

**AGRICULTURE, RURAL DEVELOPMENT, FOOD
AND DRUG ADMINISTRATION, AND RE-
LATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2019**

TUESDAY, APRIL 24, 2018

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

The subcommittee met at 2:30 p.m. in room SD-124, Dirksen Senate Office Building, Hon. John Hoeven (chairman) presiding.

Present: Senators Hoeven, Collins, Moran, Merkley, Tester, Udall, and Baldwin.

U.S. FOOD AND DRUG ADMINISTRATION

STATEMENT OF HON. SCOTT GOTTLIEB, M.D., COMMISSIONER

OPENING STATEMENT OF SENATOR JOHN HOEVEN

Senator HOEVEN. This hearing will come to order.

Today's hearing will focus on the Food and Drug Administration's fiscal year 2019 budget request.

I want to thank Commissioner Gottlieb, Dr. Gottlieb, for being here today to discuss FDA's priorities for the upcoming year. Thanks for your public service. We really appreciate you being in this post, your hard work, and your diligence.

I think we will dispense with opening statements in the interest of time. There is a vote at 3 o'clock. So our intent is to just go on through and then hopefully adjourn by, say, 3:20 or so which would give the members time to go over and vote. But we will see how it goes. If we have to adjust, of course we will do that. So we will dispense with our opening statements.

But I would invite Dr. Gottlieb, if you do have some opening comments, to go ahead and make those opening comments.

SUMMARY STATEMENT OF HON. DR. SCOTT GOTTLIEB

Dr. GOTTLIEB. Thanks a lot, Mr. Chairman, Ranking Member Merkley, and Members of the Subcommittee. Thank you for the invitation to testify today to discuss the President's fiscal year 2019 budget request and for this Subcommittee's continued strong support of the agency.

The investment you made in the 2018 omnibus helped support programs that made 2017 the most successful in FDA's history,

with a record number of approvals of innovative and generic drugs and novel medical devices.

The President's budget request for FDA builds on these goals. Overall, the budget requests \$5.8 billion in total resources for FDA, which includes an increase of \$473 million in budget authority and \$190 million in user fees. The budget requests new resources for the FDA to make significant investments in advancing critical areas of science, domestic technology, and public health.

Today I want to focus my remarks on two of these proposals.

GENERIC DRUG PLATFORM

The first is our proposal to modernize our generic drug platform. This effort comprises two policy components.

The first element will help make the approval of new generic drugs more efficient by establishing a structured application. We believe a structured application that allows key sections of the generic drug file to be captured in a structured template will speed the review of the application to cut down on the number of review cycles that applications must undergo and reduce generic drug development timelines.

The second component of this initiative is aimed at promoting more widespread use of existing generic drugs by looking for ways to keep generic drug labels up to date with the latest information about each medicine's safety and benefits. The current statute generally requires generic drugs to have the same labeling as the brand drug that they reference. The burden to update the label with new information is typically borne by the brand company. However, when the brand reference drug voluntarily withdraws their marketing applications and therefore stops updating their labeling, FDA loses the mechanism to update generic labels. By having out-of-date labels, in turn, it can depress use of generic drugs. By one rough estimate, 1,170 reference drugs are tagged as discontinued or withdrawn by their original branded sponsors for reasons other than safety or effectiveness. If the brand drug sponsor has voluntarily withdrawn their marketing application, there is no sponsor who is responsible for making the necessary label updates that other generic applicants would follow. So these labels basically get frozen in time. These drugs may be old medicines, but many are still very useful, and some form the backbone of modern cancer regimens.

FDA can assume more responsibility ourselves to help bring these drug labels up to date. I believe if we actively take on this role, it can promote more widespread use of generic medicines. Our budget requests money to do just this.

MEDICAL PRODUCT INNOVATION INITIATIVES

Our budget also includes a request for funding to support another initiative to allow us to make sure that medical products are developed as efficiently and quickly as possible. This second effort will also help to make sure patients and providers have the most up-to-date information on which to make informed decisions in addition to improving the use of real-world evidence for the many of the products we oversee. We seek to expand our active surveillance systems to enhance our real-time understanding of medical product

performance by broadening our use of health care data to better take advantage of the data available from electronic health records. To accomplish this, several things must happen. First, the data must be high quality and interoperable, meaning that the data can be collected in one system but used in many different systems to inform patient care. And second, we must enable better integration of clinical care and clinical research.

Right now, our active post-market data monitoring systems, principally our NEST database for medical devices and our Sentinel system for drugs and biologics, depend largely on the secondary use of claims data because that is what is available to us. And as helpful as this is, we know the nation can do better. Real-time surveillance is first and foremost about safety.

But having a real-time post-market and real-world experience system will also give us more ways to use real-world evidence to expand what we know about the effectiveness of new products. New products are often safer because they can be designed to address safety issues identified through better surveillance. But we can also use data from electronic health records to broaden the indications for use of approved products, eventually conducting more late-stage development in the real world, making our pre-market development process more efficient.

NEW MEDICAL DATA ENTERPRISE

The 2019 budget includes \$100 million to advance the use of real-world experience to inform patient care and provide efficient and potentially lower cost ways to develop clinical data to expedite medical product development. The proposal gives us the capability to conduct near real-time evaluation of individual health records for at least 10 million individuals from a broad range of settings.

In closing, these are transformative initiatives that can modernize the foundation of FDA oversight and improve patient safety. Your support through the appropriations process allows us to modernize how FDA fulfills its vital consumer protection mission. And I look forward to explaining our budget request and answering your questions in detail. Thanks a lot.

[The statement follows:]

PREPARED STATEMENT OF SCOTT GOTTLIEB, M.D.

Good afternoon Chairman Hoeven, Ranking Member Merkley, and Members of the Subcommittee. Thank you for the opportunity to appear before you today to discuss the President's fiscal year 2019 Budget request for FDA.

First, I would like to thank the Committee for your continued support of the Agency. FDA has received strong bipartisan support throughout the appropriations process in recent years and fiscal year 2018 was no different. I believe this support reflects our shared commitment to the vital role FDA has protecting and promoting the public health. The funding this Subcommittee provides is essential to the Agency fulfilling its mission. The professional staff of FDA is grateful for the support of their work and the funding increases the Subcommittee provided FDA in fiscal year 2018.

Last year was a record year for medical products at FDA in several ways: novel drug approvals, generic drug approvals, and novel medical device approvals. The record number of approvals in 2017 reflects the remarkable opportunities we have at this critical inflection point in science and technology. Advances in medicine and science are providing opportunities that can fundamentally change health in America and the outlook for many patients with life threatening and chronic diseases. At the same time that we have many new opportunities offered by advanced medical technologies; we cannot lose sight of our commitment to the public health basics—

reducing smoking rates, preventing kids from initiating use of tobacco products, supporting healthy food choices that can lead to better nutrition and reduced risk of disease, and increasing vaccination rates. FDA is committed to all of these and other public health goals. With your continued support, we have more opportunity to deliver on the promises of science than at any other time in the past.

The funding provided in the President's fiscal year 2019 Budget will allow the Agency to sustain its current work—protecting the safety of the food and medical products consumers use every day—and build on these efforts by requesting additional resources to make significant progress on several important fronts; including, fostering innovation and competition to bring better and more affordable products to market, combatting the opioid epidemic, and implementing the 21st Century Cures Act (Cures).

Overall, the Budget requests \$5.8 billion in total resources for FDA—which is an increase of \$663 million or 13 percent above the fiscal year 2018 Annualized Continuing Resolution. At this total level, the Budget includes an increase of \$473 million in budget authority and an increase of \$190 million in user fees. The Budget requests considerable new resources for FDA and makes significant new investments in advancing critical areas of science, domestic technology, and public health.

As the regulatory Agency responsible for ensuring the safety and effectiveness of more than \$2.4 trillion worth of products used by consumers, I remain steadfast that these funds are critical investments in our public health agency. They will allow us to more efficiently advance safe and effective new opportunities to Americans.

FISCAL YEAR 2019 INITIATIVES

The Budget includes an increase of approximately \$400 million in additional resources to advance initiatives to promote public health and spur growth in the domestic economy. These new initiatives provide a renewed focus to some of the Agency's most intensely followed issues—facilitating regulatory pathways to increase patients' access to safe and effective drugs, biologics, and medical devices, and access to higher quality compounded drugs for the patients who need them; better informing patients and providers about pre-and post-market safety of medical products; and, increasing competition among generic drugs in order to lower the cost of generic drugs.

I believe that these new efforts represent discrete areas where targeted additional resources can help the Agency make a meaningful difference for American consumers. A few examples of the new initiatives are described below.

ADVANCING MODERN DRUG AND BIOLOGICAL PRODUCT MANUFACTURING TECHNOLOGIES, THROUGH THE DEVELOPMENT OF EFFICIENT REGULATORY PATHWAYS

Advanced manufacturing technologies, such as continuous manufacturing, can improve the agility, flexibility, cost and robustness of drug and biologic manufacturing processes. These technologies have great potential to accelerate new, more targeted therapies, enhance product quality and bolster stability in the U.S. drug supply to meet patient needs. For example, continuous manufacturing has the potential to help address and eliminate drug shortages and reduce recalls related to problems with product or facility quality. Further, with continuous manufacturing platforms for biologics, vaccine manufacturing, for example, could be ramped up on short notice, and vaccines themselves adapted over a shorter time period to address infectious diseases, such as the flu. This would help address the challenge we face annually with the flu season. As a result of the long manufacturing cycle required when using traditional egg based manufacturing technologies, manufacturers must select the flu strain that will be included in the upcoming flu season's vaccine six months prior to the flu season. By reducing the amount of time it takes to ramp up manufacturing, we can start manufacturing closer to the start of flu season to minimize or eliminate the matching issues we face, to varying degrees, each year and increase the efficacy of the flu vaccine. Advances in manufacturing could provide a more certain, and nearer-term opportunity to address challenges with flu vaccine supply and effectiveness while we continue to work on longer term, newer vaccine technology such as a universal vaccine.

Despite the promise of these manufacturing improvements, industry remains reluctant to invest in these platforms. Additional regulatory principles and tools to help manufacturers implement and assess these platforms could accelerate their adoption. It would give manufacturers greater certainty that products developed through continuous manufacturing can be efficiently reviewed and gain market entry.

In these ways, FDA can encourage industry to utilize these new technologies by developing a science-based framework that includes the regulatory tools and guidance for how products developed in these systems will be evaluated. As an additional benefit, these small-footprint, high-technology manufacturing platforms are likely to be domiciled in the U.S. As a result, their adoption could return more product manufacturing to domestic sites, which could help public health, enhance our national security, and foster job creation. The Budget requests \$58 million in fiscal year 2019 for advancing this initiative.

ESTABLISHING THE OUTSOURCING FACILITY SECTOR AS A ROBUST AND RELIABLE SOURCE OF COMPOUNDED PRODUCTS

Since Congress passed the Drug Quality and Security Act in 2013 (DQSA), patient access to better quality compounded drugs has been a chief concern for the Agency, physicians, and patients alike. Outsourcing facilities have the ability to produce and distribute larger amounts of compounded products to meet the needs of individual patients for whom such drugs are appropriate, including by making office stock that is used by hospitals and clinics. Outsourcing facilities are an important component to our health system and the Agency is committed to clarifying and appropriately tailoring policies so they can continue to provide drugs, based on the clinical need for a compounded medicine, so patients have access to the products they need.

The Budget proposes the creation of a “Center of Excellence on Compounding for Outsourcing Facilities” and expanded FDA engagement with outsourcing facilities and states to help the pharmacy outsourcing industry grow to meet its intended function and adhere to good manufacturing practices (GMPs) to protect patient health. We see an opportunity to make investments in regulatory policy and personnel that could help more compounding pharmacies become outsourcing facilities. This, in turn, would allow these pharmacies to grow and serve more patient needs, including through the provision of office stock compounded under GMP standards, promoting access to better quality compounded drugs for patients who have medical needs that otherwise cannot be met by an FDA approved drug. These new outsourcing facilities would represent a largely domestic industry and a new area of growth in the healthcare sector. The Budget requests \$25 million in fiscal year 2019 for this initiative.

BRING MEDTECH MANUFACTURING HOME: ADVANCE MEDICAL DEVICE MANUFACTURING AND QUALITY

The Budget proposes to establish a voluntary program for device manufacturers to receive an independent assessment of manufacturing and product quality criteria intended to demonstrate sustained organizational excellence. This would make the process for introducing innovations in how medical devices are manufactured more efficient and predictable. In turn, this program would encourage device manufacturers to make investments to re-tool their manufacturing processes in ways that can facilitate manufacturing innovation, encourage investment in new production methods and materials, and lead to better medical products.

This more modern and nimble framework would make it more efficient for device developers to innovate manufacturing processes in ways that can allow devices to better meet the needs of patients and the expectations of providers—such as through intelligent, automated processes that monitor and record manufacturing quality metrics, incorporating features and technological characteristics that can contribute to better options and higher quality that achieves their clinical purpose. Implementing this framework would help increase manufacturing innovation, accelerate availability of high-quality devices to patients and foster a competitive marketplace around device quality similar to other industries, such as automotive and aerospace, that could advance device innovations, reduce manufacturing costs and improve the quality and safety of medical devices. As medical devices become more complex—and given the frequent modifications made to devices—spurring advanced manufacturing and creating a competitive marketplace for device quality is critical for both driving technological innovations and assuring patient safety. The Budget requests \$12 million in fiscal year 2019 for this initiative.

CREATE A NEW MEDICAL DATA ENTERPRISE

Advances in technology have the potential to improve the availability and utility of real world evidence (RWE) and real world data¹ (RWD). This data provides researchers the opportunity to answer questions about treatment effects and outcomes more efficiently, saving time and money, while yielding answers more relevant to broader populations of patients than might be possible in a specialized research environment. This data can also help streamline clinical development and inform the safe and effective use of medical products.

The Budget proposes to advance the use of this real-world experience to better inform patient care and provide more efficient, robust and potentially lower-cost ways to develop clinical data that can inform product review and promote innovation. The Budget requests funding to establish a new capability, including the development of data and analytical tools, to conduct near-real-time evidence evaluation down to the level of individual electronic health records for at least 10 million individuals in a broad range of U.S. healthcare settings.

Expanding the FDA's capacity to use RWE to evaluate medical products would generate processes that could improve the efficiency of the regulatory process, better inform patients and providers about pre-and post-market safety, reduce some of the burdens that drive up the time and cost required to bring beneficial innovations to the market, and address barriers that can make certain important safety and effectiveness information around the real-world use of products hard to collect and evaluate. Harnessing the power and potential of RWE is especially critical for finding treatments and cures for rare disease. Establishing a strong understanding of each disease and completing clinical trials is especially challenging; however, RWE holds enormous promise for improving understanding of disease and thus, development of treatments and cures. Funding in this area will allow FDA to develop regulatory standards for use of RWE to support medical product applications. The Budget requests \$100 million in fiscal year 2019 for this initiative.

FACILITATE GROWTH AND SPUR TRANSFORMATION OF THE DIGITAL HEALTH TECHNOLOGY INDUSTRY BY SHIFTING REGULATION TO AN EFFICIENT AND NOVEL FRAMEWORK FOR RELIABLE POST-MARKET OVERSIGHT

Digital health products are at the forefront of helping us diagnose and treat our society's increasingly complex medical needs. Healthcare providers use the latest technological tools to help them screen, detect and treat diseases ranging from cancers to neurological conditions like Alzheimer's. Patients utilize mobile medical applications to manage conditions like diabetes and treat substance use disorder. However, the current regulatory framework is not well-suited for these modern technologies. Every single day, these technologies are helping patients and doctors make healthcare decisions.

