) paper has several limitations, and the Nutt et al (2014) paper itself observed that it was reporting outcomes based on the decision-conferencing process from a group of experts who were selected without any “formal criterion,” though “care was taken to have raters from many different disciplines” and primarily based on geographic location “to ensure a diversity of expertise and perspective”. In addition, the authors of the Nutt et al (2014) paper acknowledge that there is a “lack of hard evidence for the harms of most products on most of the criteria”. The authors of the Nutt et al (2014) paper did not explain what scientific information was available to the experts upon which they should base their ratings and they did not explain the derivation of the quantitative assessment of each harm criterion. It is unclear if the authors of Nutt et al (2014) paper carried out or referenced a quantitative risk analysis, a standard practice when assessing relative risk, nor did the authors indicate that they used mean levels of exposure to harmful or potentially harmful constituents HPHCs in users or other quantitative evidence as an approximation of risk. FDA does not find the results reported in the Nutt et al (2014) paper to be sufficiently conclusive on the relative risks of using different tobacco products.

FDA is also aware of the National Health Service’s position on prescribing e-cigarettes as a cessation tool. No e-cigarettes have been approved by FDA as a cessation product. Moreover, consumers often don’t know how much nicotine these devices deliver, making them unreliable for cessation efforts. There are a number of FDA-approved cessation tools on the market that have proven safety and effectiveness and FDA will continue to support and encourage research into cessation tools, including the potential role of e-cigarettes.

The final deeming rule gives FDA the tools it needs to answer important questions about e-cigarettes and how they are made, marketed and used to help establish whether, how, and to what extent they are beneficial or harmful and to whom. Furthermore, subjecting e-cigarettes to FDA’s tobacco product authorities will give manufacturers an incentive to conduct research and submit data to establish any potential public health benefit of e-cigarettes.

There are distinctions in the hazards presented by various nicotine-delivering products. Cigarette smoking is the major contributor to the death and disease attributable to tobacco use. Given this, some have advanced the view that certain new non-combustible tobacco products (including ENDS products such as e-cigarettes) may be less hazardous, at least in certain respects, than combustible products, given the known carcinogens in smoke and the dangers of secondhand smoke.

Scientific evidence may demonstrate that certain products are less harmful than others at an individual level, but the Tobacco Control Act directs FDA to also take into account the impact on the health of the population as a whole, including both users and non-users of tobacco products, in making regulatory decisions about these products.

Much remains to be learned about the risks of e-cigarettes to health, as well as their possible benefits. E-cigarettes could benefit public health if they encourage people who would otherwise not quit smoking to stop smoking altogether, while not encouraging youth or others to start use of tobacco products or encouraging former users to relapse back to tobacco use. On the other hand, e-cigarettes could be a detriment to public health. E-cigarettes have the potential to re-normalize smoking, encourage youth to initiate smoking, and/or prompt users to continue or to escalate to cigarette use—in effect, reversing the meaningful progress tobacco control initiatives have achieved to date. Other reported e-cigarette risks include dermal exposure to nicotine, childhood poisoning events, and physical harm from defective prod-

ucts (such as exploding batteries). Anecdotes illustrating both benefits and harms abound, but it is empirical scientific evidence that should drive the actions taken with respect to e-cigarettes.

Question. FDA is committed to using an evidence-based approach to the application of the principles of harm reduction to tobacco regulatory policy.

Does the FDA believe in the concept of tobacco harm reduction? Do you believe that adult smokers have the right to know about the risks and relative risks of different tobacco products and products with nicotine derived from tobacco?

Answer. Section 911 of the Federal Food, Drug, and Cosmetic Act, as amended by the Tobacco Control Act, provides a pathway for companies to seek FDA authorization to market a modified risk tobacco product. In deciding whether to issue an order authorizing the marketing of a modified risk tobacco product, FDA takes into account a variety of factors such as the relative health risks to individuals of the product, the likelihood that existing users of tobacco products who would otherwise stop using tobacco products will switch to the product, and the likelihood that persons who do not use tobacco products will start using the product.

FDA is committed to using an evidence-based approach to the application of the principles of harm reduction to tobacco regulatory policy. The Agency is also committed to providing the public with the most accurate health information and evaluating the products under our jurisdiction based on sound scientific evidence.

FDA has communicated the existence of a continuum of risk of nicotine-delivering products to the public. For example, in the proposed deeming rule, FDA asked for comments, data, and research regarding how various new tobacco products should be regulated based on the continuum of nicotine-delivering products and the potential benefits associated with these products, especially e-cigarettes.

There are distinctions in the hazards presented by various nicotine-delivering products. Cigarette smoking is the major contributor to the death and disease attributable to tobacco use. Given this, some have advanced the view that certain new non-combustible tobacco products (such as e-cigarettes) may be less hazardous, at least in certain respects, than combustible products, given the known carcinogens in smoke and the dangers of secondhand smoke.

Scientific evidence may demonstrate that certain products are indeed less harmful than others at an individual level, but FDA must also take into account the impact on the health of the population as a whole, including both users and non-users of tobacco products, in making regulatory decisions about these products.

Much remains to be learned about the risks of e-cigarettes to health, as well as their possible benefits. E-cigarettes could benefit public health if they encourage people who would otherwise not quit smoking to stop smoking altogether, while not encouraging youth or others to start use of tobacco products or encouraging former users to relapse back to tobacco use. On the other hand, e-cigarettes could be a detriment to public health. E-cigarettes have the potential to re-normalize smoking, encourage youth to initiate smoking, and/or prompt users to continue or to escalate to cigarette use—in effect, reversing the meaningful progress tobacco control initiatives have achieved to date. Other reported e-cigarette risks include dermal exposure to nicotine, childhood poisoning events, and physical harm from defective products (such as exploding batteries). Anecdotes illustrating both benefits and harms abound, but it is empirical scientific evidence that should drive the actions taken with respect to e-cigarettes.

CTP has identified e-cigarettes as an immediate research priority area, and has funded over 75 research projects since 2012 to better understand e-cigarette initiation, use, perceptions, dependence, and toxicity. This ongoing and funded research will provide important information about these products including a better understanding of e-cigarette users, reasons for use, abuse liability, user perceptions, and health effects.

Question. How will FDA share with adult tobacco consumers the different risks associated with different tobacco products?

Answer. FDA is committed to providing the public with the most accurate health information and evaluating the products under our jurisdiction based on sound scientific evidence.

FDA has communicated the existence of a continuum of risk of nicotine-delivering products to the public. For example, in the proposed deeming rule, FDA asked for comments, data, and research regarding how various new tobacco products should be regulated based on the continuum of nicotine-delivering products and the potential benefits associated with these products, especially e-cigarettes.

Under the Tobacco Control Act, FDA has authority to issue an order authorizing a product to be marketed as a modified risk tobacco product after taking into account a variety of factors such as the relative health risks to individuals of the product, the likelihood that existing users of tobacco products who would otherwise stop

using tobacco products will switch to the product, and the likelihood that persons who do not use tobacco products will start using the product. To date, FDA has not authorized the marketing of any modified risk tobacco product. FDA is currently conducting scientific review of eight modified risk tobacco product applications to determine whether the applicant has provided sufficient scientific evidence for FDA to issue an order allowing the products to be marketed as modified risk tobacco products.

Although industry has introduced newer forms of tobacco products that are not currently regulated under FDA's tobacco product authorities, it is important to note that, if such products are deemed subject to FDA's tobacco product authorities, manufacturers may not market these products as modified risk tobacco products unless they request and receive authorization from the Agency.

BIOSIMILARS

Question. The joint explanatory statement of the House and Senate Appropriations Committee on the Consolidated Appropriations Act, 2016 (Public Law 114–113), expresses the need for FDA to provide the public with a greater opportunity to review and comment on all regulatory standards for the approval and oversight of biosimilar drugs. “Therefore, FDA is directed to provide the Committees with an estimated timeline by which the agency will finalize all pending draft biosimilars guidance documents and regulations. The Committee expect[s] to receive this report no later than 60 days after enactment.” This law was enacted on December 18, 2015.

Please provide your response to this request. If you do not have that information, please explain why you have not responded to this request and when you intend to do so.

Answer. The requested report is currently in clearance. The Draft Guidance on Labeling for Biosimilar Products was released on FDA's website on March 31, 2016.

Question. Please provide us with an estimated timeline for publishing draft and final biosimilars guidances for the topics that are listed on FDA's 2016 guidance agenda.

Answer. The Food and Drug Administration (FDA) has worked diligently to issue multiple guidances on biosimilar products since enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). While FDA will continue to work on drafting guidances, reviewing submitted comments, and finalizing guidances in fiscal year 2016, FDA anticipates issuing the biosimilar guidances listed in our guidance agenda within the next 12 months. Please keep in mind that while these are our best estimates, they are subject to change and factors such as workload and a shift in priorities could influence the timeframe.

INTERNET/SOCIAL MEDIA ADVERTISING AND PROMOTIONAL LABELING OF PRESCRIPTION DRUGS

Question. In 2014 the FDA issued draft guidance for industry usage of Internet/social media platforms. Earlier this year, the FDA put out its guidance agenda for 2016 listing new and revised guidance's that are to be published this year. This list included a bullet on “Internet/Social Media Advertising and Promotional Labeling of Prescription Drugs and Medical Devices—Use of Links to Third-Party Sites”.

Can you tell us what the timeline is for producing this guidance, and will this be the final guidance for the draft put out in 2014?

Answer. The draft guidance issued in 2014 referenced above is the “Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices” draft guidance. This draft guidance is not the document listed on the guidance agenda for 2016. The guidance agenda lists the “Internet/Social Media Advertising and Promotional Labeling of Prescription Drugs and Medical Devices—Use of Links to Third-Party Sites” draft guidance. FDA continues to work toward publishing this and other draft and revised draft guidances listed on the 2016 guidance agenda.

Question. Are you working with stakeholders in crafting this guidance, and if so do you intend to do so further before putting out the updated guidance?

Answer. FDA has worked with stakeholders since November 2009, when we held a Part 15 public hearing to gather input from our stakeholders (e.g., industry, healthcare professionals, consumers, patient groups, Internet vendors, advertising agencies, and other interested parties) on how FDA can best provide guidance on the promotion of FDA-regulated medical products (including prescription drugs for humans and animals, prescription biologics, and medical devices) using the Internet and social media tools.

When this draft guidance is published, FDA will invite comments from our stakeholders on the draft. After providing this opportunity for public comment, we will review all comments received and carefully consider suggested changes, if any, as we prepare a final version of the guidance document.

INSPECTIONS—RISK BASED INSPECTIONS

Question. As FDA moves toward a more, targeted, risk-based, and efficient inspection model for importing drugs, food, and medical devices this will require better data about these facilities and the companies we are importing from. In the Omnibus, \$5 million was included for foreign high-risk inspections to continue efforts to develop and “utilize a targeted, risk-based, and efficient inspection model that incorporates commercially available information on high-risk establishments for onsite verifications.”

Can you elaborate on the risk-based decisionmaking and how you are utilizing commercial data to prioritize inspections?

