S. HRG. 114–717

NOMINATION OF ROBERT CALIFF TO SERVE AS FDA COMMISSIONER

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

ON

NOMINATION OF ROBERT CALIFF TO SERVE AS FDA COMMISSIONER

NOVEMBER 17, 2015

Printed for the use of the Committee on Health, Education, Labor, and Pensions

Available via the World Wide Web: http://www.gpo.gov/fdsys/

U.S. GOVERNMENT PUBLISHING OFFICE
97–694 PDF WASHINGTON : 2018

For sale by the Superintendent of Documents, U.S. Government Publishing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

LAMAR ALEXANDER, Tennessee, *Chairman*

MICHAEL B. ENZI, Wyoming
RICHARD BURR, North Carolina
JOHNNY ISAKSON, Georgia
RAND PAUL, Kentucky
SUSAN COLLINS, Maine
LISA MURKOWSKI, Alaska
MARK KIRK, Illinois
TIM SCOTT, South Carolina
ORRIN G. HATCH, Utah
PAT ROBERTS, Kansas
BILL CASSIDY, M.D., Louisiana

PATTY MURRAY, Washington
BARBARA A. MIKULSKI, Maryland
BERNARD SANDERS (I), Vermont
ROBERT P. CASEY, JR., Pennsylvania
AL FRANKEN, Minnesota
MICHAEL F. BENNET, Colorado
SHELDON WHITEHOUSE, Rhode Island
TAMMY BALDWIN, Wisconsin
CHRISTOPHER S. MURPHY, Connecticut
ELIZABETH WARREN, Massachusetts

DAVID P. CLEARY, *Republican Staff Director*
EVAN SCHATZ, *Minority Staff Director*
JOHN RIGHTER, *Minority Deputy Staff Director*

C O N T E N T S

STATEMENTS

TUESDAY, NOVEMBER 17, 2015

Page

COMMITTEE MEMBERS

Alexander, Hon. Lamar, Chairman, Health, Education, Labor, and Pensions Committee, opening statement 1
Murray, Hon. Patty, a U.S. Senator from the State of Washington 3
Burr, Hon. Richard, a U.S. Senator from the State of North Carolina 5
Scott, Hon. Tim, a U.S. Senator from the State of South Carolina 6
Whitehouse, Hon. Sheldon, a U.S. Senator from the State of Rhode Island 16
Isakson, Hon. Johnny, a U.S. Senator from the State of Georgia 18
Warren, Hon. Elizabeth, a U.S. Senator from the State of Massachusetts 20
Prepared statement 22
Roberts, Hon. Pat, a U.S. Senator from the State of Kansas 23
Baldwin, Hon. Tammy, a U.S. Senator from the State of Wisconsin 25
Cassidy, Hon. Bill, a U.S. Senator from the State of Louisiana 27
Franken, Hon. Al, a U.S. Senator from the State of Minnesota 28
Hatch, Hon. Orrin G., a U.S. Senator from the State of Utah 30
Bennet, Hon. Michael F., a U.S. Senator from the State of Colorado 32
Sanders, Hon. Bernard, a U.S. Senator from the State of Vermont 33
Murkowski, Hon. Lisa, a U.S. Senator from the State of Alaska 35
Casey, Hon. Robert P., Jr., a U.S. Senator from the State of Pennsylvania 37

WITNESS

Califf, Robert M., M.D., Deputy Commissioner for Medical Products and Tobacco, Department of Health and Human Services, Durham, NC 7
Prepared statement 9

ADDITIONAL MATERIAL

Statements, articles, publications, letters, etc.:
Response by Robert M. Califf, M.D. to questions of:
Senator Alexander 42
Senator Enzi 50
Senator Burr 50
Senator Isakson 53
Senator Isakson and Senator Murkowski 56
Senator Isakson and Senator Murphy 56
Senator Collins 57
Senator Hatch 61
Senator Roberts 64
Senator Cassidy 68
Senator Murray 71
Senator Sanders 82
Senator Casey 86
Senator Bennet 90
Senator Baldwin 94
Senator Murphy 96
Senator Warren 99
Comprehensive Clinical Trials Conducted by Dr. Califf 112
Drug price comparisons in the United States and Canada 117

NOMINATION OF ROBERT CALIFF TO SERVE AS FDA COMMISSIONER

TUESDAY, NOVEMBER 17, 2015

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

The committee met, pursuant to notice, at 10:05 a.m., in room SD–430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

Present: Senators Alexander, Burr, Isakson, Collins, Murkowski, Kirk, Scott, Hatch, Roberts, Cassidy, Murray, Mikulski, Sanders, Casey, Franken, Bennet, Whitehouse, Baldwin, Murphy, and Warren.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The HELP Committee will come to order. Today we're reviewing the nomination of Dr. Robert Califf to serve as Commissioner of Food and Drugs.

Dr. Califf, welcome. Congratulations on your nomination. Welcome to you and to your family members. We're glad they have been able to come up, some of them from Columbia, SC, and I enjoyed having the opportunity to meet with you in my office.

If you're confirmed to lead the Food and Drug Administration as its Commissioner, you will be in charge of steering the agency responsible for the safety and effectiveness of our Nation's medical products and protecting our country's food supply. This is a huge job.

The FDA affects nearly every single American almost every day and regulates about a quarter of all of our consumer spending in the United States, over $4 trillion annually. It is responsible for product areas as diverse as prescription drugs for humans and animals, medical devices, biologics, cosmetics, over-the-counter medications, food, and tobacco.

It's a vital mission, and we all want to make sure that the right person is leading it. The President has nominated you to do that job, and like every full-time nominee, you've been through an exhaustive process to make sure that you don't have any conflicts of interest or other problems in your background.

If you'll permit me, I had the privilege of coming before this committee about 24 or 25 years ago and sitting in the chair where you sit. It's not always a pleasant experience. One of the Democratic Senators said to me, "Governor"—my family was sitting where yours is—said to me, "Governor Alexander, I've heard some very

disturbing things about you, but I don't think I'll bring them up this morning," and Senator Kassebaum leaned over and said, "Well, Howard, I think you just did." And then he held me up for 3 months.

I don't expect that would be happening with you, because like every full-time nominee, you've been through an exhaustive process to make sure of the conflicts of interest, as I said. Before the President announced your nomination, there was an extensive vetting process by the White House and the FBI.

You submitted paperwork to the Office of Government Ethics—that's been carefully reviewed—including your financial information. They found several recusals, which you have committed to do, so there wouldn't be any remaining conflicts of interest that would prevent you from doing your job, in the opinion of the Office of Government Ethics. The form you submitted is public. It includes every source of income over $200 and every asset worth more than $1,000 and every potential conflict that the Office of Government Ethics determined would require a recusal.

I'm going through this so people will know that nominees such as yourself do this. You've answered 37 pages of questions from our committee, including some confidential questions on financial information. You've responded to written followup questions. Your responses included over 3,000 pages of articles and lectures that my staff reviewed and that any member of the committee may review.

You were nominated on September 17. Our committee staff has spent 2 months carefully reviewing everything you submitted, and my staff tells me that they haven't found anything that would call into doubt your ability to lead the FDA fairly and impartially.

You come here with impressive qualifications; a leading cardiologist, professor at one of the Nation's top medical schools. You are an expert on clinical research and you've been recognized as an author of medical publications. You've had some experience managing large organizations, and you've been the founding director of Duke's Clinical Research Institute. I'm sure Senator Burr will go into some detail about your background when he has a chance to introduce you in a few minutes.

You've conducted scores of important clinical trials. That's important to me, because it helps to have people in government who actually know what they're talking about because of the experience that they've had before. You understand how research gets done in the real world.

I'm eager to hear your priorities about how you intend to manage such a large and diverse organization. I'd like to hear what you'll be able to do to ensure that affordable drugs are available to American patients. I hope you'll agree that drugs are—that your job is to see that drugs are safe and effective, but the FDA can help market lower drug prices by approving generic drugs and other products as quickly as it possibly can so there's more choice and competition in the market.

Approval times have gotten worse instead of better. I'll be asking you about that and what you intend to do about it. Second, there has never been a more exciting time to lead the agency. We know more about biology and medicine than ever before, and that's not likely to stop anytime soon given the advancement of regenerative

cell therapies, 3D printing, and the President's Precision Medicine Initiative.

Your job, if confirmed, will be to make sure that the FDA regulation is appropriate. Too much regulation could reduce investments. Too little could make it difficult for drugs to be safe and effective. There is much work to be done. Sometimes it takes a decade to develop a drug. Sometimes it takes billions of dollars, literally.

In this committee, we're working together in a bipartisan way to help get safe cutting-edge drugs, medical devices, and treatments into American medicine cabinets and doctors' offices more quickly, and we hope to move that soon. We're looking forward to hearing what you believe needs to be done to build the FDA's capacity and to fix the impact of its regulations so that the FDA is a partner in innovation and not a barrier.

I thank you, and I look forward to hearing your testimony on these important issues.

Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman, and thank you to all of our colleagues for being here today.

Dr. Califf, thanks to you and your multigenerational family that is here with you today. I want to express my appreciation to all of you for accepting this nomination and continuing to offer your expertise—or offer your spouse or dad—in service of families and communities nationwide.

As the Chairman said, the FDA Commissioner has a critical role to play in supporting health and well-being in our country. Whether you're in a grocery store or the medicine cabinet or the emergency room, families depend on the FDA to maintain the highest standards of product safety.

As we talk about the future of the FDA and the many health challenges our country faces, it is important to note that valuable efforts have been made in recent years to strengthen the FDA and improve its services for patients and families.

Last year, the FDA approved 51 new drugs and biologics, its highest number in almost 20 years. The agency consistently approves drugs more quickly than advanced regulatory agencies in other countries, while maintaining the high standards of safety and effectiveness. The FDA has also made strides toward implementing the Food Safety Modernization Act, helping to bring our Nation's food safety system into the 21st century.

Despite these gains, the FDA faces significant challenges moving forward. There are several areas, in particular, where I hope to see continued progress. As someone who has seen personally the challenges that patients and families face due to chronic illness, I am very interested in making sure we are encouraging development of safe, effective treatments and cures for our most challenging unmet medical needs.

So-called super bugs are another growing threat and an issue Chairman Alexander and I are working on closely. As we have seen in my State and across the country, where medical devices known as duodenoscopes have been linked to tragic outbreaks of antibiotic-resistant infections, we have got to find ways to prevent

these infections and respond more quickly and effectively when any risk arises.

Especially as technology continues to evolve, we need to do more to make sure that after products reach the market, the FDA has the effective tools it needs to monitor their safety, taking full advantage of information technology.

We need to ensure that FDA continues to strengthen its generic drug and biosimilar programs. I also believe there is much more we can do to bring patients' voices into the process of developing new treatments and cures and ensure their priorities are consistently reflected in the FDA's work.

In addition, our country faces urgent public health challenges that deserve our attention. To name a few, we need to move forward on making sure families have access to nutritional information and ensuring our food supply is both safe and healthy. We need to put all of the agency's tools to work to stop tobacco companies from targeting our children. We must do more to tackle widespread illnesses, such as heart disease and diabetes, that threaten so many people in our country.

Like so many of my colleagues here today, I have heard time and again from families that the cost of prescription drugs is a significant financial burden. I believe the next FDA Commissioner has an important role to play in ensuring all patients and families have access to the prescription drugs they need.

Another critical priority is ensuring the FDA always puts science over politics. As some here will remember, several of my colleagues and I fought long and hard to ensure that medical expertise, not ideology, governed decisionmaking on the sale of Plan B over the counter. Women and families have to be able to trust the FDA not to play politics with their health.

As Congress and the administration work together to address these and many other health challenges in which the FDA plays a significant role, we need to recognize that our efforts will not be successful without additional support for the FDA. We must make sure the FDA has the resources and authority it needs to hire top experts in a highly competitive field and manage its growing workload as it navigates our increasingly global supply chain.

Many of these are issues that our committee is currently debating as we negotiate bipartisan legislation to advance medical innovation for patients and families. After careful consideration and review, I am confident that Dr. Califf would contribute leadership and expertise as we work to find new ways to advance medical innovation for patients and families and improve health and well-being across the country. He is a strong nominee for the FDA Commissioner.

Dr. Califf has an impressive history of leadership and management experience, in particular, at Duke. He would bring to this new role a record of advancing medical breakthroughs on challenging illnesses through clinical trials. Our review of his record demonstrates a longstanding commitment to transparency in relationships with industry and to working to ensure academic integrity.

Dr. Califf has made clear he will continue to uphold these values and prioritize a strong, independent FDA as Commissioner.

I have approached this nomination focused on the best interests of families and communities in Washington State and across the country and in making sure the FDA puts them first in all its work, from drug and device approvals to ensuring that a child's peanut butter sandwich is safe to eat.