As part of our efforts to support timely access to safe and effective digital health products, the FDA is working collaboratively with industry, patients and providers to establish a new paradigm for digital health technologies under which a company could market lower-risk products without FDA premarket review and market higher-risk products following a streamlined FDA premarket review if the company receives a prior third-party certification for engaging in high-quality software design and testing (validation) and ongoing maintenance. This regulatory model would be fully proven and expanded from its current pilot status to a broader program. For low-risk products, rather than evaluate each individual digital health product before the product comes to market, the FDA would instead focus its resources on validating the quality of a firm's software design and the firm's methods for certifying the quality and reliability of its underlying software performance. The agency would further reduce the time and cost of market entry of digital health technologies while assuring appropriate patient safeguards by relying on postmarket collection of real-world data to support new and evolving product functions. The Budget also proposes the creation of and resources for a Center of Excellence on Digital Health to establish this regulatory paradigm, build new capacity to evaluate and recognize third-party certifiers, and support an internal cybersecurity unit and an external public-private partnership of experts to complement the advances in software-based devices. Implementing these regulatory innovations and information technology improvements are essential for advancing technologies to improve the health and qual-

¹ Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in-home use settings, and data gathered from other sources such as mobile devices that can provide information about health status.

ity of life of patients while assuring critical safeguards. The Budget requests \$70 million in fiscal year 2019 for this initiative.

MODERNIZE GENERIC DRUG DEVELOPMENT AND REVIEW

Increasing patients' access to more affordable prescription drugs is a top issue for Americans and one that I am personally dedicated to addressing during my tenure as Commissioner. Last May, in one of my first actions as Commissioner, I announced FDA's Drug Competition Action Plan. The plan has three overarching principals: eliminate gaming by branded companies that can delay generic drug entry; resolving scientific and regulatory obstacles that can make it difficult to earn approval of generic versions of certain complex drugs; and improving the efficiency and predictability of FDA's generic review process to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before approval. As part of this process, we also prioritized review for certain generic applications where there was a lack of competition, a situation under which consumers could face high prices for some very old medicines.

The Budget builds on this plan by proposing to establish a new review platform to modernize generic drug review and support efforts to update generics labels. This investment will foster greater use of lower-cost generics as a way to improve patient access and create competition in order to lower drug costs. For example, too many generic labels remain out-of-date because there is no longer a sponsor involved that is able to update the labels with new information about safe and effective new uses for these medicines. If we incorporate into generic drug labels all of the current information about their safe and effective use, it could promote more prescribing of generic drugs, reducing overall healthcare costs. The Budget requests \$38 million in fiscal year 2019 for this initiative.

OPIOIDS

One of my highest priorities as FDA Commissioner is combatting the ongoing crisis of opioid addiction. As part of this commitment, we are reexamining the Agency's authorities and policies in this area and working to ensure that FDA has the proper tools and resources to address this epidemic as it continues to evolve.

Thanks to the support of this Subcommittee, FDA received a total of \$94 million in the fiscal year 2018 Consolidated Omnibus Appropriations Act (Public Law 115-141) signed into law last month to address the interdiction of illegal drugs, including narcotics, through our work in the international mail facilities. Recognizing the Agency's responsibility in helping to curb the flow of these counterfeit and illegal drugs from entering our communities, and the critical public health obligation that the FDA was entrusted with through these additional resources, I am pleased to report the Agency will start to invest this new funding in purchasing equipment and assessing additional technologies we might deploy before the end of this fiscal year.

But FDA's efforts related to addressing the opioid crisis are broad, and there are many new programs we would like to pursue in this mission. The Budget requests an additional \$10 million to provide technical assistance related to clinical study design related to medication-assisted treatments, and to also accelerate the development of non-opioid treatments, devices to treat chronic pain, and generic versions of opioid drug products with abuse deterrent formulations. One way FDA will use the resources is funding studies to identify additional tools and methodologies that can be used to evaluate whether differences in formulations impact abuse deterrence. These are small steps, but collectively, over time I am confident they can work together, along with the efforts of so many other of our Federal, state, and local partners to make a difference.

CURES

Implementation of Cures has been another top priority of the Agency over the past 16 months. Cures includes provisions that have the potential to impart far-reaching effects on scientific advancements in medical product development. The new law complements many efforts underway at FDA. All of these efforts are aimed at transforming the way we support product development and maintaining FDA's gold standard for safety and effectiveness. Toward these efforts, last June, the Agency published our required work plan for implementing Cures, which includes details of how the Agency will utilize the \$500 million in authorized new funds over 9 years. For fiscal year 2019, the Budget requests a total of \$70 million to support our implementation work.

I want to thank you for your support on this vital work so far. I look forward to working with you on supporting the Agency's implementation efforts in the future.

CONCLUSION

The last year was historic for the Agency. We are diligently working on a number of fronts and the vital work we do provides Americans with better ways to improve their health and welfare, and empowers consumers to make informed choices about the products they use and the foods they feed to their families. The Budget will help FDA maintain and complement our current efforts, as well as provide a renewed focus and investment in some of the Agency's and the nation's top public health priorities. I look forward to answering your questions today and to working with all of you going forward.

Senator HOEVEN. Again, Doc, thanks for being here, and we will have 5-minute rounds of questions.

FISCAL YEAR 2019 BUDGET REQUEST

The budget requests a 9.6 percent increase above last year, and that is about a 24 percent increase compared to 5 years ago. So is that a permanent increase, or do you have one-time funding increases included in there?

Dr. GOTTLIEB. A lot of the new initiatives that we are asking for resources for are one-time funding. There are some recurrent components to these, but of the new initiatives, we are asking for additional funding. And I outlined two of them today that are important to us. There are 97 FTEs that we would hire and try to continue on in perpetuity. So the balance of the resources are really allocated towards one-time expenditures to try to make some foundational changes to our regulatory platform.

Senator HOEVEN. There have been recalls over eggs and romaine lettuce. Can you give us an update on that? And then also do you have adequate funding in there for food safety activities?

RECALLS

Dr. GOTTLIEB. With respect to the egg recall, as you noted, Senator, we recalled recently 207 million eggs. Most of them had already been consumed, but we recalled eggs back to late 2017 related to a single facility, but a very large facility where we had traced back a strain of salmonella using our investigative work. The strain had a particularly identifiable molecular fingerprint. So going in and sampling patients who had become ill, we were able to trace it back to this facility. So we think we have addressed the problem with this facility. They are taking proper steps to remediate their facility to try to reduce this risk.

With respect to the romaine lettuce, it is an active investigation. We have isolated it to a particular region in Arizona where we believe it is coming from. We have information that suggests certain farms it may be coming from, but right now we have it isolated to a particular grower. So we put out general guidance that consumers should avoid romaine lettuce unless they can be certain that it did not come from Yuma, Arizona, which is the region that has been called into question.

INTERNATIONAL MAIL FACILITIES

Senator HOEVEN. For 2018, you got \$94 million for increasing inspection capacity for catching opioids at international mail facilities. You and I talked about this. Can you give us an update on how you are doing with that?

Dr. GOTTLIEB. Thank you, Senator. We are very appreciative for the resources that this Committee allocated to the agency to help in that fight.

As you know, we play a role, in collaboration with Customs and Border Protection, doing interdiction work in the international mail facilities related to not just counterfeit drugs and foreign unapproved products that may create risk to consumers but also with respect to controlled substances.

We are actively in the process of allocating that money now. We will have it fully allocated and programmed through 2019. We have already started to allocate some of those resources. And this is going to allow us to increase the number of packages that we inspect annually from 40,000 to 100,000. To give you sort of a metric, when I arrived at the agency, we had seven inspectors inspecting about 10,000 packages a year in the international mail facilities. Through resources we reprogrammed on our own, we increased it to 21 inspectors opening 40,000 packages. This new money will allow us to dramatically increase our footprint and be able to inspect upwards of 100,000 packages, maybe more once we are fully staffed out in those facilities.

Senator HOEVEN. So you feel that is on track and that you have got the resources you need to do it.

Dr. GOTTLIEB. We feel very good about our ability to allocate these resources. We feel very good about the resources that we have gotten. Look, we have 275 million packages a year coming through the international mail facilities. We estimate, based on some rough statistics that about 9 percent of those packages contain drugs. We are currently opening and inspecting .04 percent because we physically do not have the manpower to do more. So going from 40,000 to 100,000, we are still going to be looking at a fraction of a fraction, but if we are doing our job and we have good intelligence—and some of this money is going to towards building out our intelligence platforms—and we are targeting the right packages, we think we can get a meaningful representative sample of the highest risk packages that we can then conduct investigations, go back to the source, and try to shut this stuff down.

STATE COOPERATIVE AGREEMENTS

Senator HOEVEN. We also provided funding for the State cooperative agreements. You have seven States that are not signed up. Do you expect to have them signed up?

Dr. GOTTLIEB. Not every State has applied, Senator. So the States that applied for 2018—we are actively working with the States to bring them into this. The States that have applied that were not previously part of those cooperative agreements are Kentucky, Mississippi, Hawaii, and American Samoa. But the States that have not gotten their applications in for 2018—we are actively working with them to get them in next year. So we hope to have all 50 States. It is very important from my standpoint—the success of FSMA and the Food Safety Modernization Act and our platform to have these States signed up in these cooperative agreements. And we will be working with all the States, including your State, Senator. And so we are grateful for the resources to do that.

Senator HOEVEN. I have some other questions. And I also received some questions on my way in today, and I will submit those for the record, Doctor.

Dr. GOTTLIEB. Thank you.

Senator HOEVEN. Senator Merkley.

OPIOID FUNDING

Senator MERKLEY. Thank you very much, Mr. Gottlieb.

When you were addressing the opioid funding that was in the omnibus, I am not sure if you clarified whether or not, given that there is no money in the budget for this coming year, you can continue the same level of function you have under the omnibus without additional funds in this coming budget.

Dr. GOTTLIEB. Well, I appreciate the question, Senator. There was \$10 million in the budget this year. There was also an allocation made to HHS, if I remember correctly, of \$3 billion a year over 2 years, so \$6 billion total. And we are actively working with HHS and OMB to see what portion of that money is going to be allocated to FDA. So we hope to receive additional resources to help us step up this fight.

But I would be very open to working with Congress to make sure we can sustain the same level of effort with respect to the international mail facilities. As you know, this has been my top priority with respect to the enforcement activities related to our opioid interdiction work to get these IMFs staffed up and built out.

Senator MERKLEY. Thank you. I think what I heard you say is that unless money comes from another department, we need to work together to sustain the effort that FDA has on opioids.

Dr. GOTTLIEB. We do need to work together, yes.

Senator MERKLEY. Thank you.

FSMA FUNDING

Then let us turn to FSMA. And of course, we have this significant outbreak. There is no additional funding provided for food safety activities despite the nearly \$400 million increase in your budget. I know that many have talked to me about the complexity of tracing foods back to their source, especially when there are mixed products, figuring out quickly whether it is the lettuce, it is the tomatoes, it is cucumbers, where from. Can you really do FSMA well without asking for any additional money?

Dr. GOTTLIEB. Resources help, Senator. There is no question. Policy helps too. And we have taken some aggressive steps recently to try to increase the level of our footprint here to carry out our mission using mandatory recall authority for the first time recently, as you know, and also committing to disclose more information related to recalls. But there is no question we can do more with more and resources help. We appreciate the resources—

E-CIGARETTES

Senator MERKLEY. Thank you. I will follow up on that question as to how much you can do with the resources you have and whether you need more.

I am putting up a headline of an article in the “New York Times” from earlier this month. I cannot stop the schools’ struggle with vaping explosion. And the article notes that e-cigarettes have been touted by their makers to help adult smokers kick the habit. But school officials are struggling to control an explosion of vaping among high school and middle school students across the country. And they are fearful that they are creating a new generation of nicotine addicts.

As one said, it is our demon, referring to how it is affecting the students in their school and saying that they have an explosion of the use of this new, easily concealed device with a sleek, high-tech design that looks like a flash drive. It has turned the word “JUUL,” the brand-maker into a verb.

And there are studies that have now come out that show that the pods in vaping devices have a higher concentration of nicotine than individual cigarettes, accelerating the addiction, and a body of research indicating that vaping is leading adolescents to try cigarettes, which I know is the opposite of the argument made.

We now know that the additives include propylene glycol and glycerol that can form carcinogenic compounds. There is another chemical that is used to flavor some of the vaping juice that is linked to popcorn lung. Many of these things have not been thoroughly studied, and yet we have this explosion.

If we were to look at the numbers, we can see in middle school a huge explosion between 2011 and 2016. We do not have 2017 numbers yet. In high school, we have an explosion as well, nearly a tenfold increase. This is why people are so concerned.

My basic impression is that under the guise of saying that this is helpful to some adults to have candy flavors and fruit flavors to encourage them to quit smoking and turn to vaping instead, we are damaging an entire generation of our children. Do you share that concern at all?

Dr. GOTTLIEB. I am deeply concerned about this. And I am not going to countenance on my watch addicting a whole generation of young people to nicotine through e-cigarettes.

We took a robust series of actions today, and nobody watching this should underestimate our ability to follow up on those actions and take even stronger steps to shut down the youth access to these products, Senator. I do believe that the e-cigarettes, and ENDS products more generally, have the potential to offer a viable and potentially lower-risk alternative for adults who still want to access nicotine but do not want all the risks associated with combustion. But that cannot come at the expense of addicting a whole generation of young people to e-cigarettes, and we are not going to tolerate that. And that is why we took the actions we took today.

We will be following up with additional enforcement actions in the coming weeks, and I look forward to talking to you about that.

Senator MERKLEY. I do compliment you on pursuing companies that are selling to children directly in violation of the law and giving them warning letters. I just will keep coming back to the core point that as long as you allow devices that look like a flash drive, as long as they are not having to go through some kind of process, as long as you allow fruit and candy flavors, you are, in fact, facili-

tating the addiction of a generation of our children and it is not acceptable.

Thank you.

Senator HOEVEN. Did you wish to respond, Doctor?

Dr. GOTTLIEB. If I may. With respect, Senator, we will take additional enforcement actions in the coming weeks that I think are going to help illustrate both the scope of our ability to take action on the basis of something that—but just on the basis of whether or not someone could objectively believe that it is being designed in a way to appeal to youth. And I hope to come back to you and talk to you about that as well because there may be things we can do with respect to our current authorities that allow us to target on the basis of something that a reasonable person can believe it is designed in a way that might appeal to youth. But there are limitations to our current authorities as well. I think when we take our coming actions, we will demonstrate where that boundary currently is.

Senator HOEVEN. Senator Moran.

Senator MORAN. I will yield to Senator Collins. We were here at the same time, and she is senior to me.

Senator HOEVEN. Okay. Senator Collins.

Senator COLLINS. What a guy.

Senator HOEVEN. Is he not something.

Senator COLLINS. Is he not.

Senator HOEVEN. Senator Collins.

DRUG MARKET CONSOLIDATION

Senator COLLINS. Thank you very much, Senator Moran.

Commissioner, first let me commend you for your leadership at the FDA. I have been so pleased with the activist approach that you have taken. I think you are doing a terrific job, and I just want to start my questions by telling you that.

I commend you for your leadership in eliminating barriers to competition in the prescription drug market, which you and I have discussed many times. You have cracked down on REMS abuses. You promoted the development and uptake of biosimilars, all actions that needed to be done.

Recently you spoke about the dangers of market consolidation and the fact that the top three PBMs control more than two-thirds of the market; the top three wholesalers, more than 80 percent; and the top five pharmacies, more than 50 percent. You suggested that patients should not be penalized if they need a drug that is not on a formulary.

Earlier this month, Bloomberg reported that the Federal Trade Commission attorneys are looking for more cases to challenge companies' anticompetitive conduct. In my view, the FTC should not have to look very hard to find examples in the drug pricing arena, whether it be looking at mergers, market consolidation, pay for delay settlements, and patent thicket strategies.

Does the FDA actually refer cases to the FTC in this area?

Dr. GOTTLIEB. We have ongoing dialogue and collaboration with the Federal Trade Commission (FTC) in certain areas, Senator. And there are places where we would provide information and perhaps make a referral with respect to situations where we might see

a branded company taking advantage of the rules in ways that are deliberately meant to forestall intended competition. So there is a lot of ongoing dialogue with the FTC. And quite frankly, we have had a good relationship with them. We have been working with them quite closely not just on this issue but other issues as well.

Senator COLLINS. Good. I certainly hope to see more cases brought by the FTC.

DRUG REBATES

The next issue that I wanted to discuss with you is the issue of rebates. A number of players in the health care system appear to profit from the soaring costs of prescription drugs, whether it is manufacturers, insurers, intermediaries, pharmacy benefit managers, and while these players are taking larger and larger cuts, patients are often left scrambling to come up with the funds to pay for lifesaving drugs that they need.