Answer. FDA continues to improve our risk-based decisionmaking inspection models for multiple product areas. In our drug inventory, FDA is employing a site selection surveillance inspection model that runs annually on all facilities in the FDA’s inventory allowing for risk-adjusted parity between the foreign and domestic inventory. Several ongoing efforts target improvements to the quality and scope of data feeding into the risk models. Improved accuracy and completeness of data related to the inventory of foreign manufacturing sites under FDA oversight leads to improved risk model outcomes and enhanced inspection planning efficiencies. To that end, FDA uses commercially available data (e.g., the data on businesses available through FDA’s enterprise contract with Dun and Bradstreet) and commercial in-country services to verify the accuracy of firm information that feeds into the risk models.

In the food arena, FDA continues to work with our foreign counterparts to develop and implement Systems Recognition agreements. Systems Recognition agreements allow FDA to leverage the findings of the country with whom we have an agreement to help target Agency resources and increase efficiencies in our inspection model. We continue to work towards identifying a Unique Facility Identifier (UFI) that will allow for more comprehensive commercial data to be attached to an entity. In addition, the Agency continues to work to incorporate Geographic Information System (GIS) data with our inventory to extend the capabilities of our risk model. GIS data allows for the analysis of additional layers of data that can be pivotal in making risk-based determinations.

INSPECTIONS—DATA BOUNCE PROCESS

Question. It is my understanding that in 2013 the FDA’s Southwest Import District Dallas Office created a program called the Data Bounce Process. Please provide a summary of this program, and input on whether it is something that could be replicated or expanded upon.

Answer. Several years ago, FDA’s Southwest Import District (SWID) initiated a project in which some SWID offices accepted entry data from importers of medical devices prior to entry. Via a stand-alone automated process, the SWID staff checked this entry data against existing FDA databases in an effort to verify accuracy of the importer-supplied data. This process helped provide short-term feedback on whether importer-supplied data matched what FDA has in its own systems. Some firms have requested that FDA make this available to all firms importing products FDA regulates. While the agency appreciates this feedback, we have concluded that this limited operation cannot be effectively replicated on a large scale. FDA currently processes more than 34 million import admission decisions each year, and we do not have the IT capability to process a large number of additional test cases. If the program was expanded, additional test cases could easily number several million each year. Therefore, FDA is honing its targeting system to allow for the automated processing of entries where data are complete, accurate, and could fall into lower risk categories. In doing so, we may provide automated releases which increase efficiencies in terms of minimizing delays and enhancing targeting of high risk goods.

We also believe it is helpful where possible to provide instant feedback regarding the acceptability of data necessary for import processing. We are pursuing a similar process through the Automated Commercial Environment (ACE) system. ACE has the capability to screen electronic import submissions and indicate where data is lacking or fails to match syntax such that the entry is not acceptable for processing. This functionality is currently available in ACE. We also are examining opportunities to enhance our IT systems and develop outreach programs to provide immediate

feedback to the import filer when the data they provide does not match the information in our systems.

MEDICAL DEVICE INSPECTION

Question. Concerns exist with the lack of consistency, transparency, and predictability in the FDA medical device inspection process, including discrepancies in how facilities inside the US are inspected versus facilities outside the US, as well as FDA barriers to markets outside the US for products that are available to patients in the US. For example, typically five days is sufficient for the FDA to complete an overseas inspection and determine the suitability of the location to provide product into the US market while inspections inside the US can run several weeks, and even months. These discrepancies lead to variations in inspection standards and potentially competitive advantages for those who choose to manufacture outside the US.

How does the FDA plan to address the discrepancies between inspections performed by FDA within and outside the US?

Answer. A variety of factors are considered when planning and conducting inspections inside and outside the US. The majority of both domestic and foreign FDA inspections last 1 week or less but some inspections both inside and outside the US can last several weeks or longer. Medical Device inspections are conducted using FDA's Quality System Inspection Technique (QSIT), where some (Level I) or all (Level II) subsystems of the firm's quality system are evaluated. The average time to complete a domestic QSIT Level I inspection is 37 hours; 52 percent of domestic inspections are QSIT Level I. The average time to complete a domestic QSIT Level II inspection is 58.5 hours; the remaining 48 percent of domestic inspections are QSIT Level II. Foreign inspections are always QSIT Level II and take an average of 61.4 hours. In situations where a firm has had a previous inspection with a significant number of violations or a firm has received a warning letter, the inspection may last longer because the agency needs to confirm the completion of promised corrective actions and ensure no additional problems create a public health risk. In addition, when FDA identifies a large number of violations in the first few days of an inspection, FDA may extend the length of the inspection to ensure we can fully assess all quality systems and rule out additional concerns.

FDA is also engaged in an extensive Program Alignment initiative, which will create commodity-specific programs for the inspection of medical devices and radiological health products. Program Alignment allows FDA to address the increasing breadth and complexity of our mandate to protect the public health, address the impact of globalization on the food and medical product supply chains, and the ongoing trend of rapid scientific innovation and increased biomedical discovery. Program Alignment allows investigators with specialized knowledge of medical devices and radiological health products and related policies and procedures to focus on inspections of those products rather than expecting investigators to specialize in multiple product areas. Additionally, FDA is working to streamline existing processes, which are intended to improve effectiveness and consistency of inspections performed inside and outside the US.

Further, FDA allows sponsors to submit the results of a third party audit in lieu of a routine surveillance inspection conducted by FDA personnel. Specifically, certain types of audits conducted under the Medical Device Single Audit Plan (e.g., those that are accepted as substitutes for routine inspections) may be deemed to satisfy regulatory requirements of multiple international jurisdictions, and provide flexibility to device sponsors and establishments.

Question. There are reports of FDA withholding/rescinding a company's Certificate for Foreign Governments (CFG), essentially prohibiting the ability to serve markets outside the US, in instances when their products are able remain on the market in the US.

What is the FDA's process for rescinding and reinstating CFG?

Answer. A Certificate to Foreign Government (CFG) is an indication to a foreign government that FDA requirements are met at the time of its issuance. Firms request certificates to facilitate shipments to foreign countries.

FDA/CDRH will not issue a CFG to a firm that has been issued a Warning Letter for Quality Systems violations. Before FDA/CDRH will issue that firm a CFG, FDA/CDRH must have assurance that the firm addressed the violations. Once FDA/CDRH confirms the issues are addressed through an inspection or a submission to FDA from the firm, FDA will issue a letter stating that the violations appear to have been adequately addressed. Only then will FDA issue a CFG to the firm.

FDA/CDRH does not currently rescind CFGs once issued and we have not rescinded any certificates since 2009. CDRH previously rescinded certificates if we be-

came aware that a firm was in violation of the Quality System regulation. It was difficult to physically retrieve rescinded certificates, however, because in most cases CDRH found the certificate had already been sent to the foreign country.

GENERICS

Question. Recently the FDA has proposed a series of initiatives, which, together with the slowdown in generic drug approvals, are contributing to cost increases (labeling rule, same size guidance, Quality Metrics Guidance, delay in guidance for interchangeable generics).

Has FDA examined the collective effects of public health and cost to patients from the implementation of all these proposals? If not, can FDA undertake that examination and report back to the committee?

Answer. One of the initiatives identified in your question is a rule and the other three initiatives are guidance documents. The processes governing consideration of the economic impact of proposed rules and guidance documents are different, as outlined below.

With respect to the proposed rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, any final rule that is adopted will reflect FDA's consideration of public comments and would be accompanied by an analysis of the economic impact of the regulatory change described in the final rule. This regulatory impact analysis would be based on the framework described in Executive Orders 12866 and 13563, and use the best available techniques to quantify anticipated present and future benefits and costs. The regulatory impact analysis would help ensure that any regulation is adopted only upon a reasoned determination that its benefits justify its costs, and is tailored to impose the least burden on society, consistent with obtaining regulatory objectives. As part of the final regulatory analysis, FDA will estimate all of the benefits and all of the costs of the final rule. These benefits and costs will include any potential effects on public health and cost to patients from the implementation of the final rule but will not include the cumulative effects of other proposals or guidance documents. The effects of regulations and guidance documents currently in place are included in the baseline used as the starting point for estimating the effects of the rule.

The process for consideration of guidance documents, including those mentioned in your question, is governed by FDA's Good Guidance Practices (GGP) regulations (see 21 CFR 10.115). FDA's GGP regulations do not require an examination of the costs or impact to the public health associated with following the recommendations described in guidance. Should the recommendations described in guidance cause a particular hardship to its relevant stakeholders, those stakeholders may propose an alternative approach as long as that alternative approach satisfies the relevant statutes and regulations. If a guidance requests or requires that members of the public obtain, maintain, submit, retain, report, or publicly disclose information, the Office of Management and Budget (OMB) must first grant approval of these requests or requirements as an information collection request (ICR) in accordance with the Paperwork Reduction Act. Before the ICR is reviewed and approved by OMB, FDA estimates the total time, effort, or financial resources involved in providing the information and publishes a notice in the Federal Register requesting comments from the public on specific elements outlined in the Paperwork Reduction Act.

Industry, consumers and other stakeholders play a significant role in the agency's guidance development processes. FDA welcomes suggestions of topics for guidances, and in certain instances solicits draft proposals. For example, FDA may issue a "Request for Information" in the Federal Register to gain input on certain topics or participate in public workshops to engage with industry and other stakeholders on topics for which the Agency is considering developing guidance. After a draft guidance is published, comments are reviewed and considered by FDA in preparing the final guidance documents. The public can provide comments on any guidance document at any time.

DIETARY SUPPLEMENTS

Question. Within FDA's Center for Food Safety and Nutrition (CFSAN), how many FTE's are dedicated to enforcement activities? Of that number, how many are focused specifically on enforcing dietary supplement regulations?

Answer. The Office of Compliance is the focal point for enforcement activities within CFSAN, with eight (8) FTEs dedicated to dietary supplement enforcement. The Office of Dietary Supplement Programs (ODSP) is the CFSAN lead for policy development and strategic management of the dietary supplement program, which includes compliance strategy and safety assessments as well as guidelines and regulations. ODSP has authorization for 26 FTEs. Most of ODSP's FTE's devote at least

some of their efforts towards enforcement, but none are focused specifically on enforcement. CFSAN leverages its dietary supplement enforcement activities by partnering with other organizations within FDA, including the Office of Regulatory Affairs, that work on compliance and enforcement matters.

Question. In 2015, how many enforcement actions did FDA bring against dietary supplement manufacturers and marketers? How many dietary supplement good manufacturing practice inspections did FDA conduct in 2015? How many serious adverse events were reported to FDA last year? How many unique dietary supplement formulations were involved in these reports? How many new dietary ingredient notifications were filed with the Agency in 2015? And lastly, how many FTEs are devoted to dietary supplement enforcement and regulatory programs (including inspections of dietary supplement facilities)?

Answer. In fiscal year 2015 FDA issued the following warnings and brought the following enforcement actions against dietary supplement (DS) manufacturers and marketers:

- 49 Import Detentions (detentions without physical examination)
- 6 Untitled Letters
- 83 Warning Letters
- 6 Injunctions [Entered by District Courts]

(Data retrieved from FDA's Compliance Management Services database)

In fiscal year 15, FDA:

- Conducted 482 Dietary Supplement GMP inspections. Of those, 445 were of domestic facilities and 37 were of foreign facilities.
- Received 5,336 serious adverse event (AE) reports for products regulated by FDA's Center for Food Safety and Applied Nutrition. Of those serious adverse events reported, 3,098 were for dietary supplements with 3,529 unique product names reported (some AEs report multiple products).
- Received 35 new dietary ingredient notifications.