As we work toward these goals, I believe Dr. Califf would be a valuable partner. I encourage my colleagues to join me in supporting his nomination, and I look forward to working with all of you to strengthen health and well-being for the families and communities that we serve.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

Senator Burr will introduce Dr. Califf.

STATEMENT OF SENATOR BURR

Senator BURR. Mr. Chairman, thank you, and thank you to my colleagues.

Dr. Califf, welcome. Thank you for sharing your family with us. Your parents are here. Your bride is here. Your children are here, and your granddaughter is here.

Welcome, Brooke. Hope you get an extra credit at school for being here.

Dr. Robert Califf is a North Carolinian whose career has been distinguished by his unwavering commitment to patients as a respected clinician, researcher, and advisor. I'm particularly pleased to have the opportunity to introduce him here today. Dr. Califf has been nominated to serve as the next Commissioner of the Food and Drug Administration, and my colleagues and I look forward to hearing from you today.

Dr. Califf is currently serving as the Deputy Commissioner of Medical Products and Tobacco for the FDA since February of this year. In this role, he's responsible for overseeing and directing the Centers for Drug Evaluation and Research, the Centers for Biologics Evaluation and Research, the Centers for Devices and Radiological Health, the Centers for Tobacco Products, the Office of Special Medical Programs within the agency.

Prior to his work at the FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University in Durham, NC. During his time at Duke, Dr. Califf held a number of positions, including the director of Translational Medicine Institute, the director of the Clinical Research Institute. He worked to move the promising field of translational science forward as the director of Clinical Trials Transformation Initiative.

Dr. Califf is distinguished as a researcher and an author with over 1,200 peer-reviewed publications in biomedical science. He's a graduate of Duke University School of Medicine. He received his residency training in primary care at the University of California San Francisco and completed a residency in cardiology at Duke University.

Dr. Califf is a great father, a great husband, a great granddad, and is a great doctor. I'll say to my colleagues he's a great man, and that stands out the most in his qualifications.

How well the FDA fulfills its mission touches the lives of Americans each and every day, from the lifesaving treatments patients receive to the safety of the food we feed our families. The challenges facing the next Commissioner are great, but also the opportunities are as well.

Dr. Califf, congratulations on your nomination to serve as Commissioner of the Food and Drug Administration.

I urge my colleagues to thoroughly get your questions answered and expeditiously move this nomination so a permanent Commissioner of the FDA can get to work on some very serious problems within our system.

I thank the Chair. I welcome Dr. Califf.

The CHAIRMAN. Thank you, Senator Burr.

Senator Scott has a point of clarification.

STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Chairman Alexander. Senator Burr referred to Dr. Califf as if he were from North Carolina. The fact of the matter, sir, is that while he could not get into the Medical University of South Carolina, he had to go to Duke. He's actually from South Carolina.

[Laughter.]

Understanding the generational responsibilities of southerners, you realize that his parents were also from South Carolina. Therefore, we know he's a southerner.

He's from South Carolina. The North is a Yankee called North Carolina. I just wanted to make sure that that point was made clear, that you didn't insult his parents on the front row who are from Saint George, SC, which is in the low country.

Thank you very much.

Senator BURR. I welcome his parents and congratulate them on his ability to outperform the requirements for South Carolina education.

[Laughter.]

Senator MIKULSKI. Mr. Chairman.

The CHAIRMAN. OK.

Senator MIKULSKI. Mr. Chairman.

The CHAIRMAN. Senator Mikulski.

Senator MIKULSKI. While those guys are still doing border wars, I want to also just welcome Dr. Califf, because FDA is in my State. He'd be eminently qualified and look forward to supporting his nomination proceeding.

I'm glad you're the son of South Carolina who lived in North Carolina, but you're our guy, too.

I ask unanimous consent that my statement be in the record.

The CHAIRMAN. It will be.

[The prepared statement of Senator Mikulski was not available at time of press.]

The CHAIRMAN. Dr. Califf, you can see the interest the committee has in the work you're about to do. Virtually every member is here. Each will have 5 minutes to have a conversation with you. I'll try to give you time to answer the questions. We want to stick pretty closely to the 5-minutes so everyone can be involved.

As I mentioned earlier, you've answered a number of questions to the committee staff, and if any Senator has additional questions, there'll be a few days after the hearing that they can ask them, and we hope you'll respond promptly to them. We'll begin a round of questions 5 minutes in length.

Dr. Califf, around the country and here in Congress, people are talking about the high cost of pharmaceutical drugs and what can be done to make those drugs affordable. Do you—oh, excuse me. I got so excited I didn't give you a chance to make your comments.

[Laughter.]

Dr. CALIFF. I've been well-instructed, Senator, not to interrupt you.

[Laughter.]

The CHAIRMAN. Dr. Califf, we look forward to your comments.

STATEMENT OF ROBERT M. CALIFF, M.D., DEPUTY COMMISSIONER FOR MEDICAL PRODUCTS AND TOBACCO, DEPARTMENT OF HEALTH AND HUMAN SERVICES, DURHAM, NC

Dr. CALIFF. Mr. Chairman and Ranking Member Murray and also Senator Burr and Senator Mikulski, thank you for your kind comments. I want to thank you and the members of the committee for inviting me here today to discuss my nomination to be Commissioner of the Food and Drug Administration.

I'm honored to be accompanied by my family today, as you've noted. Sitting behind me are my dad, a World War II veteran—and we're going to visit the monument later this afternoon—my mom, an activist-teacher and a 7-year survivor of multiple myeloma; and my wife of 42 years and high school sweetheart, Lydia. My three children and my granddaughter, Brooke, are also here with us. The support of my family and their feedback have been essential to my career success and sustaining my moral compass.

I'm honored to have been nominated by President Obama to lead the FDA. Thank you for all of your willingness to share with me your perspectives on ways the agency can better serve the American people. My primary goals, if confirmed, will be to work with you to build on the excellent workforce, relentlessly focus on the completion of priority projects, and continue to develop the science base that we need to give consumers confidence that their food and medical products are safe and give patients and clinicians an accurate understanding of the benefits and risks of medical products.

Amid ongoing revolutions in biological science and information technology, we must continue to strengthen the FDA's vital work, protecting Americans while encouraging innovations that hold promise. If confirmed, it would be an honor to lead this outstanding workforce in this remarkable time.

I've dedicated my career to advancing the public health as a physician, leader, teacher, and researcher. Like each of you, my understanding of our health system was shaped by more than just my professional life. Our daughter was born with serious congenital heart disease, requiring open heart surgery as an infant.

I still vividly remember the inspirational work of her doctors, nurses, and healthcare team and the uncertainties of that experience, including the discovery that one of our daughter's cardiologists had faked his medical credentials. We experienced firsthand

as a family how important it is to find a critical balance between innovation and safeguarding patients.

When I started in cardiology, heart attack was the leading cause of death in America, and our understanding of it was limited. It was agonizing that one of six patients that I saw in our intensive care unit with a heart attack died during the first hospitalization. The intensely personal experience dealing with catastrophic illness and personally witnessing the death of many people drove us to relentlessly invent and develop effective treatments.

I had the privilege to serve as a leader of global networks of doctors and nurses, researchers, computer scientists, and statisticians who joined forces to develop and evaluate clot-busting drugs and lifesaving technologies, including stents and defibrillators, that have helped millions of Americans. These efforts have cut the risk of death from heart disease by more than half and highlight for me the importance of bringing these advances to patients as fast as safely possible.

Indeed, it's not enough to develop new treatments. We must prove they are safe and effective and deploy them in a systematic way that reaches all Americans and eventually the global population. Our initial quality registries for bypass surgery, angioplasty, and heart attack have become global standards, including adoption by CMS as quality measures, to improve the public health by advancing evidence-based therapies and reducing medical errors.

A successful FDA is a critical factor for better public health in this changing world. The FDA must be prepared to set policies that channel innovative technologies for safe and effective use. Also, I firmly believe that the best way to make this progress is for different sectors in today's healthcare ecosystem to collaborate.

I've led efforts to help academic researchers collaborate with industry in a documented and transparent manner that retain their independence and primary role in caring for patients. More recently, I've had the pleasure of jointly leading a number of projects with patients, consumers, and community leaders, I believe, to the great benefit of research and public health.

My first priority as Commissioner would be to strengthen and better support FDA's talented and dedicated workforce. While FDA scientists make decisions every single day about hundreds of products, as technology advances, these decisions are becoming more complex. It's essential that we keep pace.

My next priority as Commissioner is working with you to fulfill the ambitious agenda that we set together. The Food Safety Modernization Act, for example, will help assure Americans their food is safe. The Deeming Rule for tobacco products will help us continue to reduce tobacco-related deaths. And, of course, the user fee programs are entering a period of renegotiation.

My third and final priority among the leading ones as Commissioner would be to further develop the science base that informs FDA's decisionmaking—my real professional love. By taking advantage of extraordinary advances in biomedicine and information sciences, we can build the right infrastructure that will unlock greater amounts of useful evidence about food, tobacco, and medical products at a dramatically lower cost.

Finally, we can't forget that health and disease fail to recognize national boundaries. In concert with our global colleagues, we must continue to develop sophisticated systems for monitoring the safety and quality of products produced outside our borders.

The FDA is poised to leverage the acceleration in biomedical knowledge to a new era of enhanced safety and effective treatments. If confirmed, I would be honored to lead the agency in this exciting time.

Thank you for allowing me to testify before you today, and I'm happy to take your questions.

[The prepared statement of Dr. Califf follows:]

PREPARED STATEMENT OF ROBERT M. CALIFF, M.D.

INTRODUCTION

Mr. Chairman and Ranking Member Murray, I want to thank you and members of the committee for inviting me here today to discuss my nomination to be Commissioner of Food and Drugs in the office of the Food and Drug Administration (FDA). I'm honored to be accompanied by family today. Sitting behind me are my dad, a WWII Veteran, my mom, a 7-year survivor of multiple myeloma and my wife of 42 years and high school sweetheart, Lydia. My three children and my granddaughter Brooke are also with us. The support of my family and their feedback have been essential to my career success and moral compass.

I am honored to have been nominated by President Obama to lead the FDA. Thank you all for your willingness to share with me your perspectives on ways the FDA can better serve the American people. My primary goals, if confirmed, would be to work with you to build on the excellent workforce, relentlessly focus on the completion of priority projects, and continue to develop the science base needed to give consumers and patients even more confidence that their food is safe and their medical products are safe and effective. I also believe that we need to continue to improve our efforts to give patients and clinicians an accurate understanding of the benefits and risks of medical products.

My service as Deputy Commissioner for Medical Products and Tobacco has underscored for me both the opportunity and the gravity of this undertaking. Amid ongoing revolutions in biological science and information technology, we must continue to strengthen the FDA's vital work in protecting the American people while encouraging innovations that hold promise to improve their health. If confirmed, it would be an honor to lead this outstanding workforce in this remarkable time.

BACKGROUND

My career has been dedicated to advancing the public health as a physician, leader, and researcher. But, like each of you, my understanding of our health system was shaped by more than just my professional life. Our first daughter was born with a serious congenital heart defect requiring open heart surgery as an infant. I still vividly remember the inspirational work of her doctors and the uncertainties of that experience—including the shocking discovery that one of our daughter's cardiologists was an imposter with faked medical credentials. My family has experienced firsthand how important it is to find a critical balance between innovative treatments and appropriate safeguards for patients. The American people need access to cutting edge treatments, but also must be able to trust the information they are given about that treatment.

As a medical student, I worked with one of the first computerized medical databases and witnessed the potential for computer technology to inform decisions about health and healthcare. When I started in cardiology, heart attack was the leading cause of death in the United States and our understanding of the cause of this leading cause of death in America was limited. It was agonizing that one of six patients with a heart attack died during their first hospitalization. This intensely personal experience of dealing with a catastrophic illness and its consequences on victims of the disease and their families drove us to be relentless about inventing and developing effective treatments. Together with a global network of doctors and nurses, and with an extraordinary team of researchers, computer scientists, and statisticians, I had the privilege to serve as a leader on efforts to develop "clot busting" drugs that restore blood flow to the heart, improve the recovery of the heart muscle and help prevent future heart attacks. We also worked together to develop and

evaluate life-saving technologies, including balloon angioplasty, cardiovascular stents, and implantable defibrillators, that have helped millions of Americans. These efforts have decreased the risk of death from heart disease by more than half. This condition that was once a death sentence is now treatable thanks to drugs and medical products, highlighting for me the importance of bringing these advances to patients as fast as safely possible. Much of my work has been at the intersection of public health and research, including large-scale efforts to improve our national clinical trial research infrastructure and innovative community-based projects undertaken in close collaboration with underserved patients and their communities.

Indeed, it is not enough to develop new treatments. We must prove they are safe and effective, and deploy them in a systematic way that reaches all Americans, and eventually the global population. Our initial quality registries for bypass surgery, angioplasty and heart attack have become global standards, including adoption of derivatives of our quality measures by CMS, to improve the public health by advancing evidence-based therapies and reducing medical errors.