I recently was at a pharmacy in Maine, and the couple who were in front of me in line, when they saw that their co-pay was going to be \$111, just turned around and left. And the pharmacist, in response to my inquiry, told me this happens every day, and that is so troubling to me.

So on its face, the idea of rebates that are paid by prescription drug manufacturers' sound like a good thing. PBMs negotiate drug prices with manufacturers and then provide rebates to insurers, which ought to bring down premiums for everyone. In practice, however, this means that for those who are least able to pay, including those who have very high co-pay requirements or high deductible plans and those who do not have insurance at all and paid these prices out of pocket, end up, ironically, subsidizing the costs for others. Something seems broken here.

How would you suggest that we rectify the rebate problem to bring down costs for patients?

Dr. GOTTLIEB. I am a little bit outside my regulatory domain here, but there are a number of things we can do to try to encourage straight discounting and not rebating, which I think your analysis is spot on in terms of the rebate money is—effectively the patient who is out of pocket is subsidizing the premiums for the patients who do not need health care. It is kind of the opposite of what we believe insurance should be. So there are things we can do.

We can try to require more of the rebates to be paid to the patient at the point of care. You can probably, as a condition of contracting, make it harder for intermediaries to be paid on the list price versus the net price, and that would discourage rebating because you would compress the spread between list and net.

We worry about this in the context of I see the stacked rebates in the market as a potential impediment to the entry of biosimilars into the market. And to the extent that we want to promote biosimilar development and market entry, the rebates do form one impediment to market access.

Senator COLLINS. Thank you.

Thank you, Mr. Chairman. And thank you, Senator Moran.

Senator HOEVEN. Senator Tester.

GENERIC DRUGS

Senator TESTER. Thank you, Chairman Hoeven and Ranking Member, for having this hearing.

Dr. Gottlieb, I want to echo Senator Collins' comments. I appreciate the work you have been doing, and I wish you the best moving forward. Hopefully you can keep it up.

I want to talk about generic drugs because when there are multiple generic drugs on the market, that competition helps the consumer. Your agency has the final say in what products can go on the shelf and which ones cannot. In the past the FDA has been slow to approve cheaper generic drugs. I think a little over a year ago, they had about 4,000 generic drug applications that were waiting for approval.

In the justification for your budget request, you said that the FDA has approved more generic drug applications this year than ever before. That is good news. I commend you on that.

What I want to know is, with this budget request, are you asking for the resources to be able to keep up with the rate for generic drug approvals?

Dr. GOTTLIEB. Thank you for the question, Senator.

We have almost fully eliminated that backlog. Last year, as you noted, we approved over 1,000 generic drugs, which was a record for the agency, and we hope to best that record this year.

The budget request that we are asking for with respect to the new initiative—the resources that would go towards the generic drug approval process we think can fundamentally transform that process by moving towards an application process that would be much more seamless and lower cost for the generic manufacturers. It would allow us to do assessments more quickly and give feedback on the quality of the application right up front so we can reduce what we call cycling.

One of the reasons why the generic drug review process is longer than it ought to be and we want to get review times down is not because it takes us a long time to review the application, but the applications undergo multiple cycles of review. We have to go back to the sponsor and request more information. They resubmit the application. It undergoes another review cycle.

We had a very similar problem and I will close here, but we had a very similar problem with respect to our new drug review process. When I was last at the agency 10 years ago, we made a deliberate effort to reduce the multiple cycles of review. We were successful in doing that. Now we are making a concerted effort to do the same thing on the generic drug side.

Senator TESTER. Doctor, what is the backlog right now?

Dr. GOTTLIEB. I believe we might have fully eliminated the backlog. I can get you exact details on that.

[The information follows:]

Currently at FDA, there is a healthy generic drug pipeline assuring the continued expansion of the generic drug program and continuing access to high quality, affordable generic drugs for the American public.

The Generic Drug User Fee Amendments (GDUFA) authorized the collection of additional funds for FDA to review generic drug applications, inspect facilities, and perform other regulatory actions. Under GDUFA, by the end of fiscal year 2017, FDA would take regulatory action on 90 percent of the applications that were submitted to the agency prior to the start of GDUFA, once referred to as the backlog.

Taking regulatory action meant FDA was expected to review these applications and provide a response to the applicant in the form of an approval, tentative approval, refuse-to-receive decision, or a complete response letter. In 2016, FDA reached that 90 percent milestone delivering on this commitment more than a year ahead of schedule—and ending any backlog.

As of March 2018, there were 4,194 ANDAs submitted to the FDA that have not yet been approved. Of those, 391 ANDAs are in tentative approval status. Roughly half are under assessment at FDA within their GDUFA goal dates and roughly half have been returned to industry with details of deficiencies that must be addressed. The Office of Generic Drugs shares this information on FDA.gov in the “Activities Report of the Generic Drugs Program (fiscal year 2018)—GDUFA II Quarterly Performance.”

It is one of FDA’s highest priorities to encourage generic drug development to foster drug competition, and we want to keep that generic pipeline strong. In January 2018, the Agency issued a draft guidance for industry on “Good ANDA Submission Practices,” to help reduce the number of review cycles by helping applicants avoid the common deficiencies that lead to review delays. The Agency is committed to processing and assessing applications at these record levels.

Senator TESTER. That would be good.

You just have to help me out here. A little over a year ago, there was a 4,000 generic drug application backlog. You approved 1,000 and you are caught up. What happened to the other 3,000?

Dr. GOTTLIEB. I do not believe that the backlog was 4,000, but I can get you precise numbers on that, Senator. But the 1,000 that we approved are new applications.

Senator TESTER. I guess the question is that of those applications, did any of them drop off the list, or do they stay there as a backlog?

Dr. GOTTLIEB. I would have to come back to you and tell you what the backlog is, but it is substantially worked off.

Senator TESTER. And so can you give me any idea how long it takes right now from the time they come in and ask for generic approval, assuming everything goes fine?

Dr. GOTTLIEB. We have committed that applications coming in that meet certain requirements we are going to review in 8 or 10 months on the initial review.

I will tell you, though, the one thing to keep in mind is that there is always going to be a certain number of applications that are with the agency because there are so many applications filed with the agency.

Senator TESTER. I have talked to many doctors that say, you know, generics come along, they do a good job. Somebody will buy up this generic. They will tweak it a little bit and jack the price through the roof. Do you have control over that? They will buy a generic. They will change it but really not enough to do any more than just say we have changed it.

Dr. GOTTLIEB. Typically, so if you are talking about someone who might take a short-acting drug and turn it into a longer-acting formulation or reformulate it where it can be delivered through another route of delivery—typically we would not forestall that kind of incremental innovation. I think it is really incumbent upon the market to decide whether or not they want to pay for it.

Senator TESTER. I know but if that drug is not there anymore, if that prescription drug is not there anymore because they have changed it a little bit and pulled it off, and now it is basically the same drug with a minor modification—I do not know. I am not a chemist. So if I am not correct on this, you will have to tell me.

But they modify it very minor and then jack the prices up because it is no longer the generic that was approved by you.

Dr. GOTTLIEB. If the initial generic—so you are spot on. But if the initial generic drug was not withdrawn for safety reasons—

Senator TESTER. Yes.

Dr. GOTTLIEB. Then that Reference Listed Drug (RLD), still exists and another generic company could come in and develop a generic copy to the original formulation.

DRUG RE-IMPORTATION

Senator TESTER. Okay. That is fine.

I just want to talk just very briefly on re-importation because people think this is a panacea. And I have bought drugs for my kid when I was in Mexico when he could not breathe. Okay? And it was great. They were cheap.

But there have been reports of counterfeit drugs coming into this country. I think a \$34 million fine was levied on an outfit out of Canada that was exporting to us drugs that were not what they said they were.

Do you have the capacity to be able to determine, if we were to go down that re-importation line or importation line, whichever, to have the capacity—how many people would that take to make sure that somebody who is taking insulin actually has insulin?

Dr. GOTTLIEB. We have not costed it out recently. We would have to put in place a substantial regulatory architecture to provide anything that would approximate the level of assurance that we can currently provide with the closed pharmaceutical system. And it would still create, arguably, gaps.

Senator TESTER. Okay. Thank you.

Senator HOEVEN. Senator Moran.

Senator MORAN. Mr. Chairman, thank you.

ONCOLOGY CENTERS OF EXCELLENCE

Dr. Gottlieb, thank you for your presence here. I would join my colleague, Senator Collins, in complimenting you. I appreciate the efforts that you make responding and keeping me and others informed. And I just want to express my gratitude for that being the case. You do your job as it should be done.

I indicated to you and I wanted to indicate publicly that my association of NCI centers, National Cancer Institute Centers, was in my office this morning and they too were complimenting you and FDA in regard to the Oncology Centers of Excellence that we funded in the omnibus bill and how well they are working in the battle against cancer and the efforts that are occurring at FDA. It caused us to have a conversation about the importance of NIH and FDA's collaboration and efforts in the battle to rid us of diseases. And so I want to continue my efforts in regard to NIH, but I also want to be very helpful to the folks at FDA.

DIETARY FIBER

I could not have a conversation without mentioning the issue of dietary fibers. The first time I met you we had this conversation and subsequently in every conversation. You were in my office re-

cently and explained kind of the status of where this issue is. I would guess if I ask you the question. When can we expect a rule delaying the compliance deadline to be finalized? You would tell me soon. Would you tell me anything else?

Dr. GOTTLIEB. I can tell you very soon.

[Laughter.]

Senator MORAN. Proving my point about how good you are, but not necessarily how responsive you are.

In that regard, you told me that there could be two tranches of decisions made in regard to specific applications. Am I saying that somewhat fairly?

Dr. GOTTLIEB. That is right, Senator. So, as you know, the initial rule identified seven fibers that met the definition of dietary fiber, and then we received citizen petitions from 12 additional petitioners to try to have their fibers elevated.

FDA put out scientific guidance outlining how we are going to make decisions on those citizen petitions, and we put out some additional guidance to help petitioners understand how to approach the agency. We are going to ultimately make decisions on those citizen petitions again very soon. We will probably approve an initial tranche, and then there will be a period of time in which we will probably approve another tranche. What we are trying to do is work with as many of those sponsors as possible to get them over the line.

Now that we have provided the scientific guidance and they understand how we make decisions, there might be cases where we want to go back to sponsors and help them develop some additional information if we believe we can get to yes, but they just need a little bit more information in to the agency to get over that line.

So we have been in touch with all the petitioners. At this point, they should all have feedback where they stand, and the ones who need to do a little bit more work—we are trying to help them and work with them.

Senator MORAN. You explained that to me when you were in my office, and it made sense to me. It seemed like a common sense way of addressing this issue. After you left, the thought occurred to me that you need to make certain that those who are not accepted in the first tranche do not appear to be a de facto denial because there would be market consequences, I assume, as those they deal with would rush to those that were approved not knowing what is going to happen with the second tranche. So I think how you do that matters.

Dr. GOTTLIEB. And we are going to be mindful in terms of how we message that. My concern here has been in part—and obviously, my concern is to get this right and make sure we do the right thing for consumers, but also that if there is a manufacturer who is close to being able to cross the line but needs a little bit more information, if we reject them, it could effectively forestall their opportunity to come back because you are right. Everyone is going to rush to the others. And so if I can work with that sponsor, who otherwise has a good product but was not sophisticated or did not know how to submit all the right information the first time, and try to help them get across the line, that is one of our goals here.

Senator MORAN. I am expressing support for your plan. I only add the caveat that there could be consequences to those that would be in a second tranche.

Dr. GOTTLIEB. I appreciate that.

PARTIALLY HYDROGENATED OILS

Senator MORAN. Partially hydrogenated oils. Food manufacturers continue to work to remove partially hydrogenated oils from the marketplace. I understand some of the foods made with partially hydrogenated oils can have a shelf life of up to 3 years or possibly longer.

My question. There are a few more things I would frame this question, but as the clock runs—what is your plan in regard to foods that have a shelf life longer than the date in which you make a determination that they needed to be removed from the marketplace? I guess the question is, does the agency not consider it necessary for companies to recall products containing partially hydrogenated oils already in commerce on the date of the compliance date? Would they have to withdraw them that date or when they expire?

Dr. GOTTLIEB. I would have to get back to you. I think the question relates to whether or not the agency is going to allow a de minimis level of PHOs to persist because most food manufacturers have reformulated to remove the partially hydrogenated oils.

You know, what we do in this area I can tell you is going to be mindful that if food manufacturers do need to remove even de minimis levels and they have to contemplate reformulating their food, we would provide them sufficient time to do that and be mindful of the disruption issues and the costs of compliance here. I think that is what you are referring to.

But I would have to get back to you specifically on whether or not there is someone still on the market past a point in which we would allow some level—how we would treat that.

Senator MORAN. If you would do so, that would be great.

My final question is, Dr. Gottlieb, how do you define “very soon”?

Dr. GOTTLIEB. Well, some of these decisions are outside my hands because we have to do this through rulemaking with OMB. It is not to pass the buck, but we are going to have an answer back within a matter of weeks and not months, Senator.

Senator HOEVEN. Just tell him somewhere between now and soon.

[Laughter.]

Senator MORAN. Thank you for your help, Mr. Chairman.

Senator HOEVEN. Senator Udall.

ANTIBIOTIC RESISTANCE

Senator UDALL. Thank you, Mr. Chairman.

Dr. Gottlieb, last month Congress lost Representative Slaughter, a dogged champion of efforts to combat antibiotic resistance. And I was proud to join another champion, Senator Feinstein, as the co-sponsor of legislation both she and Representative Slaughter developed to reduce the overuse of antibiotics in agriculture that creates drug-resistant bacteria. The FDA’s decision last year to end the use

of medically important antibiotics for use in animal growth promotion was a good start to reducing overuse.

But the agency can and must do more on this issue. We know that antibiotics are sometimes appropriate to ensure that animal health is maintained, but we need the right policies and data to make sure that we are using those drugs judiciously and using alternatives whenever possible. The FDA surveys species-specific sales of antibiotics for use in animals but does not track why the antibiotics are being purchased and administered or their eventual use on the farm.

To reduce antibiotic use, do we not need more data on why they are being used in the first place?

Dr. GOTTLIEB. We could always benefit from more information. We do get some data on use on the farm already through the National Antimicrobial Resistance Monitoring System. USDA makes data available and collects and makes data available to us. But we can and will be doing more in this regard.

And I had the opportunity to talk to Congresswoman Slaughter about our efforts here. We are going to be rolling out in the next couple of months our plan for what we will do to build on some of the good work that has already been done and looking at some additional steps we can take to make sure that there is judicious use of antibiotics in the farm setting.

NATIONAL ANIMAL HEALTH MONITORING SYSTEMS

Senator UDALL. The USDA's National Animal Health Monitoring System has begun collecting voluntary on-farm data related to antibiotic use and resistance, and they will begin reporting this data later in the year.

Do you agree with me that this is potentially a vital source of information that will help inform both public health stakeholders and the growers themselves about when antibiotics are working or not working, what resistance they may engender, and when it may be advantageous to consider antibiotic alternatives that may actually work better in a given situation?

Dr. GOTTLIEB. You know, I do agree with you, Senator. That was the data I was referring to that USDA is collecting. That is the species-specific data on use on the farm. You know, more data is helpful certainly, and this information in particular is going to help us target our policies.

Senator UDALL. And I realize this is a cross-agency effort. Can I get your commitment to work with the USDA and other agencies to address the urgent issue of antibiotic resistance?

Dr. GOTTLIEB. We work very closely with them. I meet personally with Secretary Perdue on a monthly basis. We have set up those meetings. We have an interagency working group, and we talk quite regularly. The relationship has been very strong and collaborative.

E-CIGARETTES

Senator UDALL. That is great.

The Ranking Member asked about the e-cigarettes but did not address the specific part of the toxic chemicals that are in there. The FDA has a responsibility to minimize harm to the public. Part

of this duty is minimizing harmful exposure to toxic chemicals emitted from e-cigarettes.

Under your leadership, will the FDA pursue product standards to set safe thresholds for the level of toxic chemicals like formaldehyde used in e-cigarettes?