FDA devotes just over 100 FTEs to dietary supplement enforcement and regulatory programs, including inspections of dietary supplement facilities. Approximately 26 of those FTEs are located in CFSAN's Office of Dietary Supplement Programs (ODSP), which serves as the CFSAN lead for policy development and strategic management of dietary supplement program, including enforcement and regulatory programs. CFSAN's Office of Compliance has approximately 8 FTEs focused on dietary supplement enforcement activities.

Additionally, ORA devotes several FTEs to dietary supplement enforcement and regulatory programs, allocated in fiscal year 15 as follows: approximately 8.45 FTE for sample collections and analyses; 54 FTEs expended for inspections for domestic and foreign dietary supplement firms; and 5 FTEs in the Office of Enforcement and Import Operations, Division of Enforcement, providing support for dietary supplement enforcement and regulatory program activities.

Question. Given that the Office of Dietary Supplement Programs (ODSP) within the Center for Food Safety and Applied Nutrition (CFSAN) at FDA was only created in December 2015, what is the budget and FTE count for ODSP for the remainder of 2016? What is the proposed budget and FTE count for fiscal year 2017?

Answer. In fiscal year 2016, the Center for Food Safety and Applied Nutrition provided the Office of Dietary Supplement Programs (ODSP) a budget of \$4.6 million to include funding for payroll and non-payroll requirements. The fiscal year 2016 budget includes 26 approved positions (FTE). The proposed fiscal year 2017 budget for ODSP is \$5.9 million and includes additional funds for hiring to reach the approved level of 26 FTE.

Question. What does the Office of Dietary Supplement Programs (ODSP) within the Center for Food Safety and Applied Nutrition (CFSAN) at FDA consider to be the top enforcement priorities in the dietary supplement industry for fiscal year 2017? How were these priorities selected?

Answer. Using risk based prioritization, the Office of Dietary Supplement Programs (ODSP) has determined that in fiscal year 2017 it will use its current authorities and available resources to monitor the safety of dietary supplement products and take compliance and enforcement actions, such as:

- Taking action to remove from the market supplement products that are dangerous to consumers;
- Taking action, in conjunction with FDA's Center for Drug Evaluation and Research, to remove from the market products that contain undeclared pharmaceutical agents and are labeled as dietary supplements;
- Enforcing the dietary supplement good manufacturing practices (GMP) regulations, giving priority to cases with GMP violations that meet the following criteria:

- Potentially compromise product safety;
 - Fail to ensure product quality due to lack of testing, procedures, and records; and
 - Result in consumer deception, when, for example, manufacturers do not verify the identity of their raw materials
- Taking action against supplement products that bear claims to treat diseases which can result in serious risk of harm to the consumer (such as egregious claims of benefit in treating serious diseases) or widespread economic fraud. These priorities reflect a risk-based determination of how ODSP's limited resources can best be deployed to protect the public health.

Question. What is the status of FDA's effort to finalize the draft New Dietary Ingredient notification guidance?

Answer. FDA published its draft guidance for industry entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (the NDI Draft Guidance) for public comment in July of 2011. FDA reviewed public comments and met on several occasions with industry, consumers, and members of Congress to better understand the concerns raised. We considered the views expressed at those meetings and the many public comments received on the draft guidance as we worked on revisions to provide additional explanation and clarification. The comments received on the original draft guidance caused FDA to conclude that the best course of action would be to reissue the guidance as a revised draft that contains clarifications on several key issues that were the subject of confusion or misinterpretation. We are currently in the later stages of preparing a revised draft guidance, and we hope to publish the revised draft guidance in the near future. All interested individuals and groups will have an opportunity to review and comment on the revised draft guidance before FDA issues any final guidance.

Question. How many facilities are registered as dietary supplement manufacturers with FDA through biannual registration as required by the Food Safety Modernization Act?

Answer. As of March 2, 2016, there are a total of 12 744 (6,522 domestic and 6,222 foreign) facilities that have selected food product categories that indicate that they manufacture/process, pack, or hold dietary supplements. Of this total, 7,164 (3,876 domestic and 3,288 foreign) registrations were renewed during the 2014 Biennial Registration Renewal period (October 1, 2014 through December 31, 2014). Under current food facility registration regulations at 21 CFR 1.233(g), the type of activity conducted at a facility is optional information and is not required to be submitted with a registration submission; therefore not all registrations include this information. Currently, there are a total of 4,953 (1,482 domestic and 3,471 foreign) facilities that manufacture/process, pack, or hold dietary supplements that have provided activity type information identifying themselves as "manufacturers/processors."

OVER-THE-COUNTER ANTISEPTICS

Question. The Food and Drug Administration (FDA) is currently re-writing the 1994 tentative final monograph for over-the-counter (OTC) antiseptics. In the 1994 tentative final monograph, FDA delineated several categories associated with antiseptic hand washes, including one specific to food handlers and recognized that different categories of users need different regulatory treatment due to the possible risk to public health (78 Fed.Reg.76444).

Does the FDA intend to recognize the different categories associated with antiseptic hand washes included in the 1994 tentative Final Monograph?

—If not, does FDA intend to include food handlers as a part of the 2013 Consumer Hand Wash Monograph?

—If so, does FDA intend to specify different regulatory conditions that would be associated with antiseptic washes used in the context of food preparation?

—And, if this is the case, does FDA intend to have a more substantive dialogue with stakeholders to ensure clarity about how the rule will be applied in the consumer and food preparation sectors?

Answer. In 1994, FDA identified a category of nonprescription (over-the-counter) antiseptics marketed for use in food handling and processing, and requested relevant data and information regarding these antiseptic products (59 FR 31402 at 31440). FDA continues to consider antiseptics for use by food handlers to be a separate and distinct monograph category from consumer antiseptic monographs, which are labeled and marketed for different intended uses and which raise different issues. The consumer wash rulemaking is not intended to affect products indicated for use by the food industry. In fact, the 2013 consumer antiseptic wash proposed rule specifically mentions that antiseptics for use by the food industry would not be discussed in that proposed rule (78 FR 76444 at 76446). We intend to consider over-

the-counter antiseptic products for use by the food industry separately from consumer wash antiseptics. FDA intends to communicate with stakeholders at the time of publication of the final rule on consumer antiseptic hand washes.

Question. If FDA does not intend to include food handlers in the final monograph, will it be explicitly stated in the regulation and material associated with its release in order to prevent confusion about what should or should not be used by food establishments?

Answer. In 1994, FDA identified a category of nonprescription (over-the-counter) antiseptics marketed for use in food handling and processing and requested relevant data and information regarding these antiseptic products (59 FR 31402 at 31440). FDA continues to consider antiseptics for use by food handlers to be a separate and distinct monograph category from consumer antiseptic monographs, which are labeled and marketed for different intended uses and which raise different issues. The consumer wash rulemaking is not intended to affect products indicated for use by the food industry. In fact, the 2013 consumer antiseptic wash proposed rule specifically mentions that antiseptics for use by the food industry would not be discussed in that proposed rule (78 FR 76444 at 76446). We intend to consider over-the-counter antiseptic products for use by the food industry separately from consumer wash antiseptics. FDA intends to communicate with stakeholders at the time of publication of the final rule on consumer antiseptic hand washes.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. In the Ag-Omnibus end-of-year funding bill for the FDA, we included language to have the compliance date for the FDA final menu labeling regulations be in-line with FDA completing and publishing final guidance that has been in the works for over a year. We thought it is only fair for those who are regulated to have the answers to their numerous questions/concerns, to allow them to forward and allow adequate time to properly comply with these regulations.

Can you tell us the status of the guidance?

Answer. On September 11, 2015, FDA issued the draft guidance for industry, “A Labeling Guide for Restaurants and Retail Establishments Selling Away-From-Home Foods—Part II (Menu Labeling Requirements in Accordance with 21 CFR 101.11).” FDA received a wide range of substantial comments from a variety of stakeholders. FDA is carefully considering all comments received as we work to finalize the guidance. We expect to publish the final guidance in the spring of 2016.

Question. Are you planning to incorporate some of the comments and provide some flexibility that many of the regulated establishments are seeking, into the final document?

Answer. FDA appreciates the extensive input received from stakeholders throughout the process of establishing requirements for menu labeling and in developing guidance to assist industry in complying with the regulations. The menu labeling regulations provide flexibility for covered establishments, such as the ability to choose among several options for determining calorie and other nutrition information for standard menu items. The draft guidance reflects the flexibility of the regulations. We are carefully considering the comments and will incorporate changes as appropriate. We will also work flexibly and cooperatively with establishments covered by the menu labeling final rule to facilitate compliance. We will provide educational and technical assistance for covered establishments and for our state, local, and tribal regulatory partners. We believe this cooperative approach will facilitate successful implementation in a practical way.

Question. I am concerned that many believe the industry has been the only reason for the delay in the menu labeling implementation. Do you agree that the FDA had a predominant role in the delay? The FDA took 3½ years to finalize the regs (April 1, 2011 Proposed Rule followed by Dec. 1, 2014 Final Rule) and then another 10 plus months to issue draft guidance when the FDA itself could not answer the questions from the regulated businesses such as grocery stores and others?

Answer. The successful development and implementation of a complex rulemaking such as menu labeling requires sustained dialogue and close collaboration with the affected industry and other key stakeholders. We recognize that implementing menu labeling requirements nationwide in a collaborative manner has taken a significant amount of time and resources.

As we developed the menu labeling rule, we became increasingly aware of the complexity of the American retail food industry, particularly with respect to foods prepared away from home. FDA received a wide range of substantial comments on the proposed rule from consumers, various food industries, trade associations, and other key stakeholders.

As we move toward implementation, to assist stakeholders with further understanding the menu labeling requirements we have been meeting and will continue to meet with industry groups to discuss the requirements. We will also continue to provide webinars and presentations and respond to industry questions submitted to the Agency's menu labeling inbox. We will work flexibly and cooperatively with establishments covered by the menu labeling final rule to facilitate compliance. We will also provide educational and technical assistance for covered establishments and for our state, local, and tribal regulatory partners. We believe this collaborative approach will facilitate compliance with the requirements in a flexible and practical way.

As you know, the House passed legislation to make some changes to the FDA menu labeling regs so certain entities would have a better opportunity to implement and comply with these regulations. I was joined by Senator King in introducing the Senate companion bill. The bill does not exempt supermarkets, convenience stores, or delivery operations from the menu labeling regulations, but allows some practicality for providing nutritional information to customers based on the different ways that foods are prepared and sold across various venues and formats.

For instance, the House passed bill has provisions such as:

- Preserving local foods or fresh items that may only be sold at one or two store or restaurant locations.
- Allowing for use of a menu or menu board in a prepared foods area or next to a salad bar instead of individually labeling every item
- Allowing an establishment 90-days to take corrective actions to fix an error and clearly stating that oversight authority rests with FDA (and states/municipalities that work with FDA) ;
- Allowing items that are normally ordered off-premises (pizza delivery) to have nutritional information posted as the ordering decision is made online as a means for compliance.