LEADING THE FDA

A successful FDA is a critical factor for better public health in this changing world. We are currently witnessing a revolution in biomedical science and information technology that empowers consumers to make choices about their health and health care. Today our food safety system is undergoing the most comprehensive update since it was established and we are working to ensure that medications prescribed to animals do not reduce their effectiveness in humans. Against this backdrop of revolutionary change, the FDA must be prepared to set policies that channel these innovative technologies for safe and effective use—protecting the public while approving products with clear benefit.

I firmly believe that the best way to make this progress is for different sectors in today's health care ecosystem to collaborate. I led efforts at Duke University Medical Center to help academic researchers collaborate with industry in a documented and transparent manner that *retained their independence and primary role in caring for patients*. Similarly, the United States, and indeed the entire world, depends on a strong, unbiased FDA that can work with industry to advance critical technologies while still making independent determinations to ensure that scientific potential is translated into safe and effective products. To advance, we must find common ground with industry and academia on the science without compromising this fundamental role of the FDA.

More recently, I have had the pleasure of jointly leading multiple projects along with patients, consumers and community leaders, to the great benefit of research and public health. The emergence of consumers and patients as active participants in the process of developing therapies and devising protocols for evaluation is an important theme to improve the relevance of our work to the people we serve.

The Importance of the Workforce and Infrastructure

My first priority as Commissioner would be to strengthen and better support FDA's talented and dedicated workforce. However, the products we evaluate are increasingly complex. Sustaining the quality of FDA's scientific workforce may be more important than any particular policy because it is our day-to-day decisionmaking that protects the public without impeding technological progress. FDA scientists are making decisions every single day about hundreds of products—but as technology advances these decisions become more complex. Americans must be able to depend on a strong FDA workforce that keeps up with the rapidly changing world.

Completion of Critical Priorities

My next priority as Commissioner would be to carry our critical priorities over the finish line. With your guidance, the FDA has embarked on an ambitious agenda to keep pace with our changing society. The Food Safety Modernization Act will enhance our ability to assure Americans of the safety of the food supply. The Deeming Rule for tobacco products will be the basis for continuing our success in reducing tobacco-related deaths. Several high priority initiatives are underway, including the Combating Antibiotic Resistant Bacteria (CARB) initiative, medical counter measurement development, and the Precision Medicine Initiative to name a few. And, of course, the user fee programs that have been so successful in providing resources for review of medical products are entering a period of renegotiation.

Focusing on the Science Base

My third priority as Commissioner would be to further develop the science base that informs FDA's decisionmaking across drugs, devices, food safety, and more. If

we build the right infrastructure, FDA can realize the potential of revolutionary advances in biological and information sciences that will unlock greater amounts of useful evidence about food, tobacco and medical products at dramatically lower cost.

We must also take advantage of the astounding opportunity afforded by the fact that the majority of Americans have an electronic health record and smart phones. The groundbreaking Sentinel system demonstrates the power of evidence to inform FDA's decisionmaking and act quickly on safety issues and we have a similar plan for medical device surveillance. I am committed to the development of a national system for surveillance and evidence generation that will improve patient safety and provide a much more efficient way to understand the benefits and risks of medical products when used in practice.

In addition, the proliferation of the Internet allows many patients, advocates, and caregivers to be reached directly, both to impart information and to solicit their perspectives and experiences. I am greatly encouraged to see that FDA expects industry to involve patients directly in the process of technology development and assessment, but recognize that we are just beginning to understand the *science* of consumer engagement. Further, as ever-growing amounts of information become available to consumers about the benefits and risks of medical products, we must ensure that it is high-quality information.

Finally, we cannot forget that while the FDA has the well-being of Americans as its mission, we are operating in a global environment. Because health and disease do not recognize national boundaries, the FDA must be in constant communication with the global scientific and regulatory communities. We should continue to develop sophisticated and robust information systems for monitoring the safety and quality of medical products and food produced outside of our borders in concert with our global colleagues.

SUMMARY

The FDA is poised to leverage the acceleration in biomedical knowledge to lead to a new era of enhanced safety and effective therapies, and, if confirmed, I would be honored to lead the Agency in this exciting time. Thank you for allowing me to testify before you today and I am happy to take your questions.

The CHAIRMAN. Thank you, Dr. Califf. We'll now begin a 5-minute round.

Dr. Califf, around the country and in Congress, there's lots of talk about the high cost of pharmaceutical drugs. Do you believe, in terms of drugs, that it's accurate to say that the FDA's statutory mission is to promptly and efficiently make sure that drugs are safe and effective?

Dr. CALIFF. Senator Alexander, that is our primary mission. We also can have an impact on the cost of drugs by performing that function effectively.

The CHAIRMAN. Let me talk about that just a little bit. Do you agree that it's not your job to set the price of drugs?

Dr. CALIFF. It is not our job to set the price of drugs.

The CHAIRMAN. Let's talk about generic treatments. If generic treatments can move more rapidly through the FDA process in a safe and effective way, that would be one way to create more competition and presumably lower the cost of drugs. Despite getting about a billion dollars in new funds over the last 3 years, generic manufacturers estimate that the FDA's median approval time for generic drugs has gone from 30 months in 2011 to 48 months in 2014.

Is that accurate, based on your knowledge? Or can you explain how the FDA, with the availability of a billion new dollars, could have actually presided over a situation where the approval of generic drugs has gone from 30 months in 2011 to 48 months in 2014, especially since a more rapid approval, if safe and effective, might have had some effect of lowering drug prices?

Dr. CALIFF. Senator Alexander, bear with me. I appreciate the question. Bear with me for just a second while I explain this. First of all, as you point out, 88 percent of American prescriptions now are generic. We have made tremendous progress. But we can do even better.

You also know that we're well ahead of the generic drug User Fee Act goals that were set. We can still do better, and I'm all in favor of that.

Explaining the backlog is really important, and here's the way to think about it. We started with a huge backlog, thousands of applications that were waiting until the user fees came in. The easy ones, the ones that were good, were well-written, went through quickly. The new ones, the ones that are pertinent to getting the first generic on the market are put in what we call a fast lane, and they're going through quickly.

We have this backlog of applications that are requiring back-and-forth, because we want generic drugs to be just as safe and effective as the innovator drugs. When the applications are not complete, or there are questions about manufacturing, those get held up. I'm confident you'll see over the next several years as that backlog is cleared that new applications are going through very quickly.

The CHAIRMAN. Thank you, Dr. Califf. This question will require just a short answer. Will you take a look, if you're confirmed, at the FDA's policy of issuing non-guidance documents instead of rulemaking?

I've talked with Shaun Donovan, Director of the Budget, and the administration OMB had some pretty strong policies and firm views on the difference between rulemaking, which involves consultation and is legally binding, and guidances, which are not legally binding. Will you take a look at that? Because there is a bipartisan concern that agencies of the Federal Government, including FDA, are issuing guidances as if they were legally binding.

Dr. CALIFF. Senator, I will commit to working with you on that and taking a careful look at it.

The CHAIRMAN. I'd like, in my remaining time, to ask you to comment on a management issue at FDA. We hear that even when products are similar, experiences of applicants varies quite a bit. Regulated parties ought to be treated in consistent and predictable ways. Why do you think that even with similar products, the experience of some applicants is so different, and what could you do to make sure that regulated parties are treated in consistent and predictable ways?

Dr. CALIFF. Senator Alexander, I appreciate the question. Having spent several decades on the other side of the fence, working on new therapies, I can appreciate people's concerns. The primary reason is really that each individual medical product is different. The clinical trials that need to be done, even if they're similar, can have nuances that are critical.

Still, we are committed at the FDA, and Dr. Woodcock, who you know well—I'm working very closely with her, and we're going to do everything we can to produce a more even template across the FDA so that the standards are the same. I wouldn't want anyone

to come away thinking you can take a cookie cutter and develop a drug or a device. You've got to treat each one differently.

The CHAIRMAN. Thank you, Dr. Califf.

Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman.

Dr. Califf, in contrast to some of our previous FDA nominees who have come from the public health sector, you are a physician and a researcher with a specialty in large clinical trials. As a result, throughout your career, you have partnered extensively with pharmaceutical and other industry companies, and I want to just ask you some questions about that.

During your past clinical trial and consulting work you've done, how have you ensured industry views have not biased your work, and what do you plan to do to ensure you are able to lead the FDA without any undue influence?

Dr. CALIFF. Thank you, Senator Murray. It's important to really divide this into two parts. The clinical trials we do—that were done at Duke during my tenure and are still being done there—if funded by industry—remembering that many of our clinical trials are funded by foundations, and we're one of the largest NIH grantees, also—but when funded by industry, we have an ironclad contract, which I believe your staff has a copy of, that guarantees the independent right to publish, guarantees access to the database, and in the majority of cases, we actually have the database. We are running the trial, and we publish the papers with input from the companies, but they have absolutely no right to change what we say. We have the final right of publication.

These trials are also done, usually, with international steering committees representing many countries, providing an independent voice that's really needed. So, yes, industry funds the trial, so they need to have their products evaluated. We have an independent voice, guaranteed by contract. I believe you'll find that 100 percent of the studies that I've been involved in have been published so that they're in the public record for people to view.

Senator MURRAY. What do you see as the appropriate role of industry in working with the agency on key challenges like trials and the surveillance?

Dr. CALIFF. It's critical here to separate the role of industry for individual applications versus what we call the precompetitive space. That is, what are the right methods—how do we understand, for example, how to streamline the clinical trial process? How do we share information as medical products are rolled out to the public to make sure we understand the risks that may only be seen in the post-market phase.

In the individual applications, there is no role for industry other than to present its case, that it has a product that meets the criteria for safety and effectiveness, and it's the FDA's role to independently judge that application. The American public completely depends on having confidence that the FDA is independent in those reviews and judgments about individual products.

In that precompetitive space, we've got to work together. Industry funds 70 percent of clinical research, for example, globally. NIH is a minority funder. I'm pleased to say we're working closely with the NIH right now, and we'll bring industry in into what will be

a dramatically lower cost but much more effective clinical research system.

Senator MURRAY. I very much appreciate that. I do want to turn to an issue that I've raised a number of times this year. We know that patients across the country, including in my home State in Seattle, got serious antibiotic-resistant infections from duodenoscopes. As I have investigated this issue further, it seems to me that we need to make significant improvements in how FDA monitors medical devices on the market to identify safety issues more quickly and prevent the tragedies that we have seen with this.

What steps would you take to improve the post-market surveillance system for devices and better protect patients?

Dr. CALIFF. Thank you for bringing that up. First, let me just say as a cardiologist and someone with administrative responsibilities at Duke Hospital, when ERCP, the procedure you're referring to, was first developed, it was in the United Kingdom, and those doctors came over to Duke and we were one of the first places to do it. I have firsthand experience on the importance of that procedure, typically in people who are critically ill.

We need to really work on our post-market surveillance in devices, and I really hope that you'll help us with this. The Sentinel system that you all have helped with—industry has, too—but really developed by the FDA by Janet Woodcock, with Jeff Shuren's help, by the way, from devices—is a model in drugs. We have 170 million Americans' claims data, so that when there's a problem with a drug, we can look almost in real time.

We need the same system on the device side. We have plans to do that. We're going to have to work together with you to figure out how to fund it and how to fold it in with that Sentinel system. Imagine these duodenoscopes—if there had been such a system, we would have seen the problem very early. Industry could contribute to that, but we could see it independently of industry and act on it much more rapidly.

Senator MURRAY. I very much appreciate that. This is something I'm very concerned about as we move forward, so I appreciate your response and look forward to talking with you more about that.

Thank you, Mr. Chairman.

Dr. CALIFF. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

The next four Senators are Burr, Whitehouse, Isakson, and Warren.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

Dr. Califf, the animal rule was finalized on October 27 of this year after a significant and, in my opinion, inexcusable delay, given the importance of the rule. I'm pleased that the rule has been finalized, as it will provide more certainty for those working to develop medical countermeasures to protect American people in the event of a public health emergency, whether it's natural or the result of a man-made attack on our country.

If confirmed, how would medical countermeasures be prioritized within the agency, and how would you ensure that the FDA is advancing the development and review of these products toward the goal of a timely approval?

Dr. CALIFF. Senator Burr, thank you for that question, and I'm amazed at the attention and intensity you all have today, given the fact that we're all worried about the issue that you're bringing up. It can be either man-made or something that's totally unanticipated, for example, with an infection.

We're committed to working on this. I was pleased to be able to get the guidance out for the animal rule, which you had requested. It's going to take a concerted effort, not just by the FDA. As happened with the Ebola crisis, which we've all just witnessed, when the Federal agencies work together, a lot can be done to quell a crisis and deal with things.