Dr. GOTTLIEB. We are pursuing product standards in this regard, Senator. We are also actively contemplating what additional science we can do on our own right now to look at the toxicology associated with e-cigarettes. We will be putting out a guidance document very soon that will outline how companies can evaluate toxicology in the setting of e-cigarettes. In the event that a sponsor wanted to take one of these through the OTC route and get it approved as a new drug, they would have to do toxicology studies to satisfy the new drug approval requirements. And we are going to be putting out guidance outlining how they can do that. That is in some ways an attractive opportunity to all parties but particularly to the FDA because it does allow us to get very precise data around these issues.

Senator UDALL. Great. Thank you very much. Thanks for your answers. I will put my opioid question in for the record so Senator Baldwin can get her question in before the vote.

Senator HOEVEN. Thank you, Senator.

Senator Baldwin.

STANDARDS OF IDENTITY DAIRY PRODUCTS

Senator BALDWIN. Thank you, Mr. Chairman and Ranking Member.

Welcome back, Commissioner.

I want to bring up a topic that you and I have talked about before. I am really concerned about the proliferation of mislabeled products in the marketplace that are using dairy's good name but have absolutely no dairy ingredients. These products are violating the Food and Drug Administration's existing regulations, and they are getting away with it because of inaction by the agency.

It is a matter of fairness to the farmers and dairy producers and processors who I have worked with over many years. You know, they market their dairy products using dairy terms. Farmers must meet exacting standards for the content of the milk they deliver. The processors abide by specific requirements for things like butterfat content that ensure that when a consumer selects a certain dairy product, they know what they are getting and that it will perform in recipes as expected. Imitation products should not be able to use dairy's good name when they are doing none of the things required to use that label.

Now, the omnibus legislation that we passed included yet another instance of congressional direction on this issue, and it is time for the FDA to act.

So I first want to ask you what FDA is doing to enforce existing standards of identity for dairy products.

Dr. GOTTLIEB. Well, I appreciate the question, Senator. I announced about 3 weeks ago that we will be issuing a request for information related to our overall approach to standards of identity. And we are committed to taking a fresh look about what we are doing here.

You are right that milk is defined in the current standard of identity as being something from a lactating animal, and people have been using the term on things that are not derived from a lactating animal, as you and I will agree. But FDA having not stepped into this in the past, there is now a lot of commercial activity going on.

I think what we are going to be looking in particular and where I would like to see information, to the extent people can contribute to our dialogue on this and inform us—you mentioned this is an issue of fairness. I would not dispute that. But it is also a question of public health from our standpoint, and if consumers are being confused and misled about the nutritional status or quality of milk because of the way certain products are being labeled, that is something we would want to take a look at, and that is something that would certainly inform the decisions we make here.

So we will be issuing an RFI. That is an opportunity for us to collect information that could form the basis of regulatory action here.

Senator BALDWIN. So I just have to comment, and I view this as an urgent issue. This could be addressed right away if the FDA issued guidance to industry and declared its intent to enforce existing regulations.

Do you agree that you have the authority to proceed based on your existing regulations?

Dr. GOTTLIEB. I think that we would want to develop a careful administrative record here. Look, I am not a lawyer, but a lot of the physicians at FDA talk about the law, so I will take liberties here as well.

We have exercised enforcement discretion for a period of time now that for us to reverse our current posture might take more than just issuing guidance. We might want to develop a careful administrative record informed by data. And that is the intent of the RFI, which is to collect information that can inform a substantial administrative record that would sustain review.

Senator BALDWIN. So I would say for the record that I do not believe that there needs to be further review or study. What we need is the FDA to act and issue guidance on enforcement of its existing dairy standards of identity.

Our dairy farmers are in crisis right now. They are seeing very, very challenging times. The price of milk has been low for quite some time, the price that our farmers are paid. Some of the Farm Bill risk management tools that have been passed are not working the way we hoped they would, and I am sure we will all work together to adjust that. The trade negotiations that are going on right now have an impact and some uncertainty with regard to export markets for our dairy farmers. Canadian pricing of a certain class of milk is causing additional injury.

I am not saying this is the problem in totality. What I am saying is that there is a perfect storm of challenges to the dairy industry right now in my State. And when I have to explain what the Dairy Pride Act is, that it is a measure—I just cannot tell you how absurd this sounds outside the beltway—that it is a measure to ask an agency that is not following its own rules and that could be solved if the agency simply follows its own rules.

Dr. GOTTLIEB. Well, I will affirm to you, Senator that I have actively stepped into this issue. And I hear your concerns. I appreciate your concerns. We are taking a very close and fresh look at this.

Senator BALDWIN. Thank you.

Senator HOEVEN. Thank you, Senator.

Again, Dr. Gottlieb, thank you for being here today.

ADDITIONAL COMMITTEE QUESTIONS

For Members of the Subcommittee, any questions that you would like to submit for the hearing record should be turned in to Subcommittee staff within 1 week, which is Tuesday, May 1st, and we would appreciate it if we could have responses back from FDA within 4 weeks. Does that sound reasonable?

Dr. GOTTLIEB. It sounds reasonable, looking at my staff.

Senator HOEVEN. They are all nodding yes. That is a good sign.

Dr. GOTTLIEB. They are smiling yes. Thank you.

Senator HOEVEN. Thanks to them. And, Doc, thanks for being here. We appreciate it very much.

Dr. GOTTLIEB. Thanks, Mr. Chairman.

QUESTIONS SUBMITTED BY SENATOR JOHN HOEVEN

RARE DISEASES

Question. Mr. Commissioner, under your leadership the FDA has continued to embrace the 2012 directive from Congress that the FDA should follow the science in considering therapies for rare diseases with great unmet medical need under the accelerated approval pathway. You have publicly stated on a number of occasions that this pathway is particularly appropriate for therapies to treat rare diseases with no existing biomarkers or where the patient population is so small that a traditional large clinical trial may be infeasible.

Is this still a pathway you believe is the appropriate—and often only—pathway for the FDA to review novel therapies for certain rare diseases?

Answer. The accelerated approval pathway has been instrumental in addressing unmet medical needs for serious or life-threatening diseases or conditions, many of which are rare diseases. Between 2007 and 2017, FDA approved 52 drugs and biologics under accelerated approval. Of these, 37 were for orphan-designated drugs, i.e., for rare diseases. The Agency notes, however, that accelerated approval is not the only appropriate pathway for studying and approving drugs and biologics for rare diseases. In some cases, use of other approaches such as innovative study designs or statistical methods, or studies involving surrogate endpoints that have been shown to correlate with clinical benefit can enable the gathering of sufficient data to support traditional approval, even if the trials are conducted in very small populations.

Furthermore, sponsors of therapies for rare diseases have frequently used FDA's expedited programs for serious conditions, including breakthrough therapy designation and regenerative medicine advanced therapy designation, to engage early with FDA reviewers to help design clinical development programs that are as efficient as possible.

Question. Would you agree that under current law a product approved under the accelerated approval process has full FDA approval and not something less?

Answer. For serious disorders, the accelerated approval pathway provides a means for developing drugs and biological products based on either a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. Approval of a drug or biological product under the accelerated approval pathway meets the statutory standard for approval. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is not itself a direct measure of clinical benefit. A surrogate endpoint that is "reasonably likely to predict clinical benefit," may support accelerated approval. One example is accelerated approval of antimicrobial drugs based on the surrogate laboratory measure endpoint of reduction of bacteria in the blood stream, which is reasonably likely to predict the clinical resolution of the infection. An intermediate

clinical endpoint is a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. For drugs and biological products granted accelerated approval, post marketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit. These post-marketing studies are known as phase 4 confirmatory trials. If the confirmatory trial does not show that the drug provides clinical benefit, the statute provides for a more streamlined process to withdraw approval of the drug (or specific indication that received accelerated approval).

Question. Is there more the agency can do to clarify any existing confusion in the patient community about the full approval status of therapies approved under the accelerated approval pathway?

Answer. As noted in response to a previous question, approval of a drug or biological product under the accelerated approval pathway meets the statutory standard for approval. It is anticipated that a report showing the status of all marketing applications approved under the accelerated approval pathway since the program's inception in 1992 will be available for posting on the FDA site soon. In addition, FDA's May 2014 final guidance, Expedited Programs for Serious Conditions—Drugs and Biologics, is helpful in explaining the accelerated approval program and its relationship to traditional approval.

NUTRITION INNOVATION STRATEGY

Question. I would appreciate it if you could provide additional background on your March 29th presentation regarding the Nutrition Innovation Strategy.

Specifically, will the FDA frame Nutrition Innovation Strategy as a voluntary incentive for innovation, or should the industry expect it to be a second mass labeling mandate?

Answer. The Nutrition Innovation Strategy is intended to take a fresh look at opportunities to better promote public health through efforts to empower consumers to make better and more informed decisions about their diets and health, foster the development of healthier food options, and expand the opportunities to use nutrition to reduce morbidity and mortality due to chronic disease. In addition, many companies have requested certain changes regarding food labeling and standards of identity to meet consumer demands. FDA also seeks to streamline its process for reviewing qualified health claims, which are voluntary claims submitted to FDA by industry. Throughout this effort, FDA will be mindful of opportunities that may exist to allow industry flexibility for innovation while maintaining the basic nature and nutritional integrity of food products. The Nutrition Innovation Strategy is in the early stages of development and stakeholder input, including from industry, will be essential to further explore how best to promote public health in the evolving food and beverage marketplace. This summer, FDA will hold a public meeting and open a docket in the Federal Register to gather stakeholder input to further inform the strategy.

Question. With FDA's updates to the daily values used in food labeling to guide dietary choices, many manufacturers reformulated their foods to maintain existing label claims. And now the FDA will be changing the criteria to make those same claims.

How can the FDA approach this in a more efficient and less cost-intensive manner?

Answer. FDA is not planning to update the Daily Values as part of the Nutrition Innovation Strategy, as these values were recently updated as part of the Nutrition Facts label rulemaking. As part of FDA's Nutrition Innovation Strategy, the Agency will develop a comprehensive plan to modernizing our approach to health claims to support industry initiatives already underway and encourage other companies to introduce products that meet the growing consumer demand for healthier products. For example, FDA is looking to streamline its process for reviewing qualified health claims it receives from industry to enhance the efficiency of the review process. In addition, to help minimize the economic impact of label changes, FDA periodically announces uniform compliance dates for new food labeling requirements where possible. FDA is at the beginning stages of this process and plans to have extensive stakeholder engagement to seek input and further explore how to best promote public health in the evolving food and beverage marketplace. Part of this public engagement includes holding a public meeting this summer and opening a docket in the Federal Register to gather stakeholder input to further inform the strategy.

Question. The FDA has an ambitious list of work in this area—nutrient content claims, health claims, and specific claims such as natural and healthy.

What does the FDA intend to prioritize first amongst this list and how does this benefit the American people?

Answer. Today, chronic diseases such as heart disease and cancer are the leading cause of death and disability in the United States. Nearly 1 in 3 adults in the United States have high blood pressure, a leading cause of heart disease and strokes. Almost 40 percent of U.S. adults are obese, and among children and adolescents, almost one in five are obese. Poor nutrition plays a role in these patterns of chronic and preventable disease. The FDA is committed to finding new ways to reduce the burden of chronic disease through improved nutrition.

FDA is committed to finishing work on updating the Nutrition Facts label. The Agency has—and will continue—to publish technical documents on issues, such as serving sizes, to help manufacturers meet the requirements of the final Nutrition Facts label final rules. FDA has started working on updating the claim “healthy” and already solicited comment through a request for information and a public meeting in March 2017.

FDA’s new Nutrition Innovation Strategy will take a fresh look at what can be done to reduce preventable death and disease related to poor nutrition. The strategy is still in the early stages of development, but FDA has identified several areas where it believes there is opportunity to improve public health and facilitate industry innovation—claims on labels, information about ingredients in food, and standards of identity. Stakeholder input will be essential to further explore how best to promote public health in the evolving food and beverage marketplace. This summer, FDA will hold a public meeting and open a docket in the Federal Register to gather stakeholder input to further inform the Strategy.

CANCER IMMUNOTHERAPY

Question. I am very encouraged by recent breakthroughs in cancer immunotherapy and the FDA’s recent approval of several new treatments that harness this approach to fighting cancer. More than 1,500 immuno-oncology clinical trials are in some stage of development.

Given the substantial clinical benefit and unique mechanisms of action reported for tumor immunotherapy across a large number of cancers, how is the FDA planning to continue its forward momentum in immuno-oncology drug development for patients with cancer?

Answer. Cancer immunotherapies have demonstrated clinical benefit across many different types of cancer, despite different sites of origin, based upon their unique mechanisms of action. The first such approval was in May 2017 for pembrolizumab for use in MSI-high or mismatch repair deficient solid tumors that have progressed following prior treatment when there are no satisfactory alternate treatment options. In addition to such monoclonal antibody-based cancer immunotherapies, many personalized immunotherapies, including genetically-modified cellular therapies such as chimeric antigen receptor T-cells and other cellular therapies, intended for the treatment of cancer are either approved or in development. Those in development are eligible for a variety of programs intended to expedite their development and review, including fast track designation, breakthrough therapy designation, priority review, accelerated approval, and Regenerative Medicine Advanced Therapy (RMAT) designation, established under the 21st Century Cures Act.

Information about these expedited programs, as well as considerations for the clinical development of regenerative medicine therapies, are addressed in a draft guidance on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, issued in November 2017, as part of our comprehensive regenerative medicine policy framework.¹ In the draft guidance, FDA reiterates our commitment to working with sponsors of regenerative medicine therapies indicated for the treatment of cancer and encourages flexibility in clinical trial design. In addition, FDA recently issued six draft guidances related to manufacturing issues for the development of gene therapies. FDA believes that the issuance of these guidance documents will provide information to sponsors to help advance the development of immunotherapies. In addition, a recent guidance (Targeted Therapies in Low-Frequency Molecular Subsets of a Disease) provides FDA’s thinking on the development of therapies that target uncommon specific molecular defects such as those that occur in cancers or genetic disorders. This approach is applicable to immunotherapies and other types of drugs. Additionally, FDA is continuing the forward momentum on site agnostic oncology drug development by actively engaging with stakeholders at professional society meetings and providing further insight on

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this drug development approach in a perspective article published in the New England Journal of Medicine.²

Question. Specifically, how will the FDA address the need for updated clinical trial eligibility, alternative clinical and biomarker endpoints, innovative study designs and accelerated review programs?

Answer. FDA has a variety of mechanisms available to expedite the development and review of anticancer agents, including fast track designation, breakthrough therapy designation, priority review, accelerated approval, and Regenerative Medicine Advanced Therapy (RMAT) designation, established under the 21st Century Cures Act.

As specified in FD&C Act authority added by the 21st Century Cures Act, sponsors of products that have been granted RMAT designation are afforded early interactions to discuss any potential surrogate or intermediate endpoints to be used to support accelerated approval. Accelerated approval for development programs with RMAT designation can be based either on surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites.

In FDA's draft guidance, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, issued in November 2017, FDA encourages flexibility in clinical trial design for regenerative medicine therapies, and describes that FDA will consider clinical trials that incorporate adaptive designs, enrichment strategies, or novel endpoints. The guidance also describes innovative trial designs for these products.

FDA held a public meeting in April 2018 on Evaluating Inclusion and Exclusion Criteria in Clinical Trials, which included discussion of a variety of topics related to eligibility criteria in clinical trials and their potential impact on patient access to investigational drugs, and how to facilitate the enrollment of a diverse patient population. Additionally, FDA is working on multiple draft guidances related to efficient trial designs and clinical endpoints to expedite the development of drugs and biologics.

In March 2018, FDA conducted a workshop on the use of complex innovative designs (CID) in clinical trials of drugs and biological products to inform regulatory decisionmaking. The Agency plans to use the information learned at this workshop to inform the development of a pilot program as well as a draft guidance document on the same topic.

FDA's annual Accelerating Anticancer Agent Development and Validation (AAADV) workshop was developed to expedite the development and validation processes for new anticancer and cancer prevention agents. Likewise, FDA's qualification program for drug development tools, including biomarkers, can help support the use of biomarkers across drug and biologic development programs. This can help aid in optimizing drug development and evaluation, potentially expediting drug development and review of regulatory applications.