None of these provisions impact FDA's oversight or enforcement authority and no entity that is currently regulated under the menu labeling regulations would be exempt.

Question. FDA did not provide flexibility in these areas in the draft guidance that the agency released last September. Are there any provisions in this bill that FDA is planning on adopting as part of this final guidance you are working on?

Answer. FDA's menu labeling draft guidance reflects the Agency's current thinking on the menu labeling regulation (21 CFR 101.11) and does not impose new requirements. Rather, the draft guidance explains the Agency's interpretation of the regulation and contains recommendations for ways that industry can meet the menu labeling requirements. Industry may use other approaches that satisfy the regulations.

We understand that H.R. 2017, referred to as the "Common Sense Nutrition Disclosure Act of 2015," is still under consideration in Congress. If this bill, as currently written, should become law, FDA would have to engage in rulemaking to amend the current requirements and revise any associated guidance.

QUESTIONS SUBMITTED BY SENATOR STEVE DAINES

FDA FINAL RULE DEADLINES AND MARKET STABILITY LEAD-IN:

Question. On May 1, 2015, the FDA published a Proposed Rule to be added to their 1994 Tentative Final Monograph (TFM) for Healthcare Antiseptics. Yet, the FDA as indicated that this proposed rule will not be finalized until January 2018, despite having received significant public input and concerns with the proposed rule. This delay has left companies in limbo, not knowing whether their new products will need to meet a coming finalized rule to enter the market or for existing products to remain on the market and whether that finalized rule will address their concerns. As an example, this turbulence in the market has caused a 25 percent revenue reduction in 2015 for BioScience Laboratories, a Montana company, and they are currently facing additional staff reductions.

Mr. Commissioner, will the FDA continue to delay addressing concerns with this proposed rule regarding the 1994 Temporary Final Monograph (TFM) for Healthcare Antiseptics and continue to delay publishing a final rule?

Answer. In 1994, FDA published a proposed rule with the agency's tentative determinations as to which ingredients were generally recognized as safe and effective for use in nonprescription antiseptics. Since 1994, FDA's safety standards, our ability to detect and measure antiseptics in the body, and the scientific knowledge about the impact of widespread antiseptic use have evolved. For the past several years,

FDA has been actively engaged in this issue. In 2005 and again in 2014, FDA sought the advice of an FDA advisory committee made up of outside scientific and medical experts. As you know, on May 1, 2015, we published a healthcare antiseptics proposed rule (HCA PR(80 FR25166), which is part of a larger, ongoing review of antiseptic active ingredients by FDA. The HCA PR proposed that all active ingredients used in healthcare antiseptic products marketed under the OTC drug monograph system need additional safety and effectiveness data. In doing so, it proposed to revise certain testing criteria, identified important scientific data gaps for active ingredients used in certain over-the-counter healthcare antiseptic products, and requested additional data to support the ingredients' safety and effectiveness.

Because of the complexity of the HCA PR, FDA provided a public comment period of 180 days after publication, which closed on October 28, 2015. Moreover, the public and regulated industry had 12 months after publication of the proposed rule, or until April 30, 2016, to submit data or new information. Responsive comments on any new data or information may now be submitted for an additional 60 days, until June 30, 2016. Upon the close of the final comment period, FDA will review all data and information submitted to the record in order to complete a final rule. FDA intends to issue the final rule on healthcare antiseptics by January 15, 2018, which is approximately 18 months after the final comment period closes.

FOLLOW-UP

Question. Additionally, will you commit to reducing market turbulence to the full extent possible by preventing such delays in addressing public concerns with proposed rules and publishing final rules in a timely manner, as well as clearly indicating when those final rules will go into effect?

Answer. Senator, we understand your concerns. However, because of the complexity of the healthcare antiseptics proposed rule, FDA provided a public comment period of 180 days after publication, which closed on October 28, 2015. Moreover, the public and regulated industry had 12 months after publication of the proposed rule, or until April 30, 2016, to submit data or new information, and comments on any new data or information may now be submitted for an additional 60 days, until June 30, 2016. Upon the close of the final comment period, FDA will review all data and information submitted to the record in order to complete a final rule. FDA intends to issue the final rule on healthcare antiseptics by January 15, 2018, which is approximately 18 months after the final comment period closes. In the proposed rule, FDA proposed that any final rule would become effective 1 year after the date of the final rule's publication in the Federal Register.

Notice and comment rulemaking is a lengthy and multistep process. Major steps for FDA rulemaking generally include determination that a rule is needed and what the rule should say; review of relevant data; drafting, reviewing, and finalizing the proposed rule; publishing the proposed rule; a public comment period and review of the comments; revising the proposed rule as appropriate; possibly convening an advisory committee meeting, meeting with interested parties, or both; reviewing the draft final rule and finalizing it, and publishing the final rule in the Federal Register.

Even while FDA is moving forward to finalize the healthcare antiseptic rule, FDA has a very broad mandate and multiple public health priorities, with limited resources to address these priorities. FDA's Center for Drug Evaluation and Research (CDER) is responsible for regulating the safety and efficacy of both prescription and nonprescription human drugs. Like FDA as a whole, CDER must continually balance multiple important public health priorities, of which the OTC Drug Review, which includes healthcare antiseptics, is one. CDER does, and will continue to, consider the OTC Drug Review, and the antiseptic rulemakings in particular, among its priorities as it endeavors to appropriately allocate staff and resources within the context of all CDER responsibilities.

QUESTIONS SUBMITTED BY SENATOR JEFF MERKLEY

TOBACCO

Question. The longer the tobacco deeming regulation takes, the more attempts there will be to include things like the House's language last year, which would have changed FDA's deeming date, and kept e-cigarettes essentially unregulated.

What effect the House's provision last year would have had on access to tobacco products, and the deeming regulation?

Answer. This language contained in last year's House bill aimed to treat newly deemed products in a way roughly modeled on how the TCA treated newly regulated

products when the law was enacted. Specifically, the grandfather date of February 15, 2007, would be changed to the effective date of the deeming final rule, and new tobacco products introduced between the new grandfather date and 21 months afterwards would be permitted to stay on the market as long as an SE report was submitted by the end of the 21 month period. This proposed language would have eroded FDA's ability to regulate certain tobacco products to protect public health. Specifically, the House bill would exempt from FDA review those tobacco products that were marketed before the effective date of the deeming final rule. As a result, these products, including currently marketed flavored e-cigarettes, and novel tobacco products like certain dissolvables, would have been allowed to stay on the market indefinitely without oversight or a scientific evaluation of their risks, potentially threatening public health. Those tobacco products that come on the market after the 21 month transition period would be subject to FDA's premarket authority and would need a marketing order before being sold.

OPIOIDS

Question. FDA has been under fire recently for approving opioids without convening, or against the recommendations of, your advisory panels, especially when the pills are flooding the market. In response, the Agency recently announced a series of steps including re-examining the "risk-benefit" paradigm for opioids to consider public health effects; convening an advisory panel for any new opioids that don't have abuse deterrent properties; and adding additional warnings on labels, among other things.

Could you walk us through each of these decisions and the outcomes you expect they will provide? Specifically, on the risk-benefit paradigm, what will FDA consider that it wasn't already—addiction potential, number of opioids already on the market, anti-deterrence methods?

Answer. These actions are part of a number of actions the Agency outlined in a plan to reassess the approach to opioid medications announced in February. The plan is focused on policies aimed at reversing the epidemic, while still providing patients in pain access to effective medication. This comprehensive action plan will help to mitigate the problem of opioid abuse and confront the epidemic. There are four main pillars to the plan described below.

- Transparency: FDA will be more transparent and open in the approval process for this category of drugs. FDA plans to convene an expert advisory committee before approving any new drug application for an opioid that is not in an abuse-deterrent formulation (ADF). Additionally, we're going to engage the Pediatric Advisory Committee to make recommendations on pediatric opioid labeling before any new labeling is approved. The advisory committee process is going to provide opportunity for public input, which is going to help us better understand and answer the concerns people have about these drugs.
- Improving Communication: Requiring labeling changes and updates to Risk Evaluation and Mitigation Strategies (REMS), FDA hopes to improve communication with the medical community about opioids. Through labeling, our goal is to provide better information to doctors about the risks of these drugs and how to safely prescribe them. In March 2016, FDA released new labeling changes to immediate release opioid labeling that incorporate elements similar to the labeling of the extended-release/long-acting opioid analgesic products. In addition, FDA will evaluate updates to our Risk Evaluation and Mitigation Strategy (REMS) program requirements for opioids with the goal of increasing the number of prescribers who receive training on pain management and improve the safe prescribing of opioids to decrease inappropriate prescribing. That effort will complement work being done at the Department level and at the CDC to help ensure that opioids are prescribed appropriately. We believe that improving prescribing practices is a key component of ending this public health crisis. The nearly 250 million prescriptions for these types of pain killers written each year—enough for every adult in the U.S. to have a bottle of pills—is clear evidence of the work ahead of us.
- Post Marketing: FDA recently strengthened the requirements for drugmakers to conduct post-market analysis of opioid analgesics. This information, especially about long-term use, is currently lacking and we need more and better evidence on the risks of misuse and abuse associated with long-term opioid use and to better understand predictors of addiction, among other issues.
- Product Development: In March, the FDA issued draft guidance with its recommendations for studies that should be conducted to show that a generic copy of a brand-name abuse-deterrent opioid formulation is as abuse-deterrent as the brand-name drug. We believe the availability of less costly generic products

with abuse-deterrent properties may help accelerate prescribers' uptake of abuse deterrent formulations. In addition, FDA is working to improve access to naloxone, which is effective at treating overdoses. The FDA is reviewing options, including the possibility of over-the-counter availability, to make naloxone more accessible.

Question. Is there anything FDA could do to try to curb the number of pills that doctors prescribe, such as shortening the standard course of treatment for acute injuries, so there aren't as many pills left over?

Answer. There is no standard course of treatment for acute injuries described in labeling for opioid analgesics. That is because the duration of treatment will vary depending on the type of injury. It is generally left to the discretion of the treating healthcare provider to decide how many pills to prescribe once the decision has been made to prescribe an opioid analgesic.

Question. FDA has contributed significantly to improving the safety and safe use of opioid analgesics. We are continuing our work to ensure prescribers have the information they need to understand the risks associated with opioid analgesics, as evidenced by the recently announced sweeping changes FDA is requiring to the immediate-release (IR) opioid analgesic labeling, which include safety-related information similar to that added to the extended-release and long-acting (ER/LA) opioid analgesic labeling in 2014. FDA is also requiring changes to the indications for these products to better emphasize that opioid analgesics should be prescribed in situations where non-opioid analgesics are not adequate. Further, the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) requires that drug sponsors make available prescriber education to better inform healthcare professionals about the risks and appropriate use of these drugs. It is the Agency's hope that the significant actions it has taken, along with broader Departmental efforts, will lead to more careful and thoughtful prescribing, and more appropriate use of these drugs.

What role does FDA play in educating doctors and pharmacists about the risks of these drugs?