I do want to refer to the really brilliant work that's been done in the outside community, academia, industry, but also within the FDA. For those not thinking about it, the animal rule basically says in cases where we can't do human studies, but there's an emergency, what's a way in which we can extrapolate from animal studies to the benefit of humans in these catastrophic situations? We're committed. We're going to be there 24 by 7 if needed.

Senator BURR. Thank you for getting that rule out. There have been reports that the Tobacco Deeming Rule did not change the grandfather date for newly regulated tobacco products. This means that many non-combustible tobacco products, which may have a public health benefit compared to the more traditional forms of tobacco, would not be available to consumers for at least some period of time, despite their potential benefits compared to a more traditional tobacco product.

As Commissioner, how would you improve the performance of the FDA's Center for Tobacco Products with respect to the timely and predictable review of tobacco products?

Dr. CALIFF. Senator Burr, this was a new creation just a few years ago, and it started with zero employees. It's now up in the multi-hundreds. There were no rules by which the tobacco applications could come in, so those have had to be developed.

First of all, let me just say that you bring up a general issue of weighing the overall health risk of tobacco products, where they're graded from most serious to less serious. There is a pathway for doing that. We're committed to reviewing them in the timeframes that have been agreed to, and we have funding to carry out that activity. We're committed to get it done.

Senator BURR. I thank you for that commitment. I often hear from constituents in North Carolina about the importance of laboratory-developed tests. For researchers, it means the next step in creating precise therapies. For providers, LDTs help to determine accurate diagnosis and the means for more targeted treatments and therapies on behalf of patients.

As someone who has been on the front lines of research and treating patients, under your leadership, how would the agency collaborate with labs, other existing government structures such as CLIA, and the full range of stakeholders in this space to ensure that regulation of laboratory-developed tests is carried out in a workable way that moves these promising tests forward without inappropriate regulatory burdens or delays for patients and their practitioners?

Dr. CALIFF. As an academician for over 30 years, I'm well aware of the importance of laboratory-developed tests. It's sort of the place where homebrews are made to make the tests better iteratively over time. It's an important activity. On the other hand, this has become a big industry with major implications for patients, especially with precision medicine, where you have a test, and it tells you what therapy to give. That can be either really good or really bad, depending on whether it's right.

We're committed to work with the whole ecosystem, which is quite complicated, so that there is a standard for tests, so they'll have analytical validity and also clinical validity. As you may know, there's a hearing going on in the House right now about this issue that involves Jeff Shuren from FDA and also Pat Conway from CMS. There'll be a lot more to say soon about this.

Senator BURR. Thank you.

Mr. Chairman, I do have additional questions and would ask unanimous consent that those questions be allowed to be sent in writing to Dr. Califf.

I would conclude by saying this—not a question. The FDA has over 150 outstanding guidance documents in limbo at the agency. Some of these guidances remain in draft form, and others have yet to be issued. My hope is that you will take that very seriously, because without guidance, I don't know how the downstream effects are ever going to be felt of investment and development if, in fact, they don't have the guidance as to how to move forward.

I thank the Chair.

The CHAIRMAN. Thank you, Senator Burr.

Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Dr. Califf, good morning. Welcome.

Dr. CALIFF. Good morning.

Senator WHITEHOUSE. There are increasingly products emerging on the market that combine a pharmaceutical component, a drug, and a delivery component, a device. The FDA is basically broken into one path for pharmaceuticals, the drug path, and another path for devices.

I've spoken to the people who lead both the drug side and the device side about this question of the drug-device combined products, and both have said the same thing, which is that "My pathway is not suitable for that. If we're going to do that, we need to create a new pathway for that drug-device combination." Could you let me know what your thoughts are about that pathway for the drug-device combination products, and what you think a reasonable timeframe would be for FDA to have such a proposal ready for us to consider?

Dr. CALIFF. As a cardiologist, I sort of live and breathe this kind of work, because often we give lifesaving drugs systemically in acute situations. It would stand to reason in many cases if you could deliver them through a catheter, you could give them a much lower dose and do better. Maybe that's the best example to think about here.

When you have a drug that's given in full dose systemically, and you can give it at a lower dose, you don't want to go through the

whole thing as if it were a totally new dose. You can't assume that you know the risks and benefits of the lower dose. There's a strong view at the FDA that we need another pathway that will give the FDA the flexibility to require the data that's needed to assure the public that the proposed treatment is safe and effective.

Senator WHITEHOUSE. Do you agree that we need that other pathway? You said that was the opinion at the FDA. Is that your opinion as well?

Dr. CALIFF. Yes, but——

Senator WHITEHOUSE. What is the timeframe for designing that pathway and giving us something to look at here in Congress?

Dr. CALIFF. I feel like within the next year, the FDA's opinion can be adjudicated back and forth with you, and we're really happy to work with you. We have opinions on this now, so we're happy to engage and discuss with you.

Senator WHITEHOUSE. Great, because there is probably going to be legislative action that's going to be required to do this. Both of your sides of the house think that it can't be done under the existing regulatory authority, that it would require Congress to act. Do you agree with that?

Dr. CALIFF. We need some help to get the right balance here.

Senator WHITEHOUSE. Great. The last thing that I'll mention is I hope that as you go forward with your responsibilities in the space of apps and communications technology that are adapted to measuring health effects that you'll recognize that, in many respects, this is a very valuable and robust industry that could well be over-regulated if the FDA's authority over those sorts of devices extended too far. What do you see as the boundary between informational apps that the FDA should and should not regulate?

Dr. CALIFF. I had the privilege of going back to my old home, an American Heart Association meeting, just last week, and we had a whole session on this issue. I won't show the brand, but I'm wearing my own device here that has a number of apps on it that's like a whole different world than what existed 6 months ago.

There's a good statement, the trilateral statement just last year that came out from FDA, the FCC, and the Office of the National Coordinator that states the full intention to regulate based on risk. Exactly where to draw that boundary is a matter that we need to keep talking and thinking about.

For example, clearly stated in that document, a health-related app—we're monitoring my heart rate, and I'm healthy and I want to exercise more. That's not something that we want to be bothering with. If this was attached to my internal defibrillator—don't worry, I don't have one—but if I did have one, that would be something we would need to regulate, because misfiring the defibrillator could kill you.

We've got to be able to deal with that spectrum and find that middle ground, where there will be adjudication as we learn how these things work.

Senator WHITEHOUSE. You'd be looking along the lines of regulating technologies that could actually have a direct physical effect on the human body, as opposed to just getting information that causes you to think that, "Oh, gosh, my heart's better, so I'm not

going to run as much." You need to regulate that because the individual is making a different decision based on the information.

Dr. CALIFF. That's correct. Also, I would just like to add that we're going to learn as we go through this, because there may be cases where, for example, heart failure patients using the same app may be making more life and death decisions. What we don't want to do is suppress innovation.

Senator WHITEHOUSE. My time has expired, and I don't want to take—there's so many of us, and I don't want to trespass on other people's time. I thank the doctor, and my appreciation to the Chairman.

The CHAIRMAN. Thank you. That's very courteous, Senator Whitehouse.

Senator Isakson.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Dr. Califf, following up on Senator Alexander's first statement regarding guidance letters, FDA has two opportunities. One is to issue guidance letters. The other is to do rulemaking. While there are similarities, there are substantial differences. Under rulemaking, you have to do a cost-benefit analysis. Rulemaking has the force and effect of law, and guidance letters do not.

Yet FDA continues over and over again to try and implement policy through guidance letters. For example, and most recently, through a guidance letter, you're going to talk about regulating laboratories and bring them under the FDA. Guidance letters, again, don't have the rulemaking period or the comment period to be open. FDA continues to try and regulate parties more often through guidance letters than through rulemaking, which shuts out the open comment period and has confusing effects.

I have really two questions to ask. No. 1, why has FDA grown so reliant on non-binding guidance documents for rulemaking? No. 2, Do you think that's a problem?

Dr. CALIFF. Senator Isakson, I appreciate your concern with this, and one thing that's been really evident to me in my time at the FDA so far is that everybody wants to know what the FDA is thinking. There's a tremendous value in guidance documents to let people know what the FDA is thinking, and the demand for these is actually quite high.

There are other situations where you need the full force of rulemaking. I understand there is a difference. I will have to work with you—and I look forward to doing it—when things come up where you're concerned so that we can discuss it and work through it.

Senator ISAKSON. Specifically, to that offer, let me ask you the following question. Will you commit to require FDA staff to go through rulemaking when it intends to legally bind regulated parties or change their behavior in a burdensome way?

Dr. CALIFF. Senator, I believe the statement about guidance documents says they're not legally binding. They're a statement about FDA's thinking, and, of course, people would be wise when they see a guidance to consider that thinking. Personally, in developing drugs with companies, I've often taken a different path from the

FDA. I'm certainly committed to work with you to try to deal with this tension that you're feeling.

Senator ISAKSON. Thinking is a subjective thing. Rulemaking is a objective thing. When you talk about the cost of compliance with things, you ought to have the rulemaking procedure, in my judgment, rather than just a guidance letter which could affect some and not others.

Second, on sunscreen, November 26 is the first anniversary of the Sunscreen Innovation Act that this committee passed and President Obama signed, which was designed to expedite the approval of ingredients in sunscreen. As you probably know, there are sunscreens that have been available in Europe for years and, in some cases, decades that are still not available in the United States because FDA has refused to make decisions on some of those ingredients. It's been a year since we passed the expedited rule and, still, FDA hasn't done it.

Will you commit to work with us to try and bring those ingredients forward and do the proper due diligence to get those products to the market?

Dr. CALIFF. Senator Isakson, I really do look forward to working with you on this. As we discussed earlier, I have a family history of melanoma myself and a number of moles that probably should be looked at more frequently than they are. With Lydia sitting behind me, she would remind me of that.

Let me also say that part of what we need to work on is actually developing the evidence. We've asked the companies involved for specific information, which I believe they can develop, and we're very open to moving as quickly as we can if we have the right evidence.

I would just point to what's happened with people who have melanoma with these amazing new therapies, several of which have just come on the market, because the patients with melanoma have worked closely with the companies to get the clinical trials done so the effective treatments get expedited and the ineffective ones don't get out there.

Preventing melanoma is in the same category. We've got to do better. It's a rapidly growing cause of death, and I really do want to work with you personally on this issue.

Senator ISAKSON. At certain stages, a diagnosis is a death sentence for which there is no cure, and I think you know that. I've had melanoma myself and survived two of them, fortunately. Next March or April is spring break, and the kids are going to hit the beaches of America and, hopefully, a lot of Georgia's beaches, getting a lot of sun and having a lot of fun. I hope they'll also have the best sunscreen ingredients available to try and prevent melanoma from being developed.

My last comment—I'll make it quickly because it's a long question, and I know my time will be up. The FDA has sent mixed signals to pregnant women with regard to seafood. I know you all were in the process of using some determination on seafood to make recommendations as to what was good to be eaten and not eaten, and you were using results from what was called your Net Effects Report. That seems to be abandoned now.

If you would, when you take over and are confirmed, will you expedite the decisionmaking process on seafood for pregnant women and the recommendations the FDA makes?

Dr. CALIFF. Yes, sir. I look forward to working on that.

Senator ISAKSON. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Isakson.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

Dr. Califf, it's no secret that during your time at Duke University, you received significant financial support from the pharmaceutical industry, both for you, personally, and for your research. I know this is common practice for principal investigators of clinical trials, but it naturally raises questions about your relationship with the drug industry. One particular concern with industry funding of academic work is that drug companies may be able to exert influence over the conduct of those studies.

Let me ask: For the clinical trials you conducted or oversaw while at Duke, can you detail for us exactly what input pharmaceutical sponsors had, did and did not have, in the design of the trials, the analysis of the data, and the publication of the results?

Dr. CALIFF. I'm glad to do so. When industry funds a clinical trial, whether it's devices or drugs, done through our institute, the design of the trial is something that's done jointly and done very publicly, because, typically, it's done to try to get an indication from the FDA.

It actually involves industry, academia, now patients involved in the design of the trial, and the FDA. It's a very public process. The protocol is developed, and it has to be submitted both to IRBs but also to the FDA before the trial starts. The design is something that is done jointly. The final say comes from the steering committee, of course, which is the academic leadership.

The database is really the critical factor here, and all of our contracts require that we either have access to the database or we actually have the database onsite. That's been ironclad. I would say 70 percent of the studies I wanted to do, we couldn't do, because the company was unwilling to grant that right. We had to walk away, if that was not done.

That leads to publications. Publications are in the purview of the steering committee and the authors from the steering committee. Industry has a right to make suggestions, but no right to censor and no right to change any of the writing that's done unless it's agreed to by the authors.

The same holds for our public presentations, which, in the fields that I work in, are very important because evidence moves very quickly and it has a large input. Keeping that academic independence, we think, is a critical part of the effort.