OTC SWITCH

Question. The FDA has indicated in its FDA 2018 Strategic Policy Roadmap that it is working on new guidance and regulations that would change the way it approves novel Rx-to-OTC switches. We are hearing from industry that new and existing switch development programs are stalled and would benefit from the Agency's guidance and regulations in their efforts to provide consumer with a wider range of nonprescription products. As you know, switching Rx drugs to OTC can save patients and the healthcare system money while at the same time increasing treatment options.

What is the Agency's timeline to release the guidance and regulations?

Answer. The FDA expects to publish draft guidance on Innovative Approaches for Nonprescription Drug Products in calendar year 2018.

The FDA also intends to publish a proposed rule on Nonprescription Drug Products with an Additional Condition for Nonprescription Use. This proposed rule is listed on the Spring 2018 Unified Agenda of Regulatory and Deregulatory Actions with a projected publication date in 2019.

²Lemery S, Keegan P, and R Pazdur, 2017, First FDA Approval Agnostic of Cancer Site—When a Biomarker Defines the Indication, *N Engl J Med*, 377:1409–1412.

FOREIGN HIGH RISK INSPECTIONS

Question. Over the past several years the Committee has provided FDA with additional resources to develop a targeted, risk-based, and efficient inspection model for high-risk establishments for onsite verifications.

Given the challenges of expanded geography, constantly expanding inventory of foreign exporters, and finite budgetary resources, how will FDA operationalize third party site verification services to select and prioritize FDA foreign facility inspection for the following primary FDA Centers: Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Center for Food Safety and Applied Nutrition (CFSAN)?

Answer. For several years, FDA has successfully leveraged third party services to support its foreign facility inspection program, and the Agency expects that it will continue to do this in the future. For example, in fiscal year 2016, FDA spent \$5.51 million provided to Office of Global Regulatory Operations and Policy (GO) on commercial foreign onsite verification reviews in support of the expanding global coverage. FDA contracted with Dun and Bradstreet (D&B) to provide site verification information on specific facilities. D&B performed site verifications across all FDA's regulated commodities. The remaining funds were used in support of the pharmaceutical Good Manufacturing Practice (GMP) Mutual Recognition Initiative, enhancing the Center for Drug Evaluation and Research (CDER) Site Selection Model, and enhancing regulatory oversight of the foreign food inspection program in the Office of Regulatory Affairs (ORA).

In fiscal year 2017, FDA spent \$4.97 million. GO expanded the number of foreign onsite verifications and facility data provided by D&B for foreign medical device and food establishments. These specific commodities were chosen due to the value and impact that commercial onsite verifications provide these programs. For the pharmaceutical program, GO worked with CDER to issue grants for analysis that supported the development of quality scorecards for pharmaceutical facilities and products, which enhanced oversight by improving the Site Selection Model's identification of high-risk foreign facilities. For the foods program, GO worked with ORA to enhance the research and review of the inventory of high-risk facilities targeted for foreign inspections.

In fiscal year 2018, FDA spent \$4.50 million, as GO continued work with D&B to provide on-site verifications of foreign high-risk medical device and human food establishments. For the devices program, this work stream provided regulatory intelligence on complex supply chains, and business-to-business relationships. For the foods program, GO worked with ORA on the site verifications work in concert with a separate contract with a small-vendor to expand and validate data on high risk foreign facilities. Through these combined efforts, FDA improved the reliability of data for inspection planning, which allowed optimization of resource allocation and enhanced the Agency's oversight of foreign food firms. In the pharmaceutical program, GO worked with CDER to identify additional commercial services and sources for social and news media, such as Brand-Watch and LexisNexis, in an effort to increase the vitality of the Site-Selection and Risk Models and reveal signals about high-risk sites and products.

QUESTIONS SUBMITTED BY SENATOR MITCH MCCONNELL

Question. I commend your July 2017 statement prioritizing harm reduction and committing to bring "foundational rules" to the tobacco regulatory process, which is long overdue and needed to provide greater certainty for the regulated industry. As the FDA moves forward to propose a substantial equivalence rule, what is the agency doing to ensure that the impending proposed rule reflects feedback from stakeholders? What steps are being taken to ensure the rule provides clarity on how FDA plans to regulate "same characteristics" and "questions of public health" standards? Is it FDA's intent that this proposed rule will apply to all tobacco products, including so-called provisional products?

Answer. FDA's comprehensive plan for tobacco and nicotine regulation will serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death. As part of this comprehensive plan, FDA announced that it will issue foundational rules to make the product review process more efficient, predictable, and transparent for manufacturers, while upholding the Agency's public health mission. Among other things, FDA intends to issue proposed regulations outlining what information the Agency expects to be included in Premarket Tobacco Product Applications (PMTAs) and Substantial Equivalence (SE) Reports.

With respect to the proposed SE rule, the content has been informed by the Agency's experience reviewing thousands of SE reports, including questions and feedback

received from applicants during the SE review process. Moreover, when the proposed rule issues, the Agency will solicit comments from the public on all aspects of the rule and will take all of the comments into consideration before issuing a final rule. Additionally, within the proposed SE Rule, FDA intends to pose questions to solicit specific comment on whether FDA should allow streamlined SE Reports for certain types or categories of modifications.

The rule would establish requirements for SE Reports submitted after the effective date of the final regulation, not to those submitted earlier. In particular, this rule would provide greater clarity for industry on what information is required in these applications, while preserving flexibility for industry to determine their predicate, supporting data, and what type of application to submit.

Question. As you know, the proposed regulation to limit the N-nitrosornicotine (NNN) levels found in smokeless tobacco products, which was proposed on the last day of the previous Administration, is of great concern to a number of my constituents who grow tobacco or work in tobacco manufacturing facilities in the Commonwealth. What is the FDA doing to ensure that any final regulation to limit NNN levels in smokeless tobacco products is both workable and technically achievable? Does the Agency have any plans to withdraw the proposed rule and replace it with a new regulation?

Answer. The proposed rule would require that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 microgram per gram ($\mu\text{g/g}$, 1 part per million) of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by product testing.

FDA received almost 8,000 comments on the proposed rule from smokeless tobacco manufacturers, tobacco farmers, public health organizations, trade associations, academia, elected officials (Federal, state, local), Tribes, and individuals. The issues most frequently raised by commenters related to technical achievability, impact on tobacco growers, the effective date, and FDA's public health benefit analysis ("appropriate for the protection of public health"). FDA is currently reviewing and evaluating the comments to determine appropriate next steps.

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

Question. I understand that FDA continues to work towards defining the term "natural" and regulating its use on food labeling after receiving public comments on a number of relevant questions. Can you please provide an update of FDA's ongoing work on this pre-rulemaking initiative?

Answer. In late 2015, FDA sought feedback from consumers and the industry on whether FDA should define the word "natural" on food labeling (80 FR 69905). FDA received and reviewed more than 7,600 comments. FDA recognizes that consumers are trusting in products labeled as "natural" without clarity around the term. Just like other claims made on products regulated by FDA, the Agency believes the "natural" claim must be true and based on science. At the same time, FDA recognizes that there are widespread differences in beliefs regarding what criteria should apply for products termed "natural," and that many of those criteria may not be based on public health considerations. This makes it quite challenging for FDA, which is first and foremost a public health agency. FDA will have more to say on the issue soon.

Question. Despite the FDA's recent actions to solicit and review information on premium cigars and ultimately consider changing how it regulates the product, several current or pending requirements for premium cigar products remain in place. This includes the August deadlines for costly warning labels on packaging and advertising. If FDA is currently in a process that may change its approach to the premium cigar category, why does it not delay or suspend these deadlines and requirements until it ultimately comes to a final decision?

Answer. Due to the continued interest in the regulation of "premium cigars," FDA issued an Advance Notice of Proposed Rulemaking on March 26, 2018, to provide an opportunity for the public to provide new information for the Agency to consider. In particular, FDA is seeking comments and scientific data related to how to define a "premium" cigar and the patterns of use and resulting public health impacts from these products. The Agency will explore any new and different questions raised and consider additional data that is relevant to the regulatory status of premium cigars.

In the meantime, all cigars remain subject to regulation based on FDA's previous determination that there was no appropriate public health justification to exempt "premium" cigars.

The deeming rule took effect on August 8, 2016. Cigar label rotational warning plans were initially due to the Agency on May 10, 2017. The Agency provided a compliance period of three additional months to provide industry time to come into com-

pliance with the cigar warning label requirements. More than 300 companies are working toward complying with the August compliance date and have already submitted cigar warning label rotational plans to the FDA, all of which were reviewed by the Agency. Of the more than 300 cigar warning plans submitted to the Agency, almost all of them were approved.

Question. The SBA's Office of Advocacy found fault with the FDA's prior rulemaking on premium cigars for the FDA's failure to properly conduct an economic analysis on the impact of the rule on small businesses. What is your plan to make sure you have performed the necessary analysis?

Answer. In the preamble to the proposed deeming rule, FDA sought comment on two options regarding the categories of cigars that would be covered by this rule—specifically, whether all cigars should be subject to deeming or if “premium” cigars should be excluded from deeming. FDA sought those comments because while the Agency recognized that all cigars are harmful and potentially addictive, it had been suggested that different kinds of cigars may have the potential for varying effects on public health.

FDA carefully reviewed comments, data, and information submitted to the docket, including many comments from cigar users and the cigar industry, and concluded in the final deeming rule that deeming all cigars, rather than a subset, more completely protects the public health. Ultimately, FDA concluded that all cigars pose serious negative health risks, the available evidence does not provide a basis for FDA to conclude that the patterns of “premium” cigar use sufficiently reduce the health risks to warrant exclusion, and “premium” cigars are used by youth and young adults. FDA examined the impacts of the final rule, including considering the economic implications of the final rule for small entities and analyzing regulatory options that would minimize any significant impact of the rule on small entities.

More recently, as part of the Agency's comprehensive plan for regulation of nicotine and tobacco, FDA stated that it would solicit additional comments and scientific data related to the patterns of use and resulting public health impacts from “premium” cigars and consider the appropriate regulatory status of “premium” cigars. FDA published an Advance Notice of Proposed Rulemaking (ANPRM) on March 26, 2018, requesting relevant new and different information, data, and analysis not submitted in response to FDA's proposed deeming rule, on topics including, but not limited to patterns of use associated with “premium cigars” generally and among youth and young adults specifically, public health considerations associated with “premium cigars,” and the definition of “premium” cigars. On June 8, 2018, FDA extended the comment period, and the comment period for this ANPRM closes on July 25, 2018. The ANPRM does not propose a specific regulatory action. FDA will consider the submissions, which may inform regulatory actions FDA might take with respect to “premium” cigars. A future regulatory action would comply with any applicable requirements to conduct an economic analysis.

Question. With the Advance Notice of Proposed Rulemaking process underway—why does the agency continue to enforce costly requirements on premium cigars when it may amend how regulates the category? Are there steps that can be taken through enforcement discretion or otherwise to minimize these burdens while the FDA's review process takes place?

Answer. In the preamble to the proposed deeming rule, FDA sought comment on two options regarding the categories of cigars that would be covered by this rule—specifically, whether all cigars should be subject to deeming or if only those cigars not considered “premium” should be subject to deeming. FDA sought those comments because it had been suggested that different kinds of cigars may have the potential for varying effects on public health.

FDA carefully reviewed all comments, data, and information submitted to the docket, including many comments from cigar users and the cigar industry, and concluded in the final deeming rule that regulating all cigars, rather than a subset, more completely protects the public health. Ultimately, FDA concluded that all cigars pose serious negative health risks.

Due to the continued interest in the regulation of “premium cigars,” on March 26, 2018, FDA issued an Advance Notice of Proposed Rulemaking to provide an opportunity for the public to provide new information for the Agency to consider. In particular, FDA is seeking comments and scientific data related to how to define a “premium” cigar and the patterns of use and resulting public health impacts from these products. The Agency will explore any new and different questions raised and consider additional data that is relevant to the regulatory status of premium cigars.

In the meantime, all cigars remain subject to regulation based on FDA's previous determination that there was no appropriate public health justification to exempt “premium” cigars.

QUESTION SUBMITTED BY SENATOR CINDY HYDE-SMITH

Question. Commissioner Gottlieb, I am pleased that the FDA Office of the Chief Scientist has been working with the University of Mississippi Medical Center to explore ways to incorporate physiological modeling into the FDA's regulatory process for medical products. Can you please provide me with an update on that work? Is the FDA working to finalize an affiliation agreement with an academic institution like UMMC for this purpose?

Answer. Regulatory evaluation of modeling and simulation is advancing alongside the power and sophistication of the tools. Therefore, FDA formed an Agency-wide working group on modeling and simulation under the auspices of the Office of the Chief Scientist with objectives that include aligning regulatory decisionmaking with modeling and simulation and, where appropriate, employing in silico clinical trials. Completing these objectives will advance the in silico clinical trial framework for the medical product Centers and will establish the appropriate methods and guidelines necessary to implement in silico clinical trials. Scientists within FDA, particularly those leading the Modeling and Simulation Working Group, have had numerous interactions with UMMC over the last year and are working to formalize a research collaboration. FDA intends to continue advancing these methodologies and techniques from both a scientific and regulatory perspective to best take advantage of their benefits for continued product innovation and more rapid introduction of life saving technology to U.S. patients.

QUESTIONS SUBMITTED BY SENATOR JEFF MERKLEY

OVERALL BUDGET REQUEST

Question. The overall budget request for FDA is more than \$400 million for a significant number of new investments. Can you please prioritize those requests?

Answer. The President's proposed fiscal year 2019 Budget includes \$400 million for initiatives aimed at supporting new and ongoing efforts to foster more investment and innovation in the development of therapeutics and diagnostics that target unmet medical needs; advance drug and device competition; stand up new domestic industries—such as pharmacy outsourcing facilities; and create more modern, domestically-based manufacturing, including continuous manufacturing of drugs and biological products, including vaccines. These manufacturing platforms can bring more businesses back to the U.S., help lower drug and device development costs, and reduce the risk of shortages. Investing in these initiatives will help the FDA advance goals that we all share: improved treatment and diagnostic options for patients; lower healthcare costs; the development of new industries that will lead to U.S.-based jobs; and manufacturing advances that are more reliable, lower cost, and high quality.

As the Agency that regulates \$2.4 trillion of consumer products, FDA can think of no better place to make an impact. While each of the proposed fiscal year 2019 initiatives are important, FDA would highlight those that the Agency believes could be the most fundamentally transformational for FDA:

Continuous Manufacturing.—The President's fiscal year 2019 Budget Request for FDA includes \$58.2 million to promote domestic manufacturing, including continuous manufacturing. These technologies have great potential to accelerate new, more targeted therapies, enhance product quality, and bolster stability in the U.S. drug supply to meet domestic and global needs. These new manufacturing platforms may be especially important in the development of personalized medicines and innovations in cell- and gene-based therapies and vaccines.

New Medical Data Enterprise.—The fiscal year 2019 Budget request includes \$100 million to advance the use of real-world experience to better inform patient care and provide more efficient, robust, and potentially lower-cost ways to develop clinical data that can inform product review and promote innovation. Expanding FDA's capacity to utilize real-world evidence to evaluate the pre- and post-market safety and effectiveness of medical products will generate processes that could improve the efficiency of the regulatory process, better inform patients and providers about pre- and post-market safety, reduce some of the burdens that drive up the time and cost required to bring beneficial innovations to the market, and address barriers that can make certain important safety and effectiveness information around the real-world use of products hard to collect and evaluate.

Knowledge Management System for New Drug Development.—The fiscal year 2019 budget request includes \$57.5 million to build a knowledge management system and portal to existing and developing information on drug development and previous regulatory decisions. This platform would enable FDA to store and manage the collective experience of our medical review staff to identify how decisions are made across different functions, the scientific precedents established in the course of the review process, and the knowledge FDA has developed.

Question. Are they scaleable?

Answer. Yes, these projects are scaleable.

CANCER IMMUNOTHERAPY

Question. Given the substantial clinical benefit and unique mechanisms of action reported for tumor immunotherapy across a large number of cancers, how is the FDA planning to continue its forward momentum in immuno-oncology drug development for patients with cancer?