Answer. The primary tool FDA uses to educate doctors and pharmacists about the risks of prescription drugs, including opioids, is the FDA-approved product labeling. The purpose of the drug labeling is to give healthcare professionals the information they need to prescribe drugs appropriately; to understand the patients for whom the drugs are considered safe and effective; the way the drugs are intended to be used; and the risks and benefits associated with their use. In April 2014, FDA finalized sweeping changes to the labeling for extended-release and long-acting (ER/LA) opioid analgesics to help prescribers better understand the risks of misuse, abuse, neonatal opioid withdrawal syndrome, addiction, overdose, and death associated with these drugs and to more clearly describe the patient population in whom these drugs should be used. On March 22, 2016, FDA sent letters to sponsors of immediate-release (IR) opioid analgesics requiring changes similar to those finalized for the ER/LA opioid analgesics in 2014. These changes to the labeling, once finalized, are expected to emphasize that opioid analgesics should be prescribed only when other treatment options are inadequate or ineffective. For both ER/LA and IR opioid analgesics, the new labeling better enables prescribers to make decisions based on a patient's individual needs, given the serious risks associated with opioids. FDA intends these changes to enable not only a more careful and thorough approach to determining whether opioid analgesics should be prescribed for a particular patient, but also to allow prescribers to better assess whether the serious risks associated with opioids, are offset by the benefits opioids may provide in managing pain for an individual patient.

FDA also uses other tools to educate prescribers about opioid risks. For example, the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy, approved in 2012, requires manufacturers of the ER/LA opioid analgesics to make available, for free or at nominal cost, education courses from for healthcare professionals who prescribe ER/LA opioid analgesics. These continuing education courses educate prescribers about the risks of these opioid analgesics, as well as safer prescribing and use practices for these drugs. Manufacturers of ER/LA opioid analgesics are also required to conduct an assessment of the REMS and submit a REMS assessment report to the Agency for review. On May 3-4, 2016, FDA convened a joint session of the Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees to discuss the results of the 36th month ER/LA Opioid Analgesics REMS Assessment submitted by the manufacturers of the ER/LA opioid analgesics in July 2015. The Agency sought the committees' comments as to whether the REMS for this class of drugs assures safe use; is not unduly burdensome to patient access to the drug; and, to the extent practicable, minimizes the burden to the healthcare delivery system. In addition, the Agency sought the committees' com-

ments on any modifications to the ER/LA Opioid Analgesics REMS, including possible expansion of the scope and content of prescriber education, and whether to expand the REMS program to include immediate-release opioids. FDA is evaluating potential modifications to the REMS program requirements for opioids after considering advisory committee recommendations and reviewing existing requirements.

In addition, the Agency utilizes publications such as drug safety communications (DSCs) to inform prescribers and patients of safety issues that should be considered when prescribing and using these drugs. For example, on March 22, 2016, FDA issued a DSC regarding risks of serotonin syndrome for some opioids, and for adrenal insufficiency and androgen deficiency for all opioids, regardless of indication. Further, FDA officials recently published a note in the *Journal of the American Medical Association* expressing the Agency's dedication to improving the safety of these drugs, and setting forth the Agency's plan to achieve this goal in the coming months.

Question. Why not require an advisory panel for all new opioids, whether or not they have an abuse deterrent formula?

Answer. Seeking advice from external experts on matters related to opioids, including related to this emerging area of science, is a cornerstone of the FDA's 2016 Opioids Action Plan. While we're continuing to learn more about the impact that approved abuse-deterrent (AD) products are having in the community, and supporting research and development of additional technology, the agency plans to seek advisory committee recommendations on new, non-AD brand-name products, and on new AD brand-name products when they raise novel issues. We hope that this public discussion will allow for greater transparency around the FDA's decisionmaking regarding opioid products during this period of reassessment of our policies and regulatory approach to opioids. Judicious use of Advisory Committees is grounded in the recognition that advisory committee meetings demand significant resource commitments by advisory committee members, sponsors and other public participants, as well as for the FDA itself. FDA works to ensure that the finite resources of its advisory committee program are devoted to consideration of the matters in which the agency would most benefit from the advice of outside experts.

Question. Are there new abuse deterrence methods on the horizon?

Answer. Ultimately, the FDA looks forward to a future in which substantially all opioid medications are less susceptible to abuse than the conventional formulations that dominate the market today. However, we are still in the early stages of abuse-deterrent product development—the market has a small number of products using abuse-deterrent technologies, and the agency is assessing each opioid drug product's safety and efficacy on a case-by-case basis. Since the draft guidance on the evaluation and labeling of abuse-deterrent opioids was issued on January 9, 2013, the FDA has approved six extended-release long-acting opioids with labeling describing the product's abuse-deterrent properties consistent with the draft guidance: OxyContin (April 16, 2013); Targiniq ER (July 23, 2014); Embeda ER (October 17, 2014); Hysingla ER (November 20, 2014); MorphaBond (October 2, 2015); and Xtampza (April 26, 2016).

The abuse-deterrent properties of those six products are based on data and described in terms consistent with those set forth in the FDA's 2015 guidance on the topic, Abuse-Deterrent Opioids—Evaluation and Labeling. FDA is prohibited by law from disclosing confidential information about unapproved applications (e.g., 21 CFR 314.430) and is therefore unable to comment on drugs in development or in the FDA review process. Further, consistent with longstanding Agency practice, we do not discuss the substance of any matters pending before the Agency. However, FDA expects these technologies to improve and expects products containing abuse deterrent properties (both innovator and generic) to become more widely available.

Abuse-deterrent does not mean abuse-proof. Abuse-deterrent opioids are intended to deter abuse by making the products less vulnerable to attempts to manipulate the product for abuse by the oral, nasal, or intravenous routes. However, the products must be able to deliver the opioid in order to provide analgesia and so will remain susceptible to abuse to some extent.

While FDA is gathering data on the impact that approved ADFs are having in practice, and supporting research and development of additional ADF technology, the agency is also asking for advisory committee recommendations on all new non-ADF products to determine whether the benefit of non-AD products continues to offset the risks. FDA hopes that this public discussion will allow for greater transparency around the agency's decisionmaking regarding opioid products during this period of reassessment of our policies and regulatory approach to opioids.

FOOD SAFETY MODERNIZATION ACT

Question. The budget request for FSMA implementation is modest, to say the least. Last year, when FDA's budget was submitted, I was very appreciative that it finally included a realistic request to implement FSMA, and not one that relied on user fees that didn't stand a chance of happening. Congress took that request very seriously and provided full funding—so you know what our commitment is.

Even then, according to FDA's own documents—there was still going to be a funding gap of approximately \$166 million needed to successfully implement FSMA. So in a lot of ways, this budget request feels like a step backwards, even though I know we are all in agreement that FSMA has to be done right.

What happens, or does not happen, if you get exactly what you ask for in budget authority, and no new user fees? How much additional funding, no matter the source, would be a responsible level this year to continue to fully support FSMA implementation?

Answer. The fiscal year 2017 President's Budget includes a total of \$1.5 billion in proposed resources for food safety. The budget would increase food safety funding by \$211.6 million over fiscal year 2016. Specifically to support FSMA implementation, the budget proposed an increase of \$25 million in budget authority. The budget also includes two key proposed user fees to support implementation, an import user fee (\$105.3 million) and food facility registration and inspection fee (\$61.3 million). The sum of these increases represents the total resources needed for FDA to effectively implement FSMA. For example, if FDA does not receive the additional integrated food safety funds requested, we will have to reduce our planned support of State produce safety regulatory programs aligned with FDA's Produce Safety rule. It would in turn hamper education and outreach efforts to farmers.

Question. The biggest part of your proposed increase is \$11.3 million for cooperative agreements and grants to implement the produce safety rule. While state and local efforts are no doubt critical, it's concerning that there is no money to train FDA staff. Was the money provided last year for this effort enough? Are FDA staff fully trained and prepared for this entirely new way of doing business?

Answer. Training on the Produce Safety rule will be very important for both FDA and State regulators, as FDA will be working collaboratively with the National Association of State Departments of Agriculture and our State, local, and tribal partners to implement a produce safety regulatory program. Fiscal year 16 investments support ongoing work on training plans and materials for the Produce Safety Alliance pre-requisite training; the Produce Safety Regulator Training will be developed and delivered to FDA and State personnel beyond fiscal year 16. As compliance requirements phase in, additional FDA and State personnel will be identified for training.

Question. Enforcement of the both Preventative Control for Human and Animal Foods rules begins in September of this year, but guidance documents, which are important for industry to understand what's expected of them, haven't been published yet. When do you expect to publish them, and how long will that process take? Does FDA, and in turn the states and localities, have everything needed to begin enforcement of this rule, in a consistent way?

Answer. FDA is currently developing guidance documents related to the key FSMA rules, including the preventive controls rules for both human and animal food. These documents are part of a broader effort to foster and support compliance that also includes outreach; education and training programs, particularly for small and mid-sized firms; and FDA's Technical Assistance Network, through which regulated industry and other members of the public can get answers to specific questions about how the rules apply. The outreach and guidance development process will continue for years to come, but our goal is for key draft guidance documents to be available before the applicable compliance dates.

We are currently on track to issue draft implementation guidances on preventive controls for human food and on Current Good Manufacturing Practices for animal food in the coming months. Additional draft guidance documents on specific hazards and controls are on target for issuance later this year.

We are working with our state, local, and tribal partners to ensure that the new FSMA rules are implemented consistently and in a manner that encourages voluntary compliance. Adequate funding will help ensure the success of these efforts.

Question. Funding was provided to train approximately 1,000 state and local inspectors in fiscal year 16 or about 20 in each state. More than 3,000 state, local and tribal entities will be involved in FSMA implementation. How many additional people will be trained this year?

Answer. FDA's regulator training is being phased in over 3 years based on the staggered compliance dates in the Preventive Controls for human food rule, with a

focus on large firm inspections in year 1 (fiscal year 2017). FDA is on target to train 2,000 FDA and State food safety staff in 2016 in the Food Safety Preventive Controls Alliance Human and Animal Food courses, as a pre-requisite to the Preventive Controls regulator courses. In addition, the 2,000 FDA and State food safety staff will also receive modernized Good Manufacturing Practice (GMP) training for human food facilities and new GMP training for animal food facilities. In fiscal year 2016, FDA's Preventive Controls regulator courses will be offered to the subset of the 2,000 FDA and State food safety staff that will cover the large firm inventory. Food Safety staff is defined as investigators/inspectors, managers, compliance officers and Subject Matter experts, in both FDA and State.

Question. The budget also proposes \$14 million to implement the Foreign Supplier Verification Rule, which is vital considering that food imports continue to grow. The first enforcement of this rule is slated to begin in early 2017, although that timeline varies. Will this request be enough?

Answer. In fiscal year 2017, FDA is proposing an additional \$14 million in budget authority to support the Foreign Supplier Verification Program (FSVP). FDA would use these additional resources to hire staff to perform FSVP inspections, provide training and technical assistance to FDA staff and importers, and continue outreach on the new FSVP requirements.

Since FSVP is an entirely new program, FDA will need to assess the need for additional resources when we have more experience with the inventory of importers subject to FSVP and compliance rates.