Senator WARREN. Good. If I can, I just want to underline this because it is so important. I want to make sure I got this right from your question. I hear you to be saying there is no instance during your career or any instance involving Duke researchers at the Duke Clinical Research Institute during the time that you were supervising in which a pharmaceutical company provided any input

into the analysis or the publication of the clinical trial that they paid to conduct. Is that right?

Dr. CALIFF. Let me clarify one more time. By input, they could make suggestions. That's perfectly allowable in our contract——

Senator WARREN. On the analysis and on the publication?

Dr. CALIFF. On the publication. On the analysis, this is another—I'm sorry to get into details here.

Senator WARREN. That's all right.

Dr. CALIFF. The way we do our analyses—because the company has to submit the data to the FDA—is, typically, we'll have an analysis done by the company, an analysis done by our statisticians. Then we compare the results to see if they match up and resolve any discrepancies. In no case did we allow the company to do the analysis, and we just were recipients of what they said the answer was.

Senator WARREN. All right. I'll tell you what I'll do on this, just because I know we're pressed on time. I'll followup with questions for the record on this so that we can get a detailed written account of any such instances.

I've also requested copies of the contracts that the pharmaceutical industry sponsors signed with the Duke Clinical Research Institute in order to get a better understanding of what's happening here. I look forward to reviewing them before this committee moves forward with your nomination.

These agreements typically spell out in detail the relationship between the researchers and the funders. It will help us better understand what's happening here.

In the little bit of time I have left, can I just make one other point? That is your financial relationship with the industry also raises questions about what your priorities will be if you're confirmed for this job. Many in the pharmaceutical and device industry spend a lot of time and money arguing that the FDA is just too tough, that we should lower the FDA standards on safety and effectiveness, and, unfortunately, they have a lot of friends in Congress.

Dr. Califf, do you agree with these arguments and recent efforts by some lawmakers to lower the standards for FDA approval of drugs and devices?

Dr. CALIFF. If you look at my record, you'll find I've never been a proponent of lowering standards. If anything, I've argued for raising standards with better studies that show the full gamut of risk and benefit for the time that a treatment might be used. That doesn't mean we couldn't potentially be quicker or something else, but in no case would we argue to lower the standards.

Americans depend on safe drugs and devices that are also effective. A device or a drug that's safe and is not effective actually can harm someone because then they don't use what is effective. I've been staunch in that regard.

Senator WARREN. Thank you, Dr. Califf. We could abolish the FDA tomorrow and we'd see a lot of new products on the market. If they're not safe and effective, then no one is any better off.

Thank you, Mr. Chairman.

[The prepared statement of Senator Warren follows.]

PREPARED STATEMENT OF SENATOR WARREN

The position of FDA Commissioner is critical for the protection of the public's health and safety and for the advancement of science and innovation. Since Dr. Califf's nomination for this position, I have carefully reviewed a significant volume of information, including many of his published articles and work published under his direction, as well as confidential contracts between the Duke Clinical Research Institute and pharmaceutical companies governing the conduct of major clinical trials in which Dr. Califf has participated. In addition, I asked Dr. Califf detailed questions about his work, both in person at his HELP Committee nomination hearing and through subsequent written questions for the record. I have also had multiple meetings with Dr. Califf to discuss his background, his qualifications, and his plans for the agency should he be confirmed by the Senate, and I've had extensive conversations with him about concerns that have been raised about his professional relationship with the drug and medical device industries. Finally, I have consulted with several outside experts in these matters to better understand the materials I have been provided by Dr. Califf. All of this investigation was aimed at better understanding the focus and relative independence of his past work as it gives clues to his willingness, if he is confirmed as head of the FDA, to put the interests of the public first.

After carefully examining Dr. Califf's record and looking closely at his representations both to me and to the committee generally, I am satisfied that he has conducted himself with integrity as an academic researcher. For example, the language in the confidential contracts I have reviewed is consistent with what independent experts described to me as best practices designed to limit the influence of industry sponsors over academic investigators. Dr. Califf also indicated to me that there are no major trials in which he has participated that were not published, and he noted that he has repeatedly published negative trial results about products under development by the corporate sponsors that funded those trials. Dr. Califf also submitted a comprehensive list of the trials in which he played a major role. This list details the intervention under investigation in each trial and whether the trial resulted in the sponsor's preferred outcome. My staff conducted an independent analysis of the trials presented in this list, and in some instances disagreed with Dr. Califf's conclusions about whether trial results clearly strengthened or undermined the position of a corporate sponsor. Even so, after re-classifying some of the studies, the totality of the data indicate that Dr. Califf has consistently published the results of his research, regardless of whether it ultimately bolstered the interests of that work's sponsor.

My examination of the Califf nomination has raised serious questions about our current clinical trials system. I am particularly concerned with a lack of overall transparency, numerous opportunities for conflicts of interest, and a marked shortage of trials that are designed to determine which products to treat a given condition are the most effective—as well as cost-effective—for various patient populations. My examination has also raised concerns about the FDA's willingness to stand up to industry preferences in the design

and conduct of clinical trials. Dr. Califf has indicated his clear and unequivocal commitment to work hard to address these policy issues as Commissioner.

Dr. Califf and I have also discussed in some detail his views regarding other important policies at the FDA, including efforts to move the FDA's blood donation deferral policies to risk-based policies for all blood donors. We have also discussed the importance of reducing antibiotic use in animal agriculture to protect public health, including the development of meaningful metrics to evaluate the effectiveness of FDA's current policies to curb use and the need for strong enforcement of current laws and regulations. In addition, some Senators have raised concerns about the degree to which the FDA is using its current authorities to address the ongoing opioid crisis—and as a Senator from a region that has been hard-hit by this crisis, I expect Dr. Califf and the other relevant agencies to provide full and complete responses to these inquiries if this nomination is to move forward.

The FDA needs a Commissioner who cares more about public health than industry profits or Washington politics. Given that the majority of major clinical trials are sponsored by private industry, it is fair to ask whether anyone with an extensive background in clinical research can be trusted to make decisions that are independent of the industry. On the other hand, there are substantial advantages to having a leader of the FDA who is a serious, frontline researcher who understands the importance of advancing cutting-edge work that will advance the health of millions of Americans—and who is sensitive to the conflicts of interest that can arise in industry-funded research. Based on the information I have reviewed and Dr. Califf's representations, I am satisfied that he can be a strong leader for the FDA, placing the interests of patients and the American public above all others. Should he be confirmed, I plan to stay closely engaged with Dr. Califf to ensure that he advances the integrity and high standards of the FDA—and I fully intend to hold him accountable for his actions and decisions as the FDA Commissioner.

The CHAIRMAN. Thank you, Senator Warren.

The next four Senators are Senator Roberts, Senator Baldwin, Senator Cassidy, and Senator Mikulski.

Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Thank you, Mr. Chairman.

In the first place, thank you for coming by my office. We had a very nice visit. My wife is from South Carolina. I learned a long time ago you can take the girl out of the South, but not the South out of the girl.

One of your responsibilities is to make sure the FDA is committing its resources to doing the most important work. For example, the FDA has been, in some cases, a little hesitant to implement key food safety goals while putting resources toward proposals for regulating sugar, salt, and caffeine. I would refer you to the new dietary guidelines that indicate now that an increase in salt intake is

OK, and caffeine is six cups of coffee. This is my third one, so I've got three to go. Sugar, however, no.

The FDA has proposed to expand its jurisdiction by regulating laboratory-developed tests in e-cigarettes and cigars for the first time. I just want to make sure that the FDA's use of resources is to make sure the agency stays focused on accomplishing its core objectives as directed by Congress. That's just a comment. You don't have to respond.

Food Safety Modernization Act. The acronym for that is FSMA. That's a wonderful acronym. I wear two hats here. I'm chairman of the Ag Committee and a member of this distinguished committee. I'm concerned about potential overlap with these new FSMA regulations and the requirements with which farmers and ranchers already have to comply.

We need to make sure the FDA is working with the Department of Agriculture to ensure these new regs and requirements are being harmonized with those already on the books. Will you commit to working toward that end, if confirmed?

Dr. CALIFF. Yes, be glad to work with you on that.

Senator ROBERTS. Thank you, sir. I want to followup on Senator Isakson's very concise comments with regards to draft guidances. I'm particularly apprehensive of the use of the guidances as they lack transparency and can escape the important cost-benefit analysis and other scrutiny.

What are your thoughts about setting a maximum period for which draft guidance can be left outstanding without being finalized or substantially revised? And, second, when commenters have expressed concerns, shouldn't the agency be required to publicly respond to those concerns or, at least, how the concern has been addressed when a guidance is finalized or if the agency has rejected the concern?

Dr. CALIFF. Senator Roberts, I'm kind of a big advocate of transparency, so I do appreciate what you're bringing up. It's been noticeable to me, the issues that you raise. It's also noticeable, as I mentioned earlier, that every time we give people an opportunity to interact with the FDA, they seem to want to do it more, in our user fee situations, for example. The number of meetings requested always greatly exceeds the number that we have.

The critical thing to me is getting whatever the correct format is moved along as quickly as we possibly can through the process so that people understand what the FDA is really thinking, and in the case where there really needs to be a rule, they understand what the rule is and how to implement it. To get to the details here, I'd need to come by and spend some more time with you to completely understand how you see it, but I would be glad to do so.

Senator ROBERTS. I appreciate that. My final question: Where is Duke ranked right now with regards to the basketball situation?

[Laughter.]

Dr. CALIFF. I'm just glad you didn't ask about football. Duke is somewhere around No. 4 or No. 5.

Senator ROBERTS. I think they're No. 5. Would you be interested in knowing who's No. 4?

[Laughter.]

Dr. CALIFF. That might be that school in the Midwest that we often beat up on when it comes to tournament time.

Senator ROBERTS. It is the University of Kansas. I just want to point that out. I might add that South Carolina is No. 1, but we'll take care of that.

Dr. CALIFF. Oh, you mean North Carolina is No. 1.

Senator ROBERTS. Yes, that's correct.

Dr. CALIFF. UNC. I would rather have Kansas No. 1, actually, than UNC, but that's a different story.

[Laughter.]

Senator ROBERTS. I have no further questions, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Roberts, for your illuminating inquiry there.

Senator Baldwin.

STATEMENT OF SENATOR BALDWIN

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

I'm pleased to have you here today and was pleased to have an opportunity to meet with you prior to this. We all agree that it's critical for the products that are approved by the FDA to be of the highest safety and efficacy standards, and that the public must also have meaningful access to accurate information about treatments so that they can make the best healthcare decisions.

I share some of my colleagues' concerns with the ever-increasing drug prices. There's been a little bit of dialog about that already, and we can do more and should do more to improve drug accessibility, affordability, and transparency. I want to start with transparency.

Dr. Califf, the public still lacks comprehensive access to information about medical products. For example, companies do not consistently report clinical trial outcomes for drugs in the public databases, as a number of recent studies have noted. Generics are not yet able to initiate a change in their patient labeling if they learn of new safety information because the FDA has not yet finalized the generic labeling rule.

In your new role, when you receive confirmation, how would you improve access to accurate information on drugs for patients, for doctors, for researchers? How would you ensure that the FDA maintains patient safety once these medicines actually reach patients?

Dr. CALIFF. I'll try to be as quick as I can with this, because that's a very important question that you're asking. First, I'll just point out again that every study that I was involved in has been published, and I think that's a mandate. When you ask someone to participate in a human experiment, the informed consent actually says you're doing it to create generalizable knowledge. We have an obligation. Even if we don't like the study, the result was lousy, or whatever, we need to publish it.

Second, just before I left Duke, I was the co-author of a New England Journal paper pointing out the track record of *clinicaltrials.gov* reporting. One interesting side issue there is that industry is actually doing better than NIH-funded investigators, so we have work to do there. I'm pleased to say, working with the

NIH, they now have a policy that you won't get your next grant unless you put your result in *clinicaltrials.gov*. It's been very good working with Kathy Hudson and Francis Collins on making this happen.

The third element, the surveillance system that we talked about, Sentinel, and the equivalent on the device side—this is really needed. We're now dealing with generic drugs that have been on the market for up to 40 years, and we're still learning about them. We can't have a system where it depends on the innovator company to figure all this out and somehow make it public.

I give Jeff Shuren and Janet Woodcock a lot of credit. We have an approach—and we just had a meeting 2 weeks ago with other Federal agencies, and there's general agreement that we need to have a national evaluation system, which is really a public good, and if the companies can develop the best products, that's fine. We need to work toward this.

Senator BALDWIN. I want to switch gears, given the role of the FDA in food labeling. You and I had a chance to speak about one of Wisconsin's products. We're the No. 1 grower of cranberries. I know that a couple of other members of the HELP Committee represent States that have a robust cranberry industry, also.