Answer. Cancer immunotherapies have demonstrated clinical benefit across many different types of cancer, despite different sites of origin, based upon their unique mechanisms of action. The first such approval was in May 2017 for pembrolizumab for use in MSI-high or mismatch repair deficient solid tumors that have progressed following prior treatment when there are no satisfactory alternate treatment options. In addition to such monoclonal antibody-based cancer immunotherapies, many personalized immunotherapies, including genetically-modified cellular therapies such as chimeric antigen receptor T-cells and other cellular therapies, intended for the treatment of cancer are either approved or in development. Those in development are eligible for a variety of programs intended to expedite their development and review, including fast track designation, breakthrough therapy designation, priority review, accelerated approval, and Regenerative Medicine Advanced Therapy (RMAT) designation, established under the 21st Century Cures Act.

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ADDED SUGARS

Question. On the issue of added sugars, FDA's most recent suggestion to allow honey and maple syrup industry to label jars of pure honey or maple syrup as having "added sugars" with an asterisk and explaining text, has been described as further confusing the issue, and ultimately not helpful to consumers.

Can you please provide an update on FDA's most recent and planned actions to ensure clarity for consumers that pure honey and maple syrup do not have any added sugars?

Answer. FDA is sensitive to the honey and maple syrup industries' concerns regarding the declaration of added sugars on single-ingredient products. On June 19, 2018, FDA announced that the Agency is taking another look at this issue following comments received from the public regarding FDA's original March 2, 2018, draft guidance titled "The Declaration of Added Sugars on Honey, Maple Syrup, and Certain Cranberry Products." The feedback that FDA received is that the approach laid out in the draft guidance does not provide the clarity that the Agency intended. It is important to FDA that consumers are able to use the new Nutrition Facts label to make informed, healthy dietary choices. FDA looks forward to working with stakeholders to devise a sensible solution.

MEDICAL DATA ENTERPRISE

Question. The budget includes a \$100 million request to "create a new medical data enterprise", specifically conducting evidence evaluation, including electronic health records of at least 10 million individuals. What specifically are we buying with this money?

Answer. The requested funding would pay for a number of cooperative agreements and contracts that enable FDA to advance active surveillance and more modern device, drug, and biologic product evaluation.

The development of data infrastructure will be supported through continuation of existing and/or new cooperative agreements. Data infrastructure includes support for the maturation of Coordinated Registry Networks (CRNs) and other data sources. Technical developments include harmonization of minimum core data elements for a variety of clinical areas. Libraries of minimum core data elements are needed to ensure consistency and interoperability between health information systems, which contribute to consistency in how data are captured and analyzed throughout the learning healthcare ecosystem.

In addition, the funding would continue support of technical developments in structured data capture and unstructured data generation and analysis. This work with the clinical entities that provide data to registries will improve the efficiency and accuracy of data collection from clinical care in general, minimize duplication

of parallel data collection that exists today (one for clinical care and one for research). This investment could support many Federal efforts which rely on data collection.

Another cooperative agreement would be for the purpose of implementation of active surveillance using Coordinated Registry Networks (CRNs) Community of Practice and other data sources. Active surveillance requires registries to have high-quality linkages with other data sources. The cooperative agreement would require the participating parties to develop and/or apply methodologies and tools (including but not limited to, DELTA software) to enable more effective distinction between the role of device, operator, and patient characteristics as part of outlier identification of potential safety issues.

The requested funding would also support a cooperative agreement to continue work on unique device identifier (UDI) adoption in a variety of electronic data sources (e.g. electronic health records, registries, claims data). This work is needed to scale the evaluation of the impact of capturing UDI in electronic data sources on advancing device-specific studies (e.g., to address device-specific questions in the real-world setting). Capturing UDI in these electronic data sources is critical for many device studies that would use those sources because the UDI provides precise identification of the device being evaluated. FDA regulations already require inclusion of a UDI on most device labels. Use of the UDI in electronic healthcare information (such as EHRs or registries) is an essential step for the development of the National Evaluation System for health Technology (NEST).

In addition, the requested funding would be used to advance the development and use of mobile apps and related technologies for patient input. The growing use of mobile apps and related technologies provides opportunities to improve data collection. New methods for obtaining patient input and informed consent and for communication between study participants and study sponsors could reduce the time and cost of studying new medical products.

This funding would also significantly expand the FDA Sentinel initiative, including the Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety (BEST) system. BEST is administered through contracts and consists of a small number of electronic health record (EHR)-based healthcare providers and partners; the additional funding would enable us to fund contracts to bring more providers and tens of millions more patient EHR records into BEST. This will dramatically improve our data infrastructure and capabilities to gather and evaluate real-world data, especially for serious and rare adverse events, and improve our ability to meet our public health mission of ensuring the safety and effectiveness of vaccines, blood products and new advanced therapies. Biologic products differ from drugs and devices and have their own unique 'big healthcare data' needs. For instance, while most drugs in large medical databases have their own product codes, most biologic products do not. Furthermore, biologics such as blood products have their own coding system which needs to be added to each provider system. These nuances and others challenge our ability to readily identify patient uses of blood, advanced therapeutics and some vaccines—so the funding would support needed, additional EHR data sources, millions of patients, development of new data models, inclusion of new data fields, new tools and methods to specifically address these challenges.

Lastly, this increase request would also be used by the Center for Veterinary Medicine to expand surveillance by the National Antimicrobial Resistance Monitoring System (NARMS) by funding new and strengthening existing cooperative agreements and interagency agreements. This data will help provide a more complete picture of antimicrobial resistance and strengthen the basis for regulatory decisions to address this important public health challenge.

Question. How do you ensure patient privacy is maintained when doing something like this?

Answer. Patient privacy and data security are among the highest priorities for the medical data enterprise. Major sources of data (such as Sentinel, PCORNet, and Coordinated Registry Networks) are maintained behind each data owners firewall and personally identifiable information is not shared. Analysis of the data across data sources is accomplished through use of distributed analytics, where analysis is done behind the firewall and only aggregate, non-patient level data are shared. Under these procedures, data that can identify an individual patient are not shared. All aspects of the medical data enterprise advanced by FDA will: (1) build on the existing privacy and security processes/procedures established by existing data sources; (2) comply with the Common Rule, as applicable; and (3) promote development and testing of distributed analytics and other approaches designed to protect the privacy and security of patients.

Question. In what ways could this investment result in lower priced drugs and medical devices?

Answer. Production of evidence to support regulatory decisionmaking can be an expensive and time-consuming endeavor. The purpose of the new medical data enterprise is to decrease the time and cost of evidence generation and to serve as a resource that will be available for use not only by FDA but also by the device and pharmaceutical industries, academia, and other stakeholders. According to the Medical Device Innovation Consortium, the new medical data enterprise has already demonstrated “faster, safer, more cost-effective” evidence generation using real-world data sources. These efficiencies could lead to lower costs of medical products by reducing the amount of investment to be recovered through higher sales prices. In addition, the same systems being used to support regulatory decisionmaking could be used to evaluate the net benefit of medical products.

Question. Are there precursors that show this type of investment works?

Answer. Early investments in the foundations of the National Evaluation System for health Technology (NEST) and in prototype studies have already demonstrated a return on investment (ROI). CDRH has documented increasing numbers of regulatory decisions that use real-world evidence with over 50 decisions since 2015. For instance, the Transcatheter Valve Therapy (TVT) coordinated registry network (CRN) has thus far supported 23 regulatory decisions and ensured evidence-based evaluation of the application of TVT technology. Before the use of the TVT CRN, the U.S. was 42nd in the world in approval of this breakthrough lifesaving technology. It is now first in the world in approving the mitral valve-in-valve application, a new intended use for this device.

Documentation of value created by the TVT CRN is based on ROI and time saved in conducting necessary regulatory studies. For both ROI and time saved analyses, studies were compared that used the TVT CRN with those that would have been required if the registry did not exist. The decisions based on use of the TVT CRN generated evidence for three TVT device manufacturers. The ROI was estimated to be greater than 400 percent. Time saved by using the CRN ranged from months to years. The CRN method is one example of evidence generation that creates value for manufacturers and the broader device ecosystem. Claims data have been linked to other registries to further augment their value in assessing evidence of longer-term device performance. For example, Vascular Quality Initiative (VQI) registry was linked to claims data to create the Vascular Implants Surveillance and Interventional Outcomes Network (VISION) and the American Joint Replacement Registry (AJRR) was linked to claims data to contribute to Orthopedic CRN.

MODERNIZING GENERIC DRUG DEVELOPMENT AND REVIEW

Question. The budget request includes \$38 million to modernize the way FDA reviews generic drugs.

If this funding is provided, what changes would generic drug manufacturers see when interacting with FDA?

Answer. With additional funding, FDA will create a new review platform—the Knowledge-aided Assessment & Structured Application (KASA) platform—to modernize generic drug review from a text-based to a data-based assessment. The KASA will enable a structured review that will make the application review process more efficient and allow deficiencies to be spotted earlier. This will allow the FDA to provide earlier feedback to generic drug applicants that will, in turn, help to reduce multiple cycles of application review, one of our key aims and a primary focus of our overall efforts to speed market access to new generic medicines. Going through multiple review cycles is one of the primary reasons why the approval of generic drug applications is sometimes delayed many years. We anticipate the new KASA system will promote consistent drug product evaluations, enhance the predictability of regulatory decisions and facilitate generic entry by reducing the number of review cycles that applications undergo, and, ultimately, allowing more generic applications to be approved after the first cycle.

The new platform will also enable more efficient and robust knowledge management across different aspects of the FDA’s review process, helping reviewers capture and manage all of the information about products allowing for more seamless and effective product surveillance based upon quality and risk. This system will benefit both the agency and generic drug sponsors by increasing overall speed and efficiency of the pre- and post-market processes.

Having a structured template that replaces the current largely narrative-based review will allow for more consistent and predictable entry and analysis of data. Current assessments require manual review of the entire application. KASA will enable

automated analysis of some portions of the application, which will save time, and ensure consistency.

Question. Assuming that FDA received a complete application from a manufacturer, how much FDA review time could be saved by using this new system?

Answer. The Knowledge-aided Assessment & Structured Application (KASA) platform will enable a structured review that will make the application review process more efficient and allow deficiencies to be spotted earlier. This will allow the FDA to provide earlier feedback to generic drug makers that will, in turn, help to reduce multiple cycles of application review, one of our key aims and a primary focus of our overall efforts to speed market access to new generic medicines. Going through multiple review cycles is one of the primary reasons why the approval of generic drug applications is sometimes delayed many years. We anticipate the new KASA system will promote consistent drug product evaluations, enhance the predictability of regulatory decisions and facilitate generic entry by reducing the number of review cycles that applications undergo, and, ultimately, allowing more generic applications to be approved after the first cycle.

Question. How long would this system take to develop and implement?

Answer. The first stage of KASA development could be 1–2 years away, and the last stage as much as 4–5 years.

Drug pricing continues to be hindered by industry maneuvering to keep generic drugs off of the market, or to make it more difficult for them to develop their products.

Question. What are the major issues regarding generic drugs and their entry to the marketplace as soon as legally possible?

Answer. While FDA does not have a direct role in drug pricing, when more than one generic version of a drug is approved and marketed, it can spur competition and facilitate affordable options for consumers. Under the Drug Competition Action Plan, we continue to review our practices and policies to identify areas to facilitate generic drug market entry at the earliest possible date.

The Drug Competition Action Plan addresses the major issues regarding generic drugs and their entry into the marketplace in the following ways:

- Streamlining the generic drug review process to increase efficiency and effectiveness, with the ultimate goal of more approvals. By ensuring that regulatory requirements are streamlined, predictable, and science-based, we can help reduce the time, uncertainty, and cost of drug development.
- Supporting development and enhancing review of complex generic drug products, which have traditionally been more challenging and can lack generic competition, through product development meetings, pre-submission meetings, and mid-review cycle meetings for applicants and prospective applicants of complex generic drug products.
- Reducing the “gaming” that delays generic drug approvals and extends brand monopolies beyond what Congress intended. One example of such gaming is the increasing unavailability of certain branded products for comparative testing. We also see problems accessing testing samples when branded products are subject to limited distribution.

Question. We note that there are other factors that inform when a generic drug product enters the market after FDA’s approval, including a generic drug sponsor’s decision not to market the product due to business reasons, or as a result of a settlement with the brand company in a related patent litigation.

How can Congress be helpful, both with funding and legislative needs?

Answer. The Agency is continuously reviewing its authorities and regulations to ensure that we have the tools necessary to facilitate generic competition. We appreciate your attention to these very important issues, and we welcome the opportunity to work with Congress and provide feedback on any proposals you and your colleagues may have.

QUESTIONS SUBMITTED BY SENATOR DIANNE FEINSTEIN

FOOD SAFETY

Question. Over the last several months, there have been alarming reports of romaine lettuce contaminated with E. coli that has led to illnesses and even deaths throughout the United States.

The Centers for Disease Control estimates that each year, 48 million people get sick from a foodborne illness, 128,000 are hospitalized, and 3,000 die. In response to the likelihood that foodborne illness will continue to be a major public health concern, Congress passed the Food Safety Modernization Act (FSMA) in 2011. Since en-

actment, Congress has provided additional budget authority to support FSMA implementation, including for coordination and outreach with a wide cross-section of stakeholders, public health and consumer representatives as well as members of the agricultural and processed foods industries.

In order to protect the public's health, strengthen consumer confidence in American food products, and ensure this law is fully implemented, it is necessary that FDA has the resources it needs. But in the fiscal year 2019 budget request, the agency didn't include significant increases to continue FSMA implementation.

Can you provide a detailed justification for why the FDA believes the requested funding level is sufficient to continue full implementation of the Food Safety Modernization Act?

Answer. FDA appreciates Congress's support of its FSMA implementation efforts. As of fiscal year 2018, FDA has received approximately \$327 million in funding to directly support implementation.

FDA has dedicated a substantial portion of these resources to ensuring industry has tools to properly prepare for implementation of the seven foundational FSMA rules and has supported state partners in preparing for FSMA implementation. The Agency has made significant progress in these efforts, including the following:

- Established and funded public-private alliances to provide training for the Preventive Controls for Human Food (PCHF) and Preventive Controls for Animal Food (PCAF) rules, as well as jointly funding with the U.S. Department of Agriculture (USDA) produce safety and sprouts alliances to offer training on the Produce Safety Rule (PSR).
- Provided multi-year funding for state agencies (including funding 43 states in fiscal year 2018) to develop programs for helping to implement the PSR, including outreach and education to meet the specific and unique needs of their farmers and growing communities.
- Established a Produce Safety Network of FDA experts, located throughout the country, to provide technical assistance and outreach to industry and state partners.
- Issued draft guidances on the PCHF, PCAF, and Foreign Supplier Verification Programs (FSVP) rules to assist industry in meeting FSMA requirements.
- Released an online Food Safety Plan Builder to help industry create the food safety plans that are a cornerstone of the PCHF rule.
- Issued a Current Good Manufacturing Practice (CGMP) draft guidance to help industry understand and comply with relevant provisions of the PCAF rule.
- Issued draft guidances to assist industry in meeting certain supply chain requirements of the PCHF and FSVP rules.
- Initiated and continue to conduct inspectional activities under the modernized CGMP provisions for both human and animal food, PCHF, and FSVP.

Question. The President's fiscal year 2019 Budget allows the Agency to maintain the progress FDA has achieved. The Agency will continue to provide tools for successful FSMA implementation and, as always, FDA will leverage available resources for maximum impact to achieve its public health goals. How is FDA coordinating with states to ensure that farmers are able to understand and comply with the regulations that FDA has issued pursuant to FSMA?

Answer. Since FSMA was passed in fiscal year 2011, FDA has devoted significant resources to collaborations with public and private partners in state, Federal, tribal, and foreign governments, industry, and academia to help ensure produce farmers can successfully implement the FSMA Produce Safety Rule, which the Agency published in November 2015. FDA has particularly focused on developing and funding various mechanisms to offer small and very small farms and other small businesses information on how to understand, implement, and comply with applicable FSMA rules, including how to satisfy the requirements for the qualified exemptions. Two of these mechanisms specifically involve FDA's coordination with state partners: the State Cooperative Agreement Program (CAP) and the educational On Farm Readiness Reviews (OFRR) conducted by states through the National Association of State Departments of Agriculture (NASDA).