GENETICALLY MODIFIED SALMON

Question. Obviously, I was concerned for multiple reasons when the FDA approved GMO salmon last year to go into our food supply. First, I have grave concerns about what will happen when one of these fish is inadvertently released, and second, I am concerned that it won't be labeled as GMO. So I worked to include language in the Omnibus to keep the salmon out unless it was labeled or FDA published final labeling guidance. In response, FDA issued an import alert to hold any GMO salmon at the border, or return it.

To my first concern, how is FDA planning to work with the fish producers to make sure that none of these fish actually make it into the wild stock and do irreparable harm to the environment for native salmon?

Answer. The approved application pertaining to AquaAdvantage Salmon provides for specific conditions including that the GE salmon will be raised only in the two land-based, contained facilities in Canada and Panama that are described in the application. Under this approval, no other facilities or locations, in the United States or elsewhere, are authorized for breeding or raising AquaAdvantage Salmon. There are no additional "fish producers" who may raise these salmon. As the sponsor and new animal drug application (NADA) holder, AquaBounty is the sole "fish producer" under the approved application.

In terms of assuring that the GE salmon do not escape the two facilities allowed under the application, the facilities in Canada and Panama have a series of multiple and redundant levels of physical barriers to prevent eggs and fish from escaping. The facilities use land-based tanks—rather than ocean net pens, which are not allowed under the approved application. The first level of barriers (Primary Containment) includes items such as metal screens on tank bottoms, stand pipes, and incubator trays to prevent the escape of eggs and fish during hatching or rearing. Tanks also have covers, nets, jump fences, and screened overflow tanks to prevent escape over the sides of the tanks or incubators. Tank netting also keeps predators such as birds from entering the fish tanks at the outdoor facilities in Panama. All tank drains and stand pipes have covers or sleeves permanently attached to them. In order to prevent eggs or small fish from passing through the pipes or plumbing there is a closed septic system and additional screens and chlorine pucks are used to kill any escaped fish in the main drain area.

Several additional sets of barriers, also in series (Secondary, Tertiary, and sometimes Quaternary Containment), add increased physical security to these primary containment measures described above. These barriers are designed to prevent fish from entering the drainage system or sedimentation pools and the local river (in the case of the Panama facility) and include floor drain covers, barrier screens inside the drains, drum and sock filters, and a series of sedimentation ponds with outlet filters.

To augment physical containment, strict security measures and equipment are in place at both facilities. This includes locked gates for entry and exit to the properties, the presence of guard dogs, perimeter fences with barbed wire, and monitoring systems.

In addition to these physical containment measures, the approval also includes biological containment measures: producing only one sex of fish and making the female fish sterile via triploidy induction (a method used in finfish and shellfish to prevent their sexual maturation and make them sterile).

To ensure that AquaBounty maintains these physical and biological containment measures, they must follow record-keeping and reporting requirements, including ensuring that the triploidy process is within specifications and monitoring physical containment, including reporting of any likely or actual breaches of physical containment.

Furthermore, even if AquaAdvantage Salmon could somehow escape and migrate to the Pacific Ocean, there is no reasonable potential for hybridization between escaped AquaAdvantage Salmon and native Pacific salmon, which are of a different genus, *Oncorhynchus*. Farm-raised Atlantic salmon on the west coast of the United States and Canada that have escaped in the Pacific Ocean have not interbred with wild Pacific salmon and, to date, there has been no compelling evidence of any colonization and establishment (i.e., self-sustaining populations) of Atlantic salmon in these areas.

As a result of these and other conditions included in the approval, there is a very low likelihood that AquaAdvantage Salmon could escape their conditions of confinement and, in the unlikely event they did escape, it is extremely unlikely that they would establish and reproduce conditions at the facility sites.

Question. Can you make a guarantee that these fish, grown in other countries, will be contained?

Answer. The approved AquaAdvantage Salmon application allows the GE salmon to be raised only in the two land-based, contained facilities in Canada and Panama that are described in the application. Additionally, these facilities are separately regulated by the relevant regulatory bodies in each respective country. Under this approval, no other facilities or locations, in the United States or elsewhere, are authorized for breeding or raising AquaAdvantage Salmon.

If other countries choose to produce GE salmon that will not enter U.S. commerce, those countries will regulate those facilities. FDA does not have jurisdiction to regulate products that are produced outside the United States and never enter the United States.

Question. As you know, FDA approved AquaBounty's production plan to produce GM salmon eggs in Canada and ship them to Panama for fish production. If the company wanted to grow the fish in the U.S., what steps would it have to take to gain FDA approval?

Answer. FDA's approval of the application pertaining to AquaAdvantage Salmon does not allow production and grow out of the salmon in any facilities other than those in Canada and Panama. If the sponsor proposes to begin producing GE salmon in the United States (or at additional locations outside of the United States with the intent to import food from them into the United States), it first must submit a supplemental new animal drug application to FDA for the new production facilities, and this supplemental application will require its own National Environmental Policy Act analysis of potential environmental impacts of those facilities.

Question. What repercussions will there be if there is an escape?

Answer. Under the FD&C Act, a new animal drug that does not comply with its approved application is considered "unsafe" and an unsafe new animal drug is "adulterated." 21 U.S.C. §§ 360b(a); 351(a).

The FD&C Act also deems adulterated any food that contains an unsafe new animal drug. 21 U.S.C. 342(a)(2)(C)(ii). FDA may take enforcement action against adulterated drugs and foods, including refusing admission to imported foods and drugs that appear to be adulterated.

Among the conditions included in the approval, AquaBounty must maintain physical and biological containment measures and report any likely or actual breaches of physical containment. If any such breach occurred in violation of a condition established in the approved application, AquaAdvantage Salmon would be deemed "unsafe" and adulterated under these provisions and, therefore subject to FDA enforcement action, including seizure of adulterated product.

QUESTIONS SUBMITTED BY SENATOR JOHN TESTER

PREMIUM CIGARS

Question. Given that premium cigars are enjoyed by adults in moderation, and are inherently less attractive to underage smokers than other tobacco products, how are

you taking into account the unique nature of cigars when promulgating tobacco regulations?

Answer. Although all cigars are harmful and potentially addictive, it has been suggested that different kinds of cigars (e.g., small cigars, cigarillos, large cigars, premium cigars) may have the potential for varying effects on public health if there are differences in their effects on youth initiation, the frequency of their use by youth and young adults, and other factors.

In the proposed deeming rule, FDA sought comment on two options for regulating categories of cigars: option one would deem all cigars subject to FDA's tobacco control authorities, and option two would exclude premium cigars. FDA also asked what additional restriction(s) may or may not be appropriate for different kinds of cigars.

FDA reviewed all comments, data, and information submitted to the docket regarding this matter, and will address the issue in the final deeming rule.

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

OPIOIDS

Question. I have for years pushed the FDA to promote safer alternatives to powerful prescription painkillers, and to remove from the market older, less safe drugs. The FDA's announcement last month to expand access to abuse-deterrent formulations of these powerful drugs is a step in the right direction in response to my concerns. However, the FDA can and must do more.

What plans do you have to ensure the FDA is doing everything in its power to help address the significant opioid crisis we are facing in this country?

Answer. Prescription opioids with abuse-deterrent properties will not fix the problem, but they can be part of a comprehensive approach to combat the opioid epidemic. While the FDA has a responsibility to regulate drugs and help educate prescribers, addressing this epidemic requires the collaboration of multiple Federal agencies, state governments, professional organizations, and other stakeholders.

FDA is changing the Agency's approach to opioid medications. The Agency's opioids action plan, announced on February 4, will focus on policies aimed at reversing the prescription opioid epidemic while still providing patients in pain access to effective relief. This plan includes concrete steps toward reducing the impact of opioid abuse on American families and communities. The plan includes a call for a re-examination of the risk-benefit paradigm for opioids, changes to immediate-release opioid analgesic labeling, improved access to naloxone, and new advisory committee meetings to provide recommendations on pediatric approval issues and any new opioid that does not have abuse-deterrent properties. The Agency will provide updates on progress with the goal of sharing timely, transparent information on a regular basis.

The Agency's action plan is part of the Health and Human Services (HHS) initiative to address the opioid epidemic which is working towards three broad goals: 1) opioid prescribing practices to reduce opioid use disorders and overdose 2) the expanded use of naloxone, used to treat opioid overdoses and 3) expanded use of Medication-assisted Treatment (MAT) to reduce opioid use disorders and overdose. Evaluation is a critical component of the initiative to identify what works and how the most effective interventions can be taken to scale.

FDA STANDARD FOR RAW MILK CHEESE

Question. I continue to be very worried about the potential impact that the FDA's non-toxicogenic E. coli standard for raw milk cheeses could have on cheese producers in Vermont and across the United States.

The FDA's move to a standard for non-toxicogenic E. coli that requires a thousand-fold decrease in the presence of non-toxicogenic E. coli in raw milk cheeses could severely limit the production of raw milk cheeses across the country. In December, I helped to lead a bicameral and bipartisan letter to your Deputy Commissioner for Foods and Veterinary Medicine, Mike Taylor, asking several specific questions about the new standard and how it was developed, but the agency's response did not specifically answer all of our questions.

In our letter, we asked whether the science upon which this standard is based has been subject to peer review. In response, the agency cited four different articles. While the articles do support the use of non-toxicogenic E. coli as an indicator organism for food safety, they do not recommend the same level that the FDA has called for in raw milk cheeses. The first citation offered does not even seem to be in line with the agency's new standard, with the abstract specifically stating that with re-

gards to raw cow milk samples, “No relationship was detected between *E. coli* or the total bacterial count and the presence of pathogenic bacteria.” In general, the scientific papers referenced do not seem to be particularly relevant to the issues laid out in our letter, with one article discussing the results from samples of raw milk in Malaysia. Therefore, I ask again:

Does the body of scientific evidence specifically support a thousand-fold decrease in the presence of non-toxicogenic *E. coli* in raw milk cheeses?

Answer. First, we would like to clarify that the decrease in the level of non-toxicogenic *E. coli* in cheeses in the Compliance Policy Guide (CPG) is not one thousand-fold, but instead is one hundred-fold, if one compares the maximum permissible levels. Prior to the 2010 revision of the CPG, if one sample had a test result of 10,000 cfu/g or greater, the product was considered violative. Under the current CPG also, if one sample has a test result of 100 cfu/g or greater, the product would be considered violative. Of course, there is a second criterion in the 2010 CPG, namely, 10cfu/g. However, under this criterion, multiple samples from the same lot of product would have to exceed it before the product would be deemed violative.

Regarding the references provided in the letter of Deputy Commissioner Michael Taylor, the references, including the abstract you quoted, were intended to show that there is support in the scientific literature for the use of non-toxicogenic *E. coli* as an indicator of fecal contamination and insanitary conditions of production. For the 2010 CPG, we relied on the available peer reviewed literature (over 70 scientific papers), which showed that non-toxicogenic *E. coli* is generally not present in raw milk, and that when it is present, it is usually at very low numbers, i.e. <100 cfu/g. The literature also shows that the cheese making process, coupled with aging, substantially reduces any non-toxicogenic *E. coli* present. With this information, we concluded that there should not be *E. coli* in cheese unless the milk used was of poor quality, or the cheese was produced under unhygienic conditions. This conclusion has been supported by the results of our 2014–15 cheese sampling program in which the vast majority of 1606 raw milk cheese samples met the 2010 criteria.