I'm concerned that recent FDA proposals to update food nutrition labels, specifically with added sugar information, may cause some confusion for customers and others by categorizing cranberry products, which are clearly highly nutrient dense fruits that need added sugar for palatability, as somehow comparable to foods that they shouldn't necessarily be compared with. For example, should you be comparing cranberry juice to other fruit juices or to soda pop? Should you be comparing dried cranberries, craisins, to raisins or candy?

As Commissioner, how would you ensure that these and other FDA food policies appropriately account for the unique health benefits of food like cranberries and ensure that consumers are going to have the type of information, comprehensive and accurate, that will allow them to make healthy and nutritious decisions?

Dr. CALIFF. Senator Baldwin, I appreciate that, and I've noticed cranberry juice has frequently been in our refrigerator at home. It may have something to do with some health benefits that are attributed to it. It's a good example of the balancing act the FDA has to do. We've got this terrible epidemic of obesity and diabetes, so huge amounts of sugar are clearly not good for you. I don't think there's any disagreement about that. We've also got to preserve nutritious foods that do need a little sugar to make it better.

I talked with Senator Warren and with you a little bit about the fact that we need to really work on the cognitive psychology of labeling so that when we do take actions and put information out there, it's interpretable and actually helps people make good decisions. Ultimately, it's up to people to make their own decisions, but if we don't present it in a way that's clear to them, it could lead to the wrong decision.

The CHAIRMAN. Thank you, Senator Baldwin.

The next Senators are Senators Cassidy, Franken, Kirk, and Bennet.

Senator Cassidy.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. I enjoyed our meeting. Thank you for coming by. I have several questions. First, going back to the drug pricing, clearly, we've seen companies like Turing and Valeant kind of abuse the social contract, which gives you a reasonable rate of return for drug marketing, and they've gone way beyond reasonable.

I've been told in the case of Turing that an approval of a generic would take several years because clinical trials would be required to prove that the generic competitor was the equivalent to that which Turing now has as a sole source provider. We know this is a 60-year-old drug.

It comes to mind because I'm reading now, on-premise, on a compounding component that would make the same drug available. Of course, compounding—a doc has to write the prescription. In a sense, compounding is doing what generic can't do.

I guess my question is if we know, or I presume we know, that the compounded drug being sold for $1 a pill, as opposed to $750 from Turing—take that as an advertisement for anybody who wants a reasonably priced drug—if it is $1, why can we do this in the compounding space but not in the generic space? Why does it take so long to work this through the generic when we get—do you see what I'm saying? This is cognitive dissidence.

Dr. CALIFF. I know you're a doc and you have an understanding of all this. Let me just point out, as I mentioned earlier, every drug is a little bit different, and the whole goal with generics, in most cases, is not to have to do major clinical trials. It's really just showing that you actually have something that's equivalent. I believe you spent a lot of time with Dr. Woodcock on this recently.

Senator CASSIDY. Yes.

Dr. CALIFF. There's a lot we can tell about the molecular structure in some very simple pharmacodynamics type studies. We're not dependent on these large clinical trials that we have to do for the innovator drugs. When it comes to compounding, as you well know, we're working hard on the standards for compounding, because we had some disasters with compounding that have required FDA action.

Senator CASSIDY. The disasters were more related to infection control, fungi entering an injectable. This, obviously, is an oral drug, and I presume—knowing that there is liability involved, on-premise would not be selling it were it not bioequivalent.

Dr. CALIFF. I'll have to get back with you on that because I don't know the details on that particular drug. I'll be glad to do that.

Senator CASSIDY. Just because I see now that these folks have established—the business model works. Again, I have something from Valeant—a fellow who was paying $566 a prescription. It's now $5,500 a prescription. A total exploitation of the system that has been a pretty good social contract and now is breaking down because of these folks—frankly, greed.

If we're going to somehow circumvent that, we've got to come up with a more efficient way to do the generics. Again, just to make the editorial comment, it so clearly is working with compounding that it seems almost like it should work as well with generic.

Dr. CALIFF. Again, I'll have to get back with you on the specifics. I did have a pharmacy compounding operation at Duke Hospital that was required for some of our intensive care unit medicines, and I'm very aware of the complexity of compounding. It's not as simple as it may sound. I'd have to really look at the specifics of this and get back with you.

Senator CASSIDY. That's fair. Second, which is related, going to the drugs which are manufactured in India and China, I gather that the FDA recently sent out a warning that said investigators went, looked, observed holes in the walls and roof which allowed pigeons access near production equipment in multiple manufacturing areas. There's evidence, or at least suspicion, that somebody was hiding audit trails, et cetera.

I'll just say, again, cognitive dissidence. On the one hand, we're continuing to allow folks to import, even when good manufacturing procedures are obviously not being followed. Yet it seems like we're putting roadblocks up for those who are producing domestically, who could give us some relief from the exploitative pricing practices. Knowing that you're the new man on the job, I don't expect you to comment on that beyond just to make the observation.

Dr. CALIFF. Yes, I understand what you're saying, and I did have the privilege as an academic to do a lot of work in India and China over the last decade, and it is going to be a focus that we'll have to pay a lot of attention to. A large part of our food and our drugs and device supplies are coming from India and China. We certainly don't want to disadvantage Americans in that regard, either.

Senator CASSIDY. If we found those GMP were not being followed, would we shut down those supply—those components of the supply chain?

Dr. CALIFF. We can't shut down something in India or China, but we can shut down importation.

Senator CASSIDY. The ability for that to be used——

Dr. CALIFF. Yes, and we do that.

Senator CASSIDY. I got you. I yield back. Thank you.

The CHAIRMAN. Thank you, Senator Cassidy.

Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman, and I note that you, Senator Baldwin and Senator Cassidy have all talked about what we're hearing when we go back to our States about pharmaceutical costs, and that's something we really have to deal with, and the exploitation of positions that companies have gotten.

Dr. Califf, I want to talk about probably the basic question that you will face, which is the delicate balance that the FDA plays in making sure that products get to people who need them quickly, but at the same time making sure that they're safe. That's what you deal with every day. I've tried to promote this balance in legislation I have introduced with Senator Burr, the FDA Device Accountability Act of 2015.

Given your experience as an outside advisor and now as an internal leader at FDA, how can FDA use the tools at its disposal to strike this balance?

Dr. CALIFF. When it comes to cost, we do have some tools we can use to help out. The first, we've already discussed, which is doing everything we can to do a good job with the generic drug situation. We're at 88 percent now, and that's a good thing.

We now also have biologics, which—biosimilars are now coming up, and we've got over 50 applications in the works. We're going to need to do a good job with that, too, because that's a big expense and we want to make sure that people have access when it's appropriate and safe and effective. The criteria are stringent there.

One other that is very important to me, which people wouldn't normally think about that much but it's going to come up more and more, is that if we really fix our evidence generation system, that is, streamline clinical trials, get the data that we need, people wouldn't spend money on expensive drugs when they're not needed. We need to have better information for people, and several Senators have brought that up today, and we can do that in a fairly dramatic way.

And finally, we do keep track of shortages. We prevented over 100 shortages a year in each of the last 4 years. One year, it was all the way up over 200. There's a constant surveillance that goes on. There's a requirement that people notify us when there's going to be a shortage problem.

The new area that we've got to work on is when someone gets a monopoly, which is what several of you have referred to, understanding who the competitors are and making sure that they're doing the right things to be able to compete and get their products on the market.

Those are the things that we've gone through that we can clearly do fully within the FDA.

Senator FRANKEN. Quickly, I want to turn to a different issue, which is making sure that products continue to be safe once they've hit the market, once they've been approved for the market. You mentioned post-market surveillance. Does the FDA have adequate authorities here that you need to do this adequately, or do you need additional ones from Congress?

Dr. CALIFF. I'd have to get back to you on the specifics of what you might be thinking. The thing we clearly need is a better system for post-marketing. Sentinel on the drug side is revolutionary and fantastic, and on the device side, we're doing better and better. We have a plan that I hope we can really enact, because I believe when we find a problem, for the most part, we can deal with it. We've got to have good data and quickly in order to identify the problems.

Senator FRANKEN. I want to talk about generic drug labeling and the generic drug labeling rule. This has to do with the rulemaking that you are doing on generic drug manufacturers and requiring them to update their warning labels and provide new safety information. This came out of the Supreme Court decision.

What is the current plan for finalizing the FDA's generic drug labeling rule?

Dr. CALIFF. Thank you for asking. That's a very important issue. As I said, we need to make sure that if there are problems with generic drugs that come up later—and they do—with better surveillance systems that there's a way of making sure the labels are

up to date and consistent across similar products. We got a lot of comments on the proposed rule. They're under consideration. I can't talk about decisionmaking. We're in the middle of it. It's a very high priority to get this finished.

Senator FRANKEN. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Franken.

The next Senators are Senator Hatch, Senator Bennet, Senator Scott if he returns, and then Senator Sanders.

Senator Hatch.

STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you, Mr. Chairman.

I'm very pleased to be able to support your nomination. I'm very impressed with what you've been able to do, not only with your life, but all the work that you've done down there at Duke and elsewhere. To be honest with you, you deserve a lot of credit, and you're going to add a great deal to the FDA.

Let me just say this. I'm very concerned about data exclusivity. When we did Hatch-Waxman, we made sure there was enough data exclusivity time so that they could recoup the cost, because the average cost, according to what I've been told, for a pharmaceutical drug is about a billion dollars and up to 15 years or more because of the pace at FDA, and for a biological drug, about the same. The average cost is $2 billion to come up with a biological therapy that is approved by FDA.

I'm very concerned about it, because if we reduce that data exclusivity time, especially with regard to bio, you're talking about having to charge a lot more, and you're talking about our industries subsidizing other countries all over the world and paying, really, so they can have these biotherapies really at our expense, and at the same time, in order to recoup the amount of money it cost to go through FDA, the cost of these therapies is continually rising.

I just want to know if you feel that we can move ahead quicker on these matters and make it so that these companies have a chance to recoup their monies that they've invested.

Dr. CALIFF. Senator Hatch, I do understand your concern that we want to make sure that if someone invests in the development of a drug, there's a return on investment. Otherwise, people won't invest in our kind of society.

Senator HATCH. You also understand that the more it costs, the more difficult it is to recoup the funds, and the longer length it takes to recoup them as well without charging even more than we do now.

Dr. CALIFF. The FDA doesn't set the length of data exclusivity.

Senator HATCH. I know.

Dr. CALIFF. What we can do that you bring up is the cost of development is largely driven these days now by the cost of clinical trials. We think we can do trials that are actually bigger and include more patients and are more representative for a much lower cost. I hope you'll work with us on that.

Senator HATCH. I'm going to work with you on it, but that's an important issue, and it even becomes a major issue with regard to

our trade promotion authority bill and also the Trans Pacific Partnership.

Dr. CALIFF. I appreciate that.

Senator HATCH. If we don't allow enough data exclusivity time, we're not going to develop these therapies, especially in bio, because bio is one of four or five places, four or five techniques, where we can actually find treatments and cures. If we find the cures, that, over time, will save us trillions of dollars. I'm very concerned about this system working very well.

Dr. CALIFF. I've been fortunate to be a leader in the development of several biological therapies that have made a difference. So I appreciate what you're saying.

Senator HATCH. Also, Hatch-Waxman has made a real difference as far as getting—I remember when we did Hatch-Waxman, it was like 18 years to get a generic through. Today, it's—and it was very, very difficult. It's kind of automatic because——

Dr. CALIFF. We're doing better, and 88 percent of prescriptions are generic. It's been a tremendous success.

Senator HATCH. One issue that significantly affects many entities in my home State is the FDA's October 2014 proposed guidance on the regulation of LDTs, laboratory-developed tests. There has been a robust conversation on this proposed guidance between stakeholders, Members of Congress, and the FDA ever since the announcement.

Does the FDA intend to issue final guidance, or does the agency plan to allow for further comments and feedback on the next steps proposed?

Dr. CALIFF. As you may know, this is an ecosystem issue where we want to have universities continue to innovate, but we also want to assure patients that they're getting accurate test results for analytical and clinical validity. We're collecting a lot of information, ongoing feedback.

We just had 2 days at the FDA of all the stakeholders talking about next generation sequencing, which is an advanced form of this testing, so we're still collecting feedback. We want to find something that stimulates innovation but also assures patients.

Senator HATCH. Mr. Chairman, may I ask just one other question that would just requires a yes or no answer?

The CHAIRMAN. Sure.

Senator HATCH. Thank you.

Do you believe, as prior commissioners have—every one has told me this—that the Dietary Supplement Health and Education Act, DSHEA, provides adequate authority to regulate the dietary supplement industry and protect consumers from unsafe products?

Dr. CALIFF. We're fully aware of our authorities, and you're going to see a lot of action where the authorities are pertinent in the near future.

Senator HATCH. Do you agree you have enough authority?

Dr. CALIFF. We're very well aware of our authorities and plan to use them as Congress has directed.

Senator HATCH. All right. Thank you.