FDA has provided funds to state agencies to develop produce safety programs. The state agencies involved in the CAP have been funded to help implement the Produce Safety Rule, and a portion of these funds are being used to conduct education and outreach to produce farmers, as well as providing technical assistance to help them understand and comply with the Produce Safety Rule. Under the CAP, each state grantee is developing and implementing outreach and education programs that address the specific and unique needs of its farmers and growing community to ensure that they are educated and prepared for compliance.

FDA also has funded NASDA to develop programs and resources to assist State Departments of Agriculture to help implement the Produce Safety Rule. A portion of these funds are being used to develop and conduct the OFRRs that help produce farmers assess how prepared their produce farm is to comply with the Produce Safety Rule before routine regulatory inspections begin. This voluntary OFRR program was developed by the State Departments of Agriculture and Land Grant University Cooperative Extension Specialists, via the leadership of NASDA with a portion of funds provided by FDA.

Finally, FDA established the Produce Safety Network (PSN) comprising 25 regionally-based FDA personnel to support the efforts of farmers, Federal, state and local regulators, and other key stakeholders to implement the Produce Safety Rule. The PSN works with farmers to address their education needs by connecting them with educational resources provided by the state and other sources.

Question. I believe there is more the FDA can do to restore consumer confidence in the recall process, especially given that the majority of recalls are voluntary. It is critical that food recalls are quickly initiated and effectively carried out. Does the FDA regularly collect and publish the information about recalls included in the OIG Report (Report No. A-12-16-01502), such as the amount of time that elapsed from when FDA learned about a contamination problem to when a recall was initiated?

Answer. FDA is committed to continuously improving how the Agency manages situations where either contaminated or potentially contaminated foods are in the food supply, which includes FDA's handling of food recalls. FDA routinely makes information about specific recalls available to consumers and provides annual statistics associated with recalls.

FDA tracks several data points related to recalls, including recall initiation date (by fiscal year), FDA product type, recall classification, recall status, recalling state, and classification date. FDA tracks recall initiation dates, as those reflect the timing when the adequate information has been compiled to support a recall determination and Agency recall activities. Prior to the recall initiation date, situations can be very fluid, with information coming into FDA from multiple sources, some of which cannot be verified or may contradict other information coming into FDA. Due to these issues, FDA does not generally track the time period prior to the recall initiation date.

The recall data are publicly available on the FDA website at the FDA Data Dashboard in aggregated form and can be filtered according to the data points listed above. In addition to the dashboard, FDA also creates a publicly available annual enforcement statistics report, a comprehensive source of information about a variety of food related activities, including recalls, recall classifications, recalled products, food import debarments, warning letters, injunctions, and seizures. The annual report is also available on FDA's website.

FDA also provides consumers timely information about specific recalls to help them determine whether they may have been exposed to the product or if the recalled food may be in their home. Among other things, FDA reposts on its website press releases issued by companies regarding their recalls and posts information about recalls on the weekly FDA Enforcement Report that lists the Agency's recalls and the classification of the level of health hazard, as well as linking relevant recall notices to foodborne outbreak web postings. During an outbreak, FDA routinely posts information about the investigation, which can typically include significant dates in the investigation, relevant epidemiologic details, traceback linking a particular source or establishment, and the date a firm takes action. Taken together, FDA's tools for making specific recall information and aggregate recall data publicly available have helped to maintain consumer confidence in the recall process.

Question. How many times has the FDA initiated the mandatory recall process before a company decided to voluntarily recall its product?

Answer. FDA has initiated use of its mandatory recall authority three times since the Agency was granted mandatory recall authority by the FDA Food Safety Modernization Act of 2011. Two times, the firms voluntarily initiated recall after receiving a letter from FDA initiating the mandatory recall process. A third instance occurred earlier this year when Triangle Pharmedicals, LLC failed to respond to FDA's letter affording an opportunity to voluntarily initiate a recall related to the ongoing outbreak investigation of Salmonella-contaminated kratom products. On April 2, 2018, FDA proceeded to the issuance of the final order requiring mandatory recall.

Question. An annual report of this type would help ensure that the deficiencies identified in the OIG report do not persist.

Is the FDA willing to commit to providing to this Subcommittee and to the public, an annual report detailing the Agency's food recall activities?

Answer. FDA already routinely makes information about specific recalls available to consumers, as well as annual statistics associated with recalls. The FDA Data Dashboard contains compliance statistics, which includes data on recalls. Data on the dashboard can be filtered by fiscal year, FDA product type, recall classification, recall status, recalling state, and classification date. The Dashboard can be accessed on the FDA website. In addition to the dashboard, FDA also maintains a publicly available annual enforcement statistics report, which is a comprehensive source of information about a variety of food related activities, including recalls, recall classifications, recalled products, food import debarments, warning letters, injunctions, and seizures. The annual report is also available on FDA's website. In addition, FDA prepares annual reports on the use of mandatory recalls, pursuant to section 206 of the Food Safety Modernization Act. This can be accessed on the FDA website.

FDA would be happy to meet with Subcommittee staff to discuss these data and to share information provided to OIG in response to its report. The Agency continues to work with OIG to provide information about improvements associated with the recommendations in OIG Report A-12-16-01502 on FDA's food recall process.

ANTIBIOTIC RESISTANCE

Question. I strongly support the FDA's focus in recent years on the challenges of antibiotic use in animal agriculture and the need to address outstanding barriers to effective stewardship. With Guidance for Industry #209 and Guidance for Industry #213 now fully in effect, efforts to end production uses of medically important antibiotics, encourage voluntary removal of production claims by drug sponsors, and strengthen the involvement of skilled veterinarians in animal production through the mandating veterinary oversight represent a giant leap forward.

However, there are still significant problems. First, FDA announced in September 2016 that it was seeking comments on antibiotics used in feed or water that lack a defined duration of use on their label. The comment period closed over a year ago.

Please provide an update on the status of this important focus area and how you plan to make progress on these drug label duration issues in the coming year.

Answer. FDA is developing additional actions to ensure judicious use of medically important antimicrobials. Last January, FDA published its key initiatives for the next 5 years, which include the following: (1) Align antimicrobial drug products with the principles of antimicrobial stewardship in veterinary settings; (2) Support efforts to foster stewardship of antimicrobials in veterinary settings; (3) Assess the impact of strategies intended to curb the emergence of antimicrobial resistance associated with the use of antimicrobial drugs in veterinary settings.

To further build on progress and ensure judicious use of antimicrobial drugs in veterinary settings, FDA is working to incorporate these key initiatives into a more detailed multi-year plan to be published later in 2018. This plan includes steps for addressing concerns about products that lack defined durations of use.

FDA received numerous substantive comments in response to its request for public comment on duration of use. The Agency has evaluated the comments and is in the process of developing a specific strategy for addressing this issue. Any changes to such use conditions will be based on sound science and available evidence.

This continues to be an agency priority, as it will support overall efforts to foster stewardship of medically important antimicrobial drugs in food-producing animals and help preserve the effectiveness of these antimicrobials in animal and human medicine.

Question. Second, we still do not have sufficient data to determine if the changes in FDA guidance are significantly reducing the use of medically important antimicrobials in agriculture. In response to questions from Senator Udall at the hearing, you noted that more data is always better in order to understand and respond to a public health concern.

Can you provide an update as to what actions the FDA is planning on taking this year related to enhancing efforts to collect on-farm data, both through the National Antimicrobial Resistance Monitoring System (NARMS) and through joint efforts with the Centers for Disease Control and the U.S. Department of Agriculture?

Answer. FDA is committed to reducing the rate of development of antibiotic resistance by fostering the judicious use of antimicrobial drugs in animals. The Agency has issued a number of important guidance documents and regulations to support its judicious use strategy and has actively engaged in outreach efforts to support effective implementation.

The National Antimicrobial Resistance Monitoring System (NARMS) is a critical interagency collaboration between FDA, U.S. Department of Agriculture (USDA), and the Centers for Disease Control and Prevention (CDC), for tracking antimicrobial resistance in foodborne bacteria in the U.S. In June 2017, FDA's Science

Board recommended activities to enhance NARMS following the One Health framework. One recommendation was to explore a possible on-farm component implemented by the USDA–APHIS National Animal Health Monitoring System (NAHMS). NAHMS is currently exploring partnerships to conduct longitudinal studies to collect on-farm data on antimicrobial use and resistance. In addition, a meeting of USDA, FDA and CDC officials was held in May 2017 in Ithaca, NY to discuss how resistance surveillance in animal pathogens can be established, with a view to benefit animal and human health.

FDA and USDA continue to work in close collaboration to foster antimicrobial stewardship in veterinary settings and enhance data collection on antimicrobial use and resistance. FDA has provided input to USDA's Center for Epidemiology and Animal Health on surveys to collect information on antimicrobial use in animal agriculture. Additionally, FDA continues to fund two cooperative agreements to support collection of data on antimicrobial use in U.S. animal agriculture, specifically in the poultry and swine industries and on-farm use data for dairy and feedlot cattle. FDA expects these pilots to provide part of the baseline information about on-farm antimicrobial use practices and assist in developing long-term functional and efficient antimicrobial use monitoring and reporting systems for food animal production settings.

DIETARY SUPPLEMENTS

Question. I am concerned by the lack of resources dedicated to oversight of the safety of dietary supplements.

Given the growing demand for and use of dietary supplements, does the FDA have plans to request increased resources for the Office of Dietary Supplement Policy?

Answer. FDA appreciates the Committee's continued interest in the oversight of dietary supplements. The dietary supplement industry has grown steadily since enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA), when Congress found that an estimated 600 dietary supplement manufacturers in the United States produced approximately 4,000 products, with total annual sales of those products reaching at least \$4 billion. Today, nearly 25 years later, the dietary supplement market is worth in excess of \$40 billion, with current estimates ranging from 50,000 to 80,000 different products produced through a global supply chain that includes approximately 7,000 facilities. The market has grown in scope, as well as size, and now encompasses a range of products far broader than it was when DSHEA was enacted.

FDA created the Office of Dietary Supplement Programs (ODSP) in December 2015, elevating the program from its previous status as a division within the Center for Food Safety and Nutrition (CFSAN), reflecting the Agency's recognition that this evolution required a higher priority for dietary supplement regulation if FDA is to effectively fulfill its public health mission. In doing this, CFSAN realigned resources within the base to expand ODSP from 19 to 26 FTEs.

Although dietary supplement safety is a priority, there are currently no plans to request additional resources towards the dietary supplement program.

Question. Does the FDA plan on scaling up outreach and technical assistance to dietary supplement manufacturers to ensure compliance with the Dietary Supplement Health and Education Act?

Answer. Although FDA is not currently planning to scale up outreach to dietary supplement manufacturers, FDA is committed to continued engagement with stakeholders, including dietary supplement manufacturers, both through proactive outreach and by responding to inquiries to help firms understand how to comply with the Dietary Supplement Health and Education Act of 1994 (DSHEA) and related regulations. As a matter of practice, FDA regularly grants meeting requests from stakeholders, accepts invitations to participate in industry training and educational events, and strives to respond in a timely and meaningful manner to requests for technical assistance.

MAMMOGRAPHY QUALITY STANDARDS ON BREAST DENSITY REPORTING

Question. It was encouraging to see that the Food and Drug Administration has recognized the importance of patients receiving their own medical information regarding breast density when they have a mammogram by identifying the need to modernize mammography standards as part of the FDA's major goals in the Unified Agenda, as well as Commissioner Gottlieb's recognition of breast density as a risk factor for breast cancer.

What is your timeline for announcing amendments proposed in the Unified Agenda to update the regulations issued under the Mammography Quality Standards Act of 1992, particularly those related to breast density reporting directly to patients?

Answer. FDA announced in OMB's Spring 2018 Unified Agenda an estimated August 2018 publication date for its proposed amendments to the implementing regulations of the Mammography Quality Standards Act of 1992. FDA is taking this action to address changes in mammography technology and mammography processes that have occurred since the regulations were published in 1997 and to address breast density reporting to patients and healthcare providers.

Question. Will you commit to amending regulations to allow patients to receive their own personal medical information by including appropriate information about breast density on the patient's mammography summary, including, at a minimum, a qualitative assessment of the patient's personal breast density, an explanation of the effect of breast density in masking the presence of breast cancer on a mammogram, and a reminder to patients that individuals with dense breast tissue should talk with their providers if they have any questions or concerns about their summary?

Answer. FDA is committed to ensuring that patients and their healthcare providers receive all the information available from mammograms in the lay summaries and medical reports they receive, to be able to make informed breast healthcare decisions. FDA has drafted proposed amendments to the implementing regulations of the Mammography Quality Standards Act of 1992 that, among other updates, address breast density reporting, and has announced in OMB's Spring 2018 Unified Agenda an estimated August 2018 publication date for the proposed amendments.

PHthalATES

Question. Two years ago, 11 national health and consumer organizations filed a petition with the FDA requesting a ban on the use of phthalate chemicals in food contact substances due to significant health concerns. The FDA has yet to respond to this petition.

When will FDA publicly respond to this petition?

Answer. FDA continues to actively review the subject Food Additive Petition (FAP 6B4815). The petition was filed on April 12, 2016. In the Federal Register of May 20, 2016 (81 FR 31877), FDA published a notice of filing that invited comments on the petition. The Federal Register notice established July 19, 2016 as the end of the comment period. On August 8, 2016, in response to a request for an extension of the comment period, FDA reopened the comment period until September 19, 2016. On October 16, 2016, FAP 6B4815 was placed in abeyance. Abeyance is an administrative category of petitions that are filed but non-active because of deficiencies that were identified during FDA's review. A petition remains in abeyance until either the petitioner provides OFAS with the required information, requests a final decision based on the data currently in the petition, or requests withdrawal of the petition. When the petitioner provides the information required to address all deficiencies, the petition may be refilled resulting in a new filing date.

On March 12, 2018, FDA removed the petition from abeyance, and the petition is currently under review.

Question. Will FDA consider the impact of low-dose, long-term exposure of phthalate chemicals on human health when evaluating the safety of use in food contact substances?

Answer. When FDA evaluates the safety of the use of a food contact substance, FDA considers the impact of the dietary exposure to the additive and calculates exposure as an estimated daily intake which occurs over the life-time of the consumer.

Question. Will the safety evaluation go beyond short-term toxicology and fully consider other impacts such as on the endocrine and reproductive systems?

Answer. When FDA evaluates the safety of a food contact substance, FDA considers a wide range of toxicological findings, including potential toxicity of a substance that could result from impacts on the endocrine and reproductive systems.

IMPROVING DIVERSITY IN CLINICAL TRIALS

Question. The fiscal year 18 Omnibus included Senate report language on Improving Diversity in Clinical Trials and Safety Studies. Specifically, the Committee encouraged FDA action to achieve greater inclusion of racially and ethnically diverse populations in genome-wide association studies, clinical trials, and safety analysis; more complete data reporting in Clinical Drug Trials Snapshots; and Spanish-language reporting forms in the MedWatch system to address adverse events and safety concerns.

What is your timeline and plan to address each of the requested actions?

Answer. There is the potential for varying effects of treatment among demographic subgroups. Women may respond differently to treatment as compared to men, while elderly patients may be more or less sensitive to a drug. With this realization, FDA is committed to ensuring safe and effective use of medical products across the demographic spectrum. The assessment of varying treatment effects across patient subgroups from clinical studies is important to provide the best information for patients and prescribers to make treatment decisions. This assessment includes quantifying the heterogeneity of the treatment effects and determining effect modifiers and the characteristics associated with these effect modifiers.

Multiple units in the Agency are collaborating to provide additional information to the public about demographics in clinical trials, through Drug Trial Snapshots and other sources. These groups are exploring the use of innovative methodology, where applicable, to better inform treatment decisions related to subgroups of patients. Drug Trial Snapshots provide consumers with information about who participated in the clinical trials and include information on study designs, effectiveness and safety, and whether there were differences in efficacy and side effects among subgroups.