That said, as you may be aware, we have paused our testing for non-toxicogenic *E. coli* in cheese as we take another look and engage stakeholders regarding what role this indicator organism should have in identifying insanitary conditions and process failures for both domestic and foreign cheese and how the results of such testing may be used in support of preventive measures. We intend to further engage our stakeholders in the artisanal sector and scientific experts in dialogue on this issue. We will seek public comment on such issues as the use of a single bacterial criterion for both pasteurized and raw milk cheese, and the appropriate use(s) of non-toxicogenic *E. coli* as an indicator organism in pasteurized and raw milk cheese. Based on this dialogue and input, we will consider and make changes in the 2010 CPG as appropriate.

FDA STANDARD FOR RAW MILK CHEESE

Question. There is a strong desire for transparency in rulemaking and in the process that leads to policy change. I feel strongly, as do our cheesemakers and food safety advocates, that science and data must guide these decisions. The American Cheese Society has requested data to be released on the FDA’s raw milk sampling program. I have been told that your staff had initially agreed to share that data. Transparency in this case, and access to this data, could help American raw milk cheesemakers determine if and where changes need to be considered to ensure the production of safe cheese. Access to this data would also help to educate producers and inspectors to ensure that they are working together to continually enhance public health and welfare.

Has the FDA been working to respond to the American Cheese Society’s request for data? And if so when can they expect the FDA to finally release the data they had been promised?

Answer. The FDA received a request from the American Cheese Society, dated February 22, 2016, for data from the Listeria Environmental Sampling Program and the Raw Milk Cheese Program. We are diligently working to compile the requested information. The request is currently being processed under the Agency’s Freedom of Information Act program. In addition, an external report is being prepared for stakeholders that will discuss the results of the FDA’s fiscal year 2014/15 surveillance sampling assignment on raw milk cheese.

GENERIC COMPETITION/PHARMACEUTICAL PRODUCTS SUBJECT TO A REMS

Question. An essential step for generic drug manufacturers seeking to create a low-cost generic drug is to obtain samples of the brand-name drug they wish to replicate so they can conduct bioequivalence and other testing for FDA approval. Unfor-

unately, some brand-name companies appear to be impeding generic competition by refusing to provide such samples, either by imposing their own restrictions, or by claiming that distribution of their product is prohibited because of an FDA-approved safety protocol known as a “REMS”.

Additionally, some brand-name companies appear to be impeding generic competition by refusing to work with potential generic competitors to develop a single, shared safety REMS which in certain cases the FDA requires prior to approving the generic product.

Federal law expressly bars pharmaceutical companies from using REMS restrictions to block generic competition. Furthermore, in December 2014, the FDA issued guidance describing a process the Agency has developed to reassure brand-name drug companies that providing sample product to a generic competitor would not violate a REMS. Nevertheless, numerous generic companies continue to report difficulties in obtaining samples or negotiating a single, shared REMS, thus foreclosing competition.

In your experience, are some brand-name companies engaging in the practices described above, even after the adoption of FDA’s December 2014 protocol?

Answer. Yes. FDA has received more than a hundred inquiries from generic companies that want to develop generic drugs but tell us they are unable to because they cannot get access to supplies of the reference listed drug (RLD) to do testing. This is a problem that affects both REMS drugs and non-REMS drugs: in fact, the number of non-REMS products about which we have received these inquiries is actually larger than the number of products subject to REMS about which we have received inquiries.

The problem often arises when generic companies are not able to get access to the RLD through normal distribution channels (i.e., via wholesalers) because limitations on the distribution of the drug are in place. The brand company might limit the distribution of the product on its own initiative for a variety of different business reasons (for example, by selling through a central or small group of pharmacies, some of which may identify themselves as specialty pharmacies). For drugs with a REMS, an element to assure safe use (such as a pharmacy certification requirement) might impact the way the product is distributed.

We understand that some brand companies have refused to sell the RLD to generic companies for testing or have included provisions in their contracts with pharmacies/third parties that prohibit the sale of the RLD to generic companies for testing purposes. We have referred such matters that have been brought to our attention to the Federal Trade Commission (FTC) and encouraged generic companies to also raise these matters with the FTC. We have taken a number of additional steps as well.

Some brand companies have argued that selling the RLD to the generic firm for testing/development would be a violation of their REMS. To address this, we have developed a process, where appropriate, for informing the brand company in writing that FDA will not consider provision of the RLD for these purposes to be a violation of the REMS. We do this by reviewing the bioequivalence study protocols of companies that want to develop generic versions of these REMS drugs to assess whether their protocols have safety protections comparable to those in the applicable REMS. If we determine that they do, we send the brand company a letter stating so and informing them that selling the RLD to the generic company for testing and development will not be considered a violation of the REMS. (This process is described in the December 2014 draft guidance referenced in this question).

However, while these letters make clear that such sales will not subject the brand company to REMS-related enforcement action, some brand companies have argued that they have independent business reasons for not selling the RLD to the generic firm that are unrelated to their REMS and/or that they have no obligation to do so.

Finally, we note that we also continue to have concerns about brand companies blocking or delaying approval of generic drugs using the single, shared system REMS requirement. This is a separate problem from the RLD access issue described above. The development of a single, shared system (which is mandated by the Federal Food, Drug, and Cosmetic Act for REMS that include certain elements, unless FDA waives the requirement for one of the reasons set forth in the Act²) necessitates discussion and negotiation between the competitor brand and generic company and agreement on the terms of the single shared system REMS and how it will operate before the generic product can be approved. Brand companies therefore have an incentive to delay generic competition for their products by refusing to agree to single, shared system REMS terms and otherwise prolonging the negotia-

²Section 505-1(i)(1)(B)

tions over a single, shared system REMS. We see prolonged negotiations and inability to agree on the terms of a single, shared system REMS regularly.

Question. If yes, would additional tools or legislative changes assist the Agency or other entities in addressing such behavior?

Answer. The Administration has not taken a position on pending legislation in this area.

Question. Could such practices be further addressed by creating a specific cause of action for generic manufacturers to sue in court to obtain the samples they need and/or to secure good faith and timely negotiation on developing a single, shared system of distribution for products that are subject to a REMS?

Answer. The Administration has not taken a position on pending legislation in this area.

Question. How long does the FDA's process normally take to review and approve a generic company's REMS protocol, and are there steps FDA could take to expedite this review?

Answer. The timing of the review of bioequivalence study protocols for drug products subject to a REMS with elements to assure safe use varies based on several factors. These protocols require review by the two separate divisions within the Office of Generic Drugs' (OGD's) Office of Bioequivalence: the Division of Bioequivalence and the Division of Clinical Review. Because review staff in these divisions must prioritize workload to accommodate projects with GDUFA goal dates, the timing of protocol review therefore depends on the complexity of the protocols, the size of the queue, and competing workloads.

OGD has taken a number of steps to streamline and shorten the process for submission and review of bioequivalence protocols. The December 2014 draft guidance described above provides step-by-step guidance to prospective generic applicants on how to submit these protocols and what to include in them. This draft guidance was issued in order to streamline the process, improve the quality of submissions received by the Agency, and thereby reduce review time. OGD has also assigned dedicated staff to coordinate the review of these protocols across the different OGD offices and divisions. OGD continues to evaluate the protocol review process and engage in process refinements and improvements where possible to assure timely and efficient protocol reviews.

LABELING OF GENERIC DRUGS

Question. In 2013, the FDA issued a proposed rule that would ensure that generic drug companies can update their safety labels when they learn new information. This proposed rule is tremendously important because more than 80 percent of consumers take the generic version of a drug when it is available. We need generics to be able to improve their labeling, and be held accountable when they fail to do so.

Unfortunately, the FDA's proposed rule remains caught up in regulatory limbo. Last year, the FDA reopened its rulemaking to consider an industry-backed alternative that would turn existing labeling rules on their head. The industry proposal would ensure that after a generic drug enters the market, no drug company could update its label immediately upon learning of adverse side-effects. Labeling updates would be delayed, and drug companies could not be held accountable if they failed to update their safety information.

One of my constituents, Diana Levine, was able to seek justice after she was injured by a mislabeled drug precisely because of the rules the drug companies are now trying to overturn.

I am gravely concerned by the drug companies' proposal. I am also concerned by the FDA's delay in completing the rulemaking on its initial proposal, which is widely supported by patient groups and safety advocates.

The Unified Agenda for Regulatory and Deregulatory Actions currently states a release date for the final rule of July 2016, following several previous postponements. Is the rule on track to be released at that time?

Answer. The proposed rule is intended to improve the communication of important drug safety information to healthcare professionals and patients. FDA has received a great deal of public input from stakeholders during the comment periods on the proposed rule regarding the best way to accomplish this important public health objective.

These comments include a summary of FDA's meeting with the Generic Pharmaceutical Association (GPhA) on September 8, 2014, to listen to their comments and views regarding the proposed rule. In addition, on March 27, 2015, FDA held a public meeting at which any stakeholder had the opportunity to present or comment on the proposed rule, or on any alternative proposals intended to improve commu-

nication of important, newly acquired drug safety information to healthcare professionals and the public. In the February 18, 2015, notice announcing the public meeting, FDA reopened the docket for the proposed rule until April 27, 2015, to allow for the submission of written comments concerning proposals advanced during the March public meeting.

FDA is carefully considering comments submitted to the public docket established for the proposed rule from a diverse group of stakeholders including: consumers and consumer groups, academia (including economists), healthcare associations, drug and pharmacy associations, brand and generic drug companies, law firms, state governments, and Congress, including comments proposing alternative approaches to communicating newly acquired safety-related information in a multi-source environment (see Docket No. FDA-2013-N-0500).

Question. The Unified Agenda, available at <http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201604&RIN=0910-AG94>, currently lists an anticipated publication date of April 2017 for the final rule on “Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products.” The dates for rules in the Unified Agenda are projected dates that may be adjusted to reflect ongoing work on specific rules. Will the FDA commit to work expeditiously to complete the rulemaking process, with a focus on consumers and patient safety?

Answer. The proposed rule is intended to improve the communication of important drug safety information to healthcare professionals and patients. FDA has received a great deal of public input from stakeholders during the comment periods on the proposed rule regarding the best way to accomplish this important public health objective.

These comments include a summary of FDA’s meeting with the Generic Pharmaceutical Association (GPhA) on September 8, 2014, to listen to their comments and views regarding the proposed rule. In addition, on March 27, 2015, FDA held a public meeting at which any stakeholder had the opportunity to present or comment on the proposed rule, or on any alternative proposals intended to improve communication of important, newly acquired drug safety information to healthcare professionals and the public. In the February 18, 2015, notice announcing the public meeting, FDA reopened the docket for the proposed rule until April 27, 2015, to allow for the submission of written comments concerning proposals advanced during the March public meeting.