The CHAIRMAN. Thank you, Senator Hatch.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman.

Thank you, Dr. Califf, for your willingness to serve. We're delighted that you're here today.

In my view, the FDA has been extremely successful implementing the breakthrough therapy pathway, which has led to the approval of 32 lifesaving drugs and over 100 more in the pipeline. When I was first working on this bill with Senator Hatch and Senator Burr, Colorado startups were saying to me that all of the venture capital in this country was moving to Asia and moving to Europe because of the regulatory uncertainty at the FDA.

All of us want to keep jobs here, and we want to give patients safe and effective drugs as soon as possible. It looks to me like this breakthrough pathway may be achieving both, and I wonder whether you could talk about it a little bit. What have we learned about regulation, and can this kind of approach be modeled in other places at the FDA, including at the device center?

Dr. CALIFF. Thanks for your comment, and my two sons from Colorado are listening carefully, I'm sure, to your thoughts on this. Breakthrough is——

Senator BENNET. Barbara Mikulski is not here, so let me say we would gladly move the FDA to Colorado if that would make the family closer together.

[Laughter.]

The concept of breakthrough is where things look really promising early on, that it's going to make a dramatic difference, and there's an unmet need for a life-threatening condition. The FDA works closely with the industry to move things along as quickly as possible. There have been a whole series of cancer issues, in particular, that have just delighted the cancer community and people who otherwise would die.

My mom back here has multiple myeloma. She's now on her third or fourth chemotherapy treatment. It's been a tremendous success to have the community working with the FDA and with industry and with academia in a concerted effort. We don't need this for chronic common problems where there's already effective treatment. We want to make sure we don't rush things to the market that aren't safe. The real key is having the criteria to identify where this kind of activity is needed.

Senator BENNET. I want to say that, at least from my perspective, it's fashionable to criticize the agency. This is a place where the FDA has really gotten it right.

How about on the medical device side of the equation?

Dr. CALIFF. There have been issues with medical devices moving to other parts of the world. They're beginning to come back, and one of the reasons is the early device research program that's been developed by CDRH together with the community that is working with the big centers that can do the early device work, bringing those things back.

There's also an issue with devices that you know a lot about, which is, often, a device is useful in a very unusual disease, and it's a very niche activity where there's not an adequate market. We

do have a program for that. It's successful. It's a topic that we need to think about and discuss more to define ongoing criteria.

Senator BENNET. I should also say that the cancer community was vitally important in getting that piece of legislation passed to begin with. It's nice to see that some of the early drugs have been drugs that fight cancer.

Switching gears, I wonder whether you would take a few minutes to discuss with the committee how we should think about investment in life science innovation, not just as a domestic priority, but as a global economic priority to keep us competitive with other nations. This is a time when we're seeing diminishing resources in this country applied to basic science, and I wonder if you could help us understand why that's important or whether it is.

Dr. CALIFF. It's just the case that almost everyone is concerned about, living longer and being more functional in their lives, and the way we do that is through public health and also through medical products, and in the case of tobacco, reducing it, hopefully. As we go about that, the development of new medical products does require investment, because it's appropriate that there's a law that says you've got to show you're safe and effective before you come on the market.

This requires time to do the development, and it requires that you really show that you're not producing an inferior product before you come on the market. It's really a critical issue. We've got to invest.

On this note, in our work with the NIH, we're very focused on the use of biomarkers, surrogate inpoints, but also on not using them inappropriately when they're not going to work. This is really hard work to set the conditions that would excite investors to put money into biomedical science.

Ultimately, the United States is saving the world through investment in the NIH, and I want to put in a plug for continuing with the NIH investment. If not for the scientists being funded through NIH, we wouldn't have the basic science to translate into effective medical products.

Senator BENNET. Thank you. Thank you for your testimony.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Bennet.

I want to thank Senator Murkowski, who has left the hearing, and Senator Casey for allowing Senator Sanders to go next. He has been waiting patiently and he has extracurricular activities which he's attending to.

Senator Sanders.

STATEMENT OF SENATOR SANDERS

Senator SANDERS. Thank you, Mr. Chairman, and thank you, Senator Casey.

Dr. Califf, thanks very much for being with us. You and I chatted a while back, and I told you that I would not support your nomination, because I believed you were not strong enough on the most important issue that the American people are concerned about with regard to prescription drugs. That is, in our country, we pay, by far, the highest prices in the world for prescription drugs. As I un-

derstand it, about one out of five Americans cannot afford to fill the prescriptions that their doctors are writing for them.

Mr. Chairman, with your permission, I would put into the record a comparison of drug prices in the United States and Canada, which show that on major and important drugs, the prices in Canada are far, far less expensive than they are in the United States, and that's true all over the world.

[The information referred to may be found in Additional Material]

My concern, Mr. Chairman, is that while last year, the top four drug companies in this country—Pfizer, Johnson and Johnson, Novartis, and Hoffmann-La Roche—made $57 billion in profit in 1 year, I heard concern that drug companies are not doing well. They're doing quite well, and yet you have millions of Americans who cannot afford the high cost of prescription drugs.

While all of us agree that, clearly, we want great new products out on the market to save lives, for millions of people, it doesn't matter what the products are. They just cannot afford them. We need, in my view, an FDA Commissioner who is going to be aggressive and understands that very simple principle, and I'm not clear, and what I heard today confirms that I don't think you get that.

Here are some of the questions I'd like to ask to make out the point. It is not a coincidence that last year, the pharmaceutical industry spent $250 million on lobbying and campaign contributions and employ some 1,400 lobbyists. Do you think, Dr. Califf, that that type of expenditure has any impact on the fact that we pay, by far, the highest prices in the world for prescription drugs?

Dr. CALIFF. Senator Sanders, the ideal situation would be if the money went into R&D to develop an adequate picture of the risks and benefits of treatment and that was made available to people.

Senator SANDERS. Why do we pay the highest prices in the world, by far, for prescription drugs?

Dr. CALIFF. I'm not an expert on the price of drugs, Senator Sanders, but I'm certainly sensitive to the fact that in a field like cardiovascular medicine, my specialty, we need to have drugs available, because they save lives and——

Senator SANDERS. Doctors and oncologists have written to us that it doesn't matter what drugs are available because their patients can't afford them. Let me ask you this, a very simple question. As head of the FDA, you will oversee the importation of food products, vegetables, fish from all over the world. We can import lettuce and tomatoes—vegetables from farms all over the world. Somehow we cannot reimport from Canada brand name prescription drugs manufactured by the largest drug companies in the world.

Can you explain to me, and do you support, the reimportation of brand name prescription drugs from major companies from Canada and from other major industrialized countries? Yes? No?

Dr. CALIFF. Senator, as you're aware from our previous discussion, we have major concerns about reimportation. The system it would take to make sure that the drugs are adequate and safe for Americans——

Senator SANDERS. In other words, you think we can bring in fish products and vegetables from farms all over the world, but we can-

not bring from across the Canadian border brand name drugs. You don't think we have the capability of doing that?

Dr. CALIFF. We have the capability. It would add additional cost, and systems would have to be put in place to make it work.

Senator SANDERS. This is why, precisely, the American people are paying, by far, the highest prices in the world for prescription drugs. It is beyond my comprehension that you're sitting here saying we can bring in vegetables and fish from all over the world, but we cannot bring in brand name drugs manufactured by the largest pharmaceutical companies in the world from a country like Canada. I just do not accept that.

Let me ask you another question. One of the reasons we pay the highest prices in the world is—today, I can walk into a drugstore and they can tell me the medicine I use—the price has doubled because we have no regulations. Do you believe, and will you support, the right of Medicare to negotiate drug prices, which is now currently not allowed by law? Shouldn't Medicare sit down and negotiate drug prices so we can lower the prices of medicine?

Dr. CALIFF. You're aware, I believe, it is the administration's position that in certain circumstances that have been spelled out in the President's budget, negotiation on Medicare prices should be done. It's not the FDA's remit to set the prices, as we've already discussed. It is the Administration's——

Senator SANDERS. I know. But the issue of affordability is within your jurisdiction.

Let me just conclude, Mr. Chairman, and let me thank, again, Senator Casey for jumping over him here.

We all want great medicine to come onto the market, and I respect the work that you have done. At the end of the day, people are dying, people are not buying the food they need because they have to pay outrageous prices for medicine because we have been extraordinarily weak in taking on the pharmaceutical industry that is ripping off the American people.

I believe that we need a Commissioner—and I know that's not the only responsibility of the FDA—but I believe we need a Commissioner who is going to stand up to the pharmaceutical industry and protect American consumers. I'm going to have to say to you, with regret, that I think you are not that person.

Thank you very much.

The CHAIRMAN. Thank you, Senator Sanders. Senator Murkowski also stepped aside as well as Senator Casey.

Senator Murkowski, thank you for being here.

STATEMENT OF SENATOR MURKOWSKI

Senator MURKOWSKI. Thank you, Senator Alexander.

Dr. Califf, welcome. Senator Sanders has just broached very briefly the issue of fish. He says we can bring in fish from all around the world. I want to suggest to you that perhaps bringing in fish from all around when it is mislabeled and misnamed is not something that we want to do.

I would ask you again to look at the issue that we have raised repeatedly before the FDA regarding the Pollock nomenclature. This is something where we contend that you do have the regulatory authority to change the acceptable market name from Alas-

ka Pollock to Pollock so that we can put some limitation and parameters on what we're seeing from the large volume of Russian harvested Pollock that is sold to U.S. consumers as Alaska Pollock.

I have repeatedly raised this and would ask that you would work to expedite this change and remove the blockade that has been created within the FDA's bureaucracy regarding this Pollock nomenclature.

Dr. CALIFF. Senator Murkowski, I enjoyed my visit with you and I heard clearly what you said then. We are still open for comments and thinking about this. I will work with you to come to a resolution on this issue.

Senator MURKOWSKI. I do want to work with you. Again, this is something that can easily be resolved, and that's what we're looking to do here, to address it through the regulatory route as opposed to the legislative, which we will do if we have to. This is one that we can fix working together.

The last question that I have for you also relates to seafood, and this is regarding some concerns that we're hearing that the forthcoming FDA seafood advice to pregnant women on seafood consumption may not be entirely based on science. This is something, of course, that is gravely concerning.

Back in 2014, there was a statement that was released on the draft seafood advice that spells out pretty clearly that science now tells us that limiting or avoiding fish during pregnancy and early childhood can mean missing out on important nutrients that can have a positive impact on growth and development as well as your general health. The concern is that the FDA has revised that advice in a way that ignores this Net Effects Report.

The question to you this morning is: What is the status of the FDA's seafood advice for pregnant women? I guess what I'd like to hear from you, specifically, is whether or not, when that advice is released, that final seafood advice for pregnant women and nursing mothers will be based in science, namely, using the Net Effects Report.

Dr. CALIFF. I can assure you it will be based on science, and the recommendation will be something that will be very good for American people and——

Senator MURKOWSKI. Why would it not be based on the Net Effects Report?

Dr. CALIFF. We're having to balance a lot of input and considerations here.

Senator MURKOWSKI. Wouldn't that input and consideration be based on the science that went into that report?

Dr. CALIFF. We base it on all the scientific facts that can be brought to bear that accumulate over time. These will all be considered. You'll be happy with the recommendation when it comes out.

Senator MURKOWSKI. I appreciate that assurance. It doesn't necessarily get me to where I would like to be, which is a recognition that you will utilize that Net Effects Report, the report that very clearly outlines why it is important for the nutritional needs of not only the mother, but developing children as well.

Dr. CALIFF. I'm very familiar with the concept, but the detail I'm going to have to come back to you on to make sure that——

Senator MURKOWSKI. Can you tell me when we might anticipate this report then?

Dr. CALIFF. I can't give exact dates or timelines. This is a fairly straightforward issue, and it's a high priority, and we've had discussions about it recently. So it's going to move along.

Senator MURKOWSKI. I would agree that it is high priority. It is important, and it is overdue. Certainly, the science is overwhelming in its support for the recommendations, good sound recommendations based in science that pregnant and nursing women be given good advice when it comes to seafood in their diets.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murkowski, and thank you for your courtesy to Senator Sanders, even though you were chairing a hearing, and thanks also to Senator Casey.

Dr. Califf, after I call on Senator Casey, I'm going to leave for another appointment and turn over the hearing to Senator Scott, who will ask his questions, and then if there are no other Senators, he will conclude the hearing. Thank you for being here.

Senator Casey, thank you for your courtesy to Senator Sanders.

STATEMENT OF SENATOR CASEY

Senator CASEY. Mr. Chairman, thank you. Thanks for the hearing.

Doctor, we're grateful you're here, and we appreciate your commitment to public service and that of your family. I know, and we all know, that when an individual makes a commitment to service, it involves a sacrifice and a contribution in a substantial way by your family, so we're grateful for that.