Since the beginning of 2017, Drug Trials Snapshots have reported on sex, age, race and ethnicity of trial participants as well as on the geographic distribution of the trial sites (proportion of participants from U.S. trial sites). Ethnicity is presented in Snapshots as “Hispanic,” “not-Hispanic,” and “not reported. The “not reported” category provides additional explanation if available in the submitted application. For example, it may note that data were missing or not collected during the clinical trial. In the latter case, it may provide additional clarification for why that data were not collected. In some cases, regulatory authorities in certain countries do not permit collecting ethnicity data from their clinical trial sites.

FDA is also taking additional steps related to assessing clinical trial inclusion and exclusion criteria and increasing diversity in clinical trial participation, as required under the FDA Reauthorization Act of 2017 (FDARA). Sec. 610 of FDARA requires FDA to publish a draft guidance to discuss eligibility criteria for clinical trials and make recommendations of methodological approaches for a manufacturer or sponsor of an investigation of a new drug. The draft guidance will focus on three themes, as required by the statute: broadening eligibility criteria, increasing trial recruitment, and using eligibility criteria for the benefit of drugs intended for the treatment of rare diseases or conditions. Development of the guidance is on schedule to be published by July 15, 2019.

On March 16, 2018, FDA published an information collection notice in the Federal Register: Agency Information Collection Activities; Proposed Collection; Comment Request; MedWatch: The Food and Drug Administration Medical Products Reporting Program. The following statement concerning translation of MedWatch forms was included: “The Agency welcomes comments about translation of Form FDA 3500B (consumer) into Spanish and other languages.” The comment period on this notice closed on June 15, 2018. FDA continues to work on improving ways to submit MedWatch forms in Spanish and other languages.

QUESTION SUBMITTED BY SENATOR TOM UDALL

Question. Dr. Gottlieb, we appreciate FDA’s focus in recent years on the challenges of antibiotic use in animal agriculture and the need to address outstanding barriers to effective stewardship. Your efforts to end production uses of medically important antibiotics, encourage voluntary removal of production claims by drug sponsors, and strengthen the involvement of skilled veterinarians in animal production through the mandating veterinary oversight has meaningfully advanced our common objective to enhance stewardship among animal producers. But you’ve also acknowledged that more work is needed and that there are outstanding challenges we still need to address. In particular, FDA announced in September, 2016 that you planned to focus on antibiotics used in feed or water that lack a defined duration of use. You sought public feedback on this effort, and you developed a cross-functional working group to determine next steps. Can you update us on the status of this important focus area and how you plan to make progress on these drug label duration issues in the coming year? Please reply in writing and share a concrete, stepwise plan with this Subcommittee to address this issue in a timely manner.

Answer. FDA is developing additional actions to ensure judicious use of medically important antimicrobials. Last January, FDA published its key initiatives for the next 5 years, which include the following: (1) Align antimicrobial drug products with the principles of antimicrobial stewardship in veterinary settings; (2) Support efforts

to foster stewardship of antimicrobials in veterinary settings; (3) Assess the impact of strategies intended to curb the emergence of antimicrobial resistance associated with the use of antimicrobial drugs in veterinary settings.

To further build on progress and ensure judicious use of antimicrobial drugs in veterinary settings, FDA is working to incorporate these key initiatives into a more detailed multi-year plan to be published later in 2018. This plan includes steps for addressing concerns about products that lack defined durations of use.

FDA received numerous substantive comments in response to its request for public comment on the duration of use issue. The Agency has evaluated the comments and is in the process of developing a specific strategy for addressing this issue. Any changes to such use conditions will be based on sound science and available evidence.

This continues to be an agency priority, as it will support overall efforts to foster stewardship of medically important antimicrobial drugs in food-producing animals and help preserve the effectiveness of these antimicrobials in animal and human medicine.

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

DRUG AFFORDABILITY

Question. We have discussed the frustration we both share about the anti-competitive tactics used by brand drug companies to deny the sale of samples to generic manufacturers. This is a problem that has been around for a long time and it is my understanding that the FDA has limited ability to police this behavior.

Does the FDA have the clear and explicit authority to order a brand drug company to sell samples of its product to a generic manufacturer, even if the agency have found that the generic manufacturer can safely handle that sample?

Answer. FDA has never asserted authority to order a brand drug company to sell samples of its product to a generic manufacturer. FDA has issued letters stating that the Agency will not consider it to be a violation of the applicable Risk Evaluation and Mitigation Strategies (REMS) for the brand drug company to provide samples to a particular generic company for generic development.

Question. Has FDA ever actually ordered a brand drug company to sell samples to a generic manufacturer?

Answer. No. FDA has issued letters stating that the Agency will not consider it to be a violation of the applicable REMS for the brand drug company to provide samples to a particular generic company for generic development, but we have not ordered a brand company to provide samples to a generic company.

Question. It's my understanding that the FDA has some authority to levy civil monetary penalties when the agency determines a brand drug company is using the existence of a REMS program to block or delay a generic applicant. Is that correct?

Answer. FDA has authority to levy civil monetary penalties for violations of section 505–1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which (among other things) prohibits holders of brand (and generic) applications from using any REMS element to assure safe use (ETASU) to block or delay approval of either a generic or 505(b)(2) application. FDA notes that a significant number of the products about which FDA has received RLD access inquiries are not subject to a REMS with ETASU.

Question. Has the FDA ever used that authority?

Answer. FDA has not used this civil monetary penalty (CMP) authority for violations of section 505–1 of the FD&C Act.

Question. Would the FDA be required to develop a lengthy record prior to any action?

Answer. To obtain a CMP, the FDA Center with principal jurisdiction over the matter must file an administrative complaint and bears the burden of proving a violation of section 505–1 of the FD&C Act. Prior to filing a complaint, that Center would need to develop a record establishing each element of the violation. An entity against whom a CMP is sought may request an administrative hearing. The parties (the FDA Center and the drug company) may serve requests for production of documents on each other and must submit written direct testimony of their witnesses pre-hearing. At the hearing, the parties may cross-examine the other party's witnesses. Following the hearing and possibly post-hearing briefing, the presiding officer determines whether the Center has met its burden of proving the drug company's liability and determines the appropriateness of the penalty amount proposed by the Center. Either party may appeal an adverse decision to the Department of Health and Human Services' Departmental Appeals Board (Board). Appeals involve

briefing and possibly oral argument before the Board. The brand company can appeal an adverse Board decision to the Federal Court of Appeals. CMP cases, therefore, are resource-intensive and often become protracted, multi-year proceedings.

Question. Would the agency need to compile evidence that the brand's actions were designed to block or delay the generic application?

Answer. Yes. FDA would be required to compile evidence necessary to establish each of the elements of 505-1. FDA notes that because FDA is not privy to the details of business transactions between brand and generic companies, much of the evidence required to prove such violations is not within FDA's possession or control.

Question. Would this require FDA's time and resources?

Answer. Yes. As described above, CMP cases often become protracted, multi-year proceedings, requiring the Agency to expend significant time and resources on the litigation of each individual CMP case.

Question. And does the authority only apply to drugs that are behind a REMS and not drugs subject to restrictive contracting agreements?

Answer. FDA may seek to impose CMPs in circumstances where holders of brand (and generic) applications have used a REMS ETASU to block or delay approval of either a generic or 505(b)(2) application.

Question. Even if the FDA is successful in levying civil monetary penalties, does the FDA have the explicit authority to order a brand drug company to sell samples of its product to a generic manufacturer?

Answer. FDA has never asserted authority to order a brand drug company to sell samples of its product to a generic manufacturer.

ADDED SUGAR

Question. I appreciated hearing how your family has enjoyed tapping your own trees, but for you and your daughters that is a fun hobby. For many Vermont families, their livelihoods depend on maple syrup and maintaining consumer confidence. It is clear from the public comments submitted for the 'Draft Guidance for Industry: Declaration of Added Sugars on Honey, Maple Syrup, and Certain Cranberry Products' published on March 2, 2018, that maple and honey producers remain worried about this requirement, and that your offer to use an "obelisk" will not resolve the confusion for consumers for maple syrup or honey. This would alter consumer perceptions and buying habits, likely leading to consumers replacing the small amount of maple syrup used today with other refined sugar and corn sweeteners, thus encouraging poorer dietary practices rather than healthier ones.

You have said that the rational and rule for the new nutrition fact label and declaration of added sugar are "driven by the statute that is prescriptive in some places." However, the Federal Food and Cosmetics Act does offer some flexibility and exemptions. For instance Section 403(q)(2)(B) of the Federal Food and Cosmetics Act states that "If the Secretary determines that the information relating to a nutrient required by subparagraph (1)(C), (1)(D), or (1)(E) or clause (A) of this subparagraph to be included in the label or labeling of food is not necessary to assist consumers in maintaining healthy dietary practices, the Secretary may by regulation remove information relating to such nutrient from such requirement."

Applying the added sugar labeling to bottles of pure maple syrup, which makes up less than 5 percent of the table syrup market, would not assist consumers in maintaining healthy dietary practices, and could instead lead to poorer dietary practices. Have you or your staff reviewed Section 403(q)(2)(B) of the Federal Food and Cosmetics Act to determine whether it gives you the necessary authority to maintain listing total sugars on the label, but removing the added sugar information from pure maple syrup or honey packages?

Answer. The Dietary Guidelines recommends consuming no more than 10 percent of daily calories from added sugars. There is strong and consistent evidence that healthy dietary patterns, characterized, in part, by lower intakes of sugar-sweetened foods and beverages relative to less healthy patterns, are associated with a reduced risk of cardiovascular disease. Additionally, there is strong and consistent evidence that it is difficult to meet nutrient needs within calorie limits when more than 10 percent of daily calories comes from added sugars. In general, declaring added sugars on the Nutrition Facts label provides consumers with information based on the latest science and empowers them to make informed and healthy food choices.

However, FDA is sensitive to the honey and maple syrup industries' concerns regarding the declaration of added sugars on single-ingredient products. On June 19, 2018, FDA announced that the Agency is taking another look at this issue following comments received from the public regarding FDA's original March 2, 2018 draft guidance titled "The Declaration of Added Sugars on Honey, Maple Syrup, and Certain Cranberry Products." The feedback that FDA received is that the approach laid

out in the draft guidance does not provide the clarity that the Agency intended. It is important to FDA that consumers are able to effectively use the new Nutrition Facts label to make informed, healthy dietary choices. FDA looks forward to working with stakeholders to devise a sensible solution.

Question. Do you believe a change in the law is needed to alter this requirement for these two pure natural products, of which maple has considerable nutritional value, contains antioxidants, and may have additional health advantages?

Answer. FDA believes that the Agency can work in the context of its current regulatory framework to develop a solution to address maple syrup and honey producers' concerns regarding the declaration of added sugars on single-ingredient products. FDA published a draft guidance titled "The Declaration of Added Sugars on Honey, Maple Syrup, and Certain Cranberry Products: Guidance for Industry" on March 2, 2018. The guidance states FDA's current thinking to allow manufacturers of specific products to use a symbol immediately after the added sugars Daily Value, directing consumers to language that provides truthful and not misleading contextual information about "added sugars" and what it means for each of these specific products.

The draft guidance is out for public comment, and FDA recently extended the comment period by 45 days to close on June 15, 2018. Although the comment period is still open, the Agency has received comments asking for consideration of alternative approaches to what was proposed in the draft guidance to address added sugars labeling for these products. FDA will consider all proposed options once the comment period closes and will consider the feedback received in determining how best to go forward.

QUESTIONS SUBMITTED BY SENATOR TAMMY BALDWIN

Question. I am pleased that FDA announced its intention to revise the draft MOU between FDA and the states concerning pharmacy compounding published in 2015. I have heard from constituents, including family-owned compounding pharmacies in Wisconsin that have a reputation for quality, who have serious concerns that the draft MOU defines "distribution" to include "dispensing," which are typically considered separate and distinct activities. Further, I have heard concerns that states may be reluctant to sign the MOU due to concerns that it would be overly burdensome to enforce without adequate funding. Under the law, for states that don't enter into the MOU, FDA will enforce a 5 percent limit for compounding pharmacies on interstate distribution of compounded products. I am concerned that without proper clarification of the definition of "distribution" in a revised draft MOU, access would be restricted for patients who depend on compounding pharmacies in other states for unique medical needs and those who travel during the year. This would be particularly acute should a state not sign the MOU.

Will you commit to clarifying the definition of distribution in a manner that maintains sufficient patient access to the compounded medications they need?

Answer. FDA takes seriously the concerns that some stakeholders have raised about the implications of the statutory limitation on distribution of compounded drugs out of the State in which they are compounded found in section 503A(b)(3)(B)(ii) of the FD&C Act. This section provides one of the conditions to qualify for the exemptions in section 503A, which is that if a drug product is compounded in a state that has not entered into an MOU with FDA addressing the distribution of inordinate amounts of compounded drugs interstate and providing for the investigation of complaints, the compounder does not distribute compounded drugs out of the state in which they are compounded in excess of 5 percent of its total prescription orders dispensed or distributed. Stakeholders expressed concern about maintaining patient access to drugs compounded by pharmacies located in states that may decide not to enter into the MOU with FDA, once the MOU is final and offered for signature. FDA anticipates that the revisions it intends to make to the draft MOU will make it more feasible for states to enter into the MOU once it is final.

Question. What modifications does the agency plan to make to address these issues in the revised draft?

Answer. As FDA works to develop and issue a revised draft MOU for public comment in the coming months, the Agency is considering the concerns and recommendations conveyed in the 3,000 comments submitted on the 2015 draft MOU, including comments regarding the definition of "distribution" and the challenges states might face in meeting the terms of the draft MOU.

Question. Please describe what FDA is doing to consult with stakeholders, including compounding pharmacies and state boards of pharmacy, in developing a revised draft and will you open the draft to public comment?

Answer. FDA believes that the revisions that it is making in the revised draft MOU, developed in consultation with the National Association of Boards of Pharmacy, will address many of the concerns that stakeholders, including certain states, had raised regarding the draft issued in 2015. FDA will further take into consideration any comments received during the public comment period for the revised draft MOU.

Question. As FDA considers how to best redefine “healthy” on food packages, I am interested to know what considerations are being made to ensure fruits like cranberries are appropriately recognized by any new proposed definition. Cranberries are naturally tart, nutrient dense fruits with a de minimis amount of natural sugars. As such, sugar is added for palatability and processing. What are you doing to ensure that any new definition of “healthy” appropriately accounts for naturally tart, nutrient dense fruits that are sweetened to levels similar to products with natural sugars, but still deliver high levels of nutrients and other unique health benefits?

Answer. FDA recognizes that the claim “healthy” is ready for an update to be more consistent with the 2015–2020 Dietary Guidelines for Americans and current nutrition science. In September 2016, FDA published a request for information (RFI) on the use of the term “healthy” in food labeling. FDA also held a public meeting in March 2017 to discuss the use of the term “healthy” in the labeling of food and beverage products. The Agency received nearly 1,200 comments in the docket for the RFI and public meeting. FDA will take into consideration the latest Dietary Guidelines and nutrition science, including recommendations regarding added sugar consumption as part of a healthy eating pattern, as well as stakeholders’ comments, as it determines how best to update the definition of “healthy.”

Question. Additionally, as FDA begins to modernize how the Agency reviews and establishes health claims on food packages, do you anticipate any near-term changes that would impact petitions now under consideration? How is that different from the current approach and what are the long-term goals for changes?

Answer. As part of FDA’s Nutrition Innovation Strategy, the Agency intends to develop a comprehensive framework to modernize our approach on how we look at health claims to support industry initiatives already underway and encourage other companies to introduce products that meet the growing consumer demand for healthier products. FDA is looking to streamline its process for reviewing health claims it receives from industry to enhance the efficiency of the review process. The Agency is at the beginning stages of this process and, therefore, does not anticipate near-term impact on petitions currently under consideration.

FDA plans to have extensive engagement with stakeholders to seek input and further explore how to best promote public health in the evolving food and beverage marketplace. Part of this public engagement includes holding a public meeting this summer on the Nutrition Innovation Strategy. The Agency will announce the meeting details and open a docket for public comment in the Federal Register.

SUBCOMMITTEE RECESS

Senator HOEVEN. We are adjourned.

[Whereupon, at 3:20 p.m., Tuesday, April 24, the subcommittee was recessed, to reconvene subject to the call of the Chair.]