FDA is carefully considering comments submitted to the public docket established for the proposed rule from a diverse group of stakeholders including: consumers and consumer groups, academia (including economists), healthcare associations, drug and pharmacy associations, brand and generic drug companies, law firms, state governments, and Congress, including comments proposing alternative approaches to communicating newly acquired safety-related information in a multi-source environment (see Docket No. FDA-2013-N-0500).

QUESTIONS SUBMITTED BY SENATOR TAMMY BALDWIN

Question. I am encouraged by the FDA’s increased attention to the growing epidemic of prescription opioid misuse and abuse and the need to improve treatment options for chronic pain. As you mentioned in your recent article in the *New England Journal of Medicine*³, there is little high-quality evidence on the safety and efficacy of opioids as a long-term treatment for chronic pain. It is critical that we fill the gap in research and promote the development of safer treatments that pose less risk of addiction for patients experiencing chronic pain.

How is the FDA collaborating with other government agencies, including the National Institutes of Health, to prioritize the development of non-addictive therapies for chronic pain and to generate high-quality evidence to support their use?

Answer. To help combat the opioid epidemic, the FDA is encouraging drug development efforts that make it harder to abuse opioids, and the agency looks forward to the day, hopefully soon, when the majority of opioids in the United States are marketed in effective abuse-deterrent forms. However, development of and transition to use of opioids with meaningful abuse-deterrent properties is only one component of a multi-pronged approach to addressing abuse of opioid medications. For example, the FDA is also working to support the efficient development of non-opioid alternatives for treating pain that have lower (or no) abuse potential. Encouraging the development of these products requires both scientific and translational develop-

³Califf, Robert M., M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D. “A Proactive Response to Prescription Opioid Abuse.” *New England Journal of Medicine*, 4 Feb. 2016. <<http://www.nejm.org/doi/full/10.1056/NEJMSr1601307#t=article>>.

ment work. FDA has past and ongoing work in this area, supported through our participation in the ACTION Public Private Partnership⁴ (PPP) in a wide variety of areas.

ACTION is working to improve study methods for developing novel, safe, and effective analgesic drug products. Through scientific assessment of FDA's clinical trial databases and publically available data, the PPP plans to develop novel and evidence-based approaches to improve the design of analgesic clinical trials. The PPP also coordinates scientific workshops that bring together key experts, including stakeholders from industry, professional organizations, academia, and government agencies.

Additionally, as part of the FDA's recently announced plan aimed at reversing the opioid epidemic, the agency has contracted with the National Academy of Medicine to provide us with advice on how we should incorporate current evidence about the public health impact of opioid use, both for people who are prescribed opioids and for non-patients, into regulatory activities concerning opioids. We look forward to the recommendations from NAM and other experts about reassessing our risk-benefit paradigm for opioids based on the current state of the science.

FDA also continuously strives for enhanced collaboration between NIH and FDA. FDA leadership recently participated in a meeting of the FDA–NIH Joint Leadership Council, an organization through which senior leaders from both agencies address ways to facilitate new processes, such as FDA review of combination therapies and its consideration of rare disease trials with fewer patients enrolled. The participants on the FDA–NIH Joint Leadership Council work together to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. Such collaboration and integration advances the development of new products for the treatment, diagnosis, and prevention of common and rare diseases, as well as enhances the safety, quality, and efficiency of the clinical research and medical product approval process.

Question. How will the FDA in fiscal year 2017 improve post-market surveillance of medical devices? And, in addition to recalling such devices when they are found to be unsafe for patients, how will the agency better protect patients from adverse effects and complications while said devices are under investigation?

Answer. FDA takes device post market safety very seriously. There will always be limitations to how much CDRH can learn about a device before it goes to market, diligent postmarket surveillance can identify safety signals, prevent patient harm, and lead to device improvements. The Center for Devices and Radiological Health's (CDRH) current postmarket surveillance tools, such as passive reporting, limit our ability to rapidly address safety concerns.

For this reason, FDA has proposed the development of a national evaluation system for medical devices (system).

In 2011, the Institute of Medicine (IOM) published a report recommending that FDA develop and implement a comprehensive medical device postmarket surveillance strategy to collect, analyze, and act on medical device postmarket performance information. In 2012 and 2013, CDRH set out a vision and strategy⁵ for creating such a system. In 2015, two multi-stakeholder groups issued reports⁶ supporting the vision and made recommendations providing further direction for establishing this system. Further, CDRH's 2016–2017 Strategic Priorities⁷ include increasing access to and use of real-world evidence to support regulatory decisionmaking. The development of the post market evaluation system is integral to meeting those goals.

The principal challenge for implementing the system is lack of funding. The system needs investment from various stakeholders to operate and build on existing infrastructure and to establish and operate a governing body. The fiscal year 17 President's Budget contains a request for \$1.8 million for the system. While the long-term vision for the system involves multi-stakeholder participation and investment, in order to garner meaningful financial support from the private sector, the NES needs a core investment. We would like others in the medical device ecosystem, such as payers and professional societies, to also have an important role in the development of this system. Finally, this investment will support precision med-

⁴ ACTION: Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks

⁵ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm>.

⁶ <http://www.brookings.edu/events/2015/02/23-future-of-medical-device-safety-and-innovation;www.brookings.edu/about/centers/health/projects/development-and-use-of-medical-devices/mds/2016-planning-board>.

⁷ <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf>.

icine. One of the biggest problems facing the success of Precision Medicine is the challenge of determining which devices are best suited for which patients because of the high cost of developing evidence. Data that can answer these questions is generated every day as a part of routine clinical practice (evidence from clinical experience or “real world” data).

To better protect patients from potential adverse events or outcomes while a postmarket device safety issue is under evaluation, the FDA communicates clear and easily understood information about the risks and benefits of a device to patients and healthcare providers. FDA uses a range of tools to disseminate information widely, including our website and through letters and meetings with healthcare providers and patient groups.

To support increased communication on potential safety issues, in December 2015, CDRH released a draft guidance called “Public Notification of Emerging Postmarket Medical Device Signals (‘Emerging Signals’).” An emerging signal is new information about a medical device used in clinical practice that the FDA is monitoring or analyzing; that has the potential to impact patient management decisions and/or alter the known benefit risk profile of the device; that has not yet been fully validated or confirmed; and for which the FDA does not yet have specific recommendations.

Historically, FDA has communicated important information we learned about in the postmarket context after completing an analysis of available data and, in most cases, after having reached a decision about relevant recommendations for the device user community. This guidance is designed to inform the public of our evolving efforts to share information in a more timely way that allows patients to make the most informed medical decisions with their healthcare provider as close to real-time and based on the most current data as possible.

FDA has taken additional important steps to facilitate the identification and evaluation of postmarket safety concerns. FDA issued a final rule establishing a unique device identification system to provide a standardized way to identify devices across different information sources including electronic health records and device registries using unique device identifiers (UDIs).

Question. The 2015–2020 Dietary Guidelines recognized that sugar that is added to increase the palatability of naturally tart fruits, like cranberries, can aid a healthy dietary pattern by supporting the consumption of fruits and vegetables. In considering the proposed added sugar DV for labeling, what is the FDA doing to ensure that consumers will be not be misled on the healthfulness of nutrient dense products that contain added sugar, when comparing similar fruit products with equal or more intrinsic sugars and calories?

Answer. An added sugars declaration on the Nutrition and Supplement Facts labels, if finalized, would be just one piece of information that consumers can use to help them construct a healthful dietary pattern. We recognize that the added sugars declaration would be new information that consumers would not have seen before; therefore, in collaboration with Federal and other partners, we plan to engage in educational and outreach activities for consumers and health professionals about the use of information on the Nutrition and Supplement Facts labels, including any information about added sugars, if finalized. In the education and outreach activities, FDA plans to indicate that consumers should consider all of the information on the label, including total sugars and calories, when constructing a healthful dietary pattern, and not focus on just one specific nutrient.

Question. Artisan cheesemakers in Wisconsin have expressed concerns over the uncertain regulatory climate for raw milk cheese production. In particular, FDA’s approach in conducting sampling at cheese facilities as it reviews raw milk cheese and non-toxicogenic *E. coli* levels created a great deal of uncertainty and concern within the industry, despite the industry’s attempts to work with FDA. Though cheese producers cooperated extensively in providing samples, FDA did not share the results from those tests in a timely way with individual businesses or the industry. When can cheesemakers and their industry groups expect to receive comprehensive results from the Listeria Environmental Sampling Program and the Raw Milk Cheese Sampling Program?

Answer. An external report is being prepared for stakeholders that will discuss the results of the FDA’s fiscal year 2014/15 surveillance sampling assignment on raw milk cheese. We expect that report to issue in the coming months. FDA will release results of Listeria sampling conducted at cheese firms, as resources allow.

Question. As the FDA works to complete its guidance document on environmental Listeria, is there any quantitative data on incidence and levels of Listeria monocytogenes in frozen foods such as frozen vegetables and frozen food entrees? In frozen foods where Listeria monocytogenes has been implicated in the reportable

food registry, does FDA have any quantitative data? If so, please share that data with the subcommittee.

Question. FDA recently queried the database for Reportable Food Registry submissions and found thirty-eight (38) primary submissions for *Listeria monocytogenes* in frozen foods between 2009 and the present. Of these submissions, nine (9) met the criteria for reportable food and were classified as Class I recalls because there is a reasonable probability that the use of or exposure to the product will cause serious adverse health consequences or death to humans or animals. Twenty-seven (27) submissions were considered non-reportable because the food failed to meet the Class I recall standard or because it did not meet the criteria of a reportable food (e.g., the food is not regulated by FDA or the report is not submitted by a manufacturer, processor, packer or holder of food required to be registered with FDA under section 415 of the Federal Food, Drug, and Cosmetic Act). Two (2) submissions are awaiting decisions on recall classification.

FDA occasionally collects quantitative data from frozen food products on an as needed basis to assist in an investigation but has not conducted a comprehensive survey of the frozen food industry. In two investigations in the past 2 years, FDA collected quantitative data. In one investigation involving an ice cream outbreak, the data revealed that 99.4 percent of samples of the ice cream involved in the outbreak contained detectable *L. monocytogenes* at levels ranging from less than 0.03 cells of *L. monocytogenes* per gram to greater than 208 cells per gram. In the second investigation involving frozen vegetables subject to recall, FDA collected samples from thirty-three (33) product lots stored in the firm's warehouse freezer. Eight (8) lots (24 percent) tested positive for the presence of *L. monocytogenes*.

Question. The fiscal year 16 omnibus included report language that asked the Administration for a timeline for updating the dietary reference intake (DRI) for sodium as part of the fiscal year 17 budget request. An update was not included in the fiscal year 17 budget request. Can you share the specific 2016 timeline and plan for the update of the sodium DRI as requested in the Omnibus report?

Answer. FDA has prioritized updating the DRI for sodium and is collaborating with the Centers for Disease Control and Prevention and other Federal agencies to update the DRI for sodium as expeditiously as possible. A detailed timeline is not yet available.

SUBCOMMITTEE RECESS

Senator MORAN. Again, Commissioner, thank you, and, Acting Commissioner Ostroff, thank you very much for your leadership of the agency.

And we stand adjourned.

[Whereupon, at 2:42 p.m., Wednesday, March 2, the subcommittee was recessed, to reconvene subject to the call of the chair.]