I wanted to try to cover maybe three topics, one or two of which I may have to do by way of written questions. The first is children, and that's what I'll spend most of my time on, and the second is food safety, and the third is this issue that's been raised about independence and ensuring that's the case going forward.

First, with regard to kids, we're told that today is World Prematurity Day, so we're talking about premature babies born. I guess 1 in 10 born in the United States today is born prematurely. We've had legislation over time, obviously, that speaks to this. One is the recent FDA Safety and Improvement Act, which required, among other things, that FDA hire a neonatologist in the Office of Pediatric Therapeutics to work on implementation of the provisions of the act for neonates. That happened, and that hiring was done. We're grateful that that happened.

One of the areas I'll be looking at more broadly as you do your work is to focus on the implementation of changes by the FDA that come as a result of both the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, and we can amplify those later. Just with regard to treating premature infants, we know that more must be done to accelerate the development of both therapies and devices to treat infants in so-called NICUs, neonatal intensive care units.

If confirmed, I guess my first question would be: How might you use FDA's existing authority, the regulatory authority, to promote the development of cutting-edge treatments for premature babies?

Dr. CALIFF. Thanks for asking that question, Senator Casey. You may not be aware of this, but when the Children's Act first came into existence, I was one of the instigators with the phrase, children should not be therapeutic orphans, that is, doctors were forced to give treatments to children with no evidence about the right way to give the treatment.

We ended up at Duke being the coordinating center for the NIH part of this, to take drugs that were already off patent and figure out the right dose. We have a neonatal intensive care unit network from my old institute which is focused on this. I've written about 20 papers on this topic. We need to keep moving along, and we need to move on to pregnancy, which is another very high priority issue where the right doses of drugs are just not known for the most part.

Senator CASEY. The second question—and I appreciate the background of what you've been doing. The second question might take more reflection, because it's kind of a broad-based question. You can certainly amplify or add to what you say here by way of a written response. Is there anything you would hope that Congress would do to increase FDA authority in this area?

Dr. CALIFF. The food safety?

Senator CASEY. No, I'm sorry. On——

Dr. CALIFF. On children?

Senator CASEY. Yes.

Dr. CALIFF. We're in pretty good shape where we are in terms of authority. If you have good ideas, let me know. The studies could be better and could be broader. We can make that happen working with the community.

Senator CASEY. I'll move to one other question as it relates to children, so-called neonatal abstinence syndrome.

Dr. CALIFF. Yes.

Senator CASEY. We're told now among other statistics that one baby is born every 25 minutes with opioid withdrawals, meaning the equivalent of neonatal abstinence syndrome. It's increased some fivefold in the last 12 or so years.

The majority leader, Senator McConnell, and I just got a bill through both the Senate and just, I guess, yesterday, the House, which we hope will be signed into law to focus on this problem. Anything that you can tell us about either your previous work or work you can do leading the FDA on this specific issue as it relates to neonates?

Dr. CALIFF. This is a terrible problem, the concept that an unborn child would be exposed to opiates and essentially addicted at birth. We had a public meeting on this recently. Like the opioid problem all together, this is a community effort. We've all got to work on it, including the FDA.

We have a whole series of measures that we're implementing, including a major effort on physician education, which is critical. Tens of thousands of docs have now taken the required courses through the REMS program, the post-marketing. This is a huge problem. We've got a lot of work to do on this, and I look forward to working with you on it.

Senator CASEY. I appreciate that.

Mr. Chairman, could I have one more minute?

Senator SCOTT [presiding]. Certainly.

Senator CASEY. Thank you very much, and I know you're waiting.

Part of this we can develop more in a written question. On food safety, one of my constituents just recently was severely sickened with listeria in 2012, and I guess as a result of ingesting ricotta salata cheese from Italy, among many other stories I know that constituents have with regard to food safety.

I know this is a resource issue or, I should say, lack of resource issue as well. Can you tell us a little bit about what you hope to be able to do even within the confines of limited resources?

Dr. CALIFF. It's been a real privilege getting to know Mike Taylor, who heads up FSMA and heads up this part of the FDA. He's been doing this for years. A dream of his was to get FSMA put together, and we're now moving to the implementation phase.

The real key—because this is such a massive food—it's just a lot of things. High-quality analytics, like every other industry is using now, really is what we're implementing so we can target the inspections to where the highest risk is. We're even using genomics for bacteria to figure out exactly where they come from by doing complete genotyping, just like we do with people. It's really moving the science along and then realigning the workforce so that it's allocated to preempt and prevent these problems before they occur rather than just reacting.

Senator CASEY. I'll submit for the record a question about the issue that was raised about independence, and I appreciate what you said in your testimony about the Duke contract as well as your own steps you've taken since being at the FDA on recusal. I'll develop a broader question to send to you.

Dr. CALIFF. I appreciate it, and I'm glad to respond. I just wanted to note in light of Senator Warren's questions that Duke University has graciously agreed to make the contracts available, and they're either in the staff's hands or on the way. It'll be good for you to look at those.

Also, just a note that the consulting money abided by these principles, but I also made a personal decision to donate that money to not-for-profit charities. It's really just a sign that the work is something I thought was important, not the money, in this case.

Senator CASEY. Thanks, Doctor.

Thank you, Mr. Chairman, for the extra time.

Senator SCOTT. Thank you, Senator Casey.

Dr. Califf, thank you for your willingness to serve and thank you for allowing me to clear up the fact that you're a South Carolinian and not from North Carolina. That was important to me and——

Dr. CALIFF. It's great to be here with a fellow South Carolinian.

Senator SCOTT. Thank you, sir, especially since Senator Burr is now gone. We'll continue.

[Laughter.]

Dr. Califf, I am the co-founder of the Sickle Cell Caucus. We focus a lot of attention on trying to make sure that people understand and appreciate the devastating impact that sickle cell has throughout the Nation and specifically within African-American communities.

Sickle cell, while rare, is devastating to communities and families. It is also one of the most expensive diseases to treat, given the high incidence of hospital re-admission. Yet we haven't had any new treatments introduced in the market, some say for 20 or 30 years. How can we address this and create an environment that incentivizes investment in research and development for diseases that affect smaller segments of the population?

Dr. CALIFF. Thank you for asking that question. One of the regrets that I have about the wonderful opportunity at the FDA—I was glad to do it, but I left behind some things I was working on. One of those is the issue of diseases that affect minorities, particularly poor minority people, differentially.

We had a big project going on in North Carolina, West Virginia, and Mississippi looking at the population base using electronic health records. One thing that pops right out at you is that sickle cell disease, while people are children, is pretty well covered by the Medicaid system.

Senator SCOTT. Yes.

Dr. CALIFF. With first-rate care, and then when people become adults, they're on their own. They frequently live in rural places. They can't get to the big centers, and this has created a disincentive to therapeutic development.

The good news is NHLBI, with Gary Gibbons as the head—he's a good friend. I was working with him, and I think there's a comprehensive plan, including some of the designations for moving therapeutics through more quickly. I'm aware of some of the new things that are in development, and they look really good. If I wasn't here, I'd be working with those new things.

Senator SCOTT. Excellent. Thank you. Two diseases that affect my State at a rate higher than the national average are heart disease and diabetes. In 2013, heart disease was the leading cause of death in South Carolina and accounted for $3.1 billion in hospitalization costs. In 2013 as well, 11.3 percent of South Carolinians had diabetes.

We are in desperate need for cures for these two chronic conditions. However, the high risk and cost of trials, particularly Phase 3 trials, actually seems to create an incentive for researchers and investors to avoid working on medications that could help the many Americans and South Carolinians suffering with these chronic diseases.

What ideas do you have for reforming the clinical trial process to incentivize researchers and investors to delve into the high-risk but high-reward areas of medicine?

Dr. CALIFF. I'm tempted to ask how many hours you have, but I'll keep this brief. First of all, let me just make a note that in the population base studies we were doing with a CMMI innovation grant in North Carolina—unfortunately, not South Carolina—West Virginia, and Mississippi, it's really a devastating—this was focused on diabetes. We need to get it under control.

In addition to the cures that you mentioned, we also need to just deliver good healthcare to people close to where they live, and that was what our project was doing, using electronic health records to set up systems in neighborhoods so people got the care that they needed to deal with chronic disease.

On the clinical trials front, it's a problem that's related to something we discussed earlier, which is that for a disease like heart disease, where we have a lot of effective treatments already, we don't want to let something on the market that's not going to be safe and effective. We have to do adequate clinical trials.

Here's the good news. We're committed, as are all the Federal agencies, to work with industry and academia to develop a national system that delivers better clinical trial results with larger, more representative populations at a lower cost, and I would say a dramatically lower cost. The key here is using electronic health records that we already have. Almost every American has one.

We've got to overcome the interoperability hurdles and some terminology. We can do this, and that would enable people to develop new therapies at a much lower cost, but with better information about safety and efficacy.

Senator SCOTT. My final question. Back in September, I had an opportunity to ask Dr. Woodcock of the FDA about labeling of biosimilars. She stated that there were tradeoffs in various labeling decisions but did not provide any clarity as to what industry, physicians, and patients can expect and when they can expect it, which was a primary part of my question—the when.

I continue to feel as if there's a serious risk in not providing notice that a product is a biosimilar, considering that there can be small differences between biosimilars and their branded counterparts, unlike with generics. Can you provide any update on where things stand with the labeling of biosimilars?

Dr. CALIFF. What I can say, Senator Scott, is that we're working really hard on it, and it is a very tough, complicated issue. As I've already said, much of my career in cardiology was developing biological products that were highly effective. These molecules are complicated and difficult to work with. You really have to understand them.

Dr. Woodcock is actually one of the world's authorities, so I have a lot of confidence in the approaches that she's taking. The labels ultimately have to both encourage the use of biosimilars where they're as good and enable providers and patients to understand when there are differences. We're really working hard to come up with—and also have to fit in with global standards about nomenclature that exist so that as these are on the market, they can be tracked. If there's a safety problem, we can keep up with it.

Those are all the factors. I can't tell you exactly when we'll be done. Everybody is interested in this, and it's a very high priority.

Senator SCOTT. Thank you for your time today.

The hearing record will remain open for statements for 10 days. I ask that Senators submit any written questions by 5 p.m. on November 24th. Thank you for being here today.

The next HELP Committee hearing will be on mental health on Wednesday, December 2d. The committee will stand adjourned.

[Additional Material follows.]

ADDITIONAL MATERIAL

RESPONSE BY ROBERT CALIFF TO QUESTIONS OF SENATOR ALEXANDER, SENATOR ENZI, SENATOR BURR, SENATOR ISAKSON, SENATOR MURKOWSKI, SENATOR COLLINS, SENATOR HATCH, SENATOR ROBERTS, SENATOR CASSIDY, SENATOR MURRAY, SENATOR SANDERS, SENATOR CASEY, SENATOR BENNET, SENATOR BALDWIN, SENATOR MURPHY AND SENATOR WARREN

SENATOR ALEXANDER

Question 1a. The Food and Drug Administration (FDA) has been criticized for how it restricts what drug and medical device manufacturers can tell doctors and insurers about lawful uses of their products. In particular, current regulations are unclear and heavily restrict manufacturers' ability to provide truthful and non-misleading information to doctors and insurers, unless the information appears in the product's FDA-approved labeling. Often, however, this information relates to medically accepted treatments that doctors can—and frequently do—prescribe for their patients, and that the Federal Government will even reimburse. In some instances, such "off-label" uses may even be the standard of care.

In an era when information about medical products abounds on the Internet—some of it reputable, some of it not—do you think it is appropriate for FDA to maintain decades-old policies that block manufacturers from sharing factual, non-misleading information about lawful treatments with doctors and insurers?

Answer 1a. It's important to remember the fundamental public health interests underlying the Agency's current statutory and regulatory framework, including the requirements related to premarket review of medical products before they are distributed for new uses. This framework was developed over time in response to public health tragedies, which Congress addressed by requiring independent review of scientific evidence of the products' safety and efficacy. The Agency is currently examining its rules and policies, with the goal of harmonizing the important public health and safety interests served by FDA's premarket review of new uses of medical products, with the value that sharing relevant scientific information regarding unapproved uses can have in certain contexts, and with First and Fifth Amendment considerations.

I believe it is appropriate for FDA to continue examination of its rules and policies and to refine them as appropriate, in light of the important public health issues, free speech, and due process principles at stake.

Question 1b. Several courts, including the U.S. Court of Appeals for the Second Circuit and the U.S. District Court for the southern district of New York, have indicated that FDA's restrictions on manufacturers' speech may violate the First Amendment. These decisions raise the possibility that many of FDA's regulations governing the promotion of medical products could be struck down by the courts unless they are substantially revised. What proactive steps will you take, if confirmed, to avoid that situation?

Answer 1b. If I am confirmed, I will support FDA's efforts to comprehensively review its regulations and guidance documents and will make it a priority for the Agency to work on revising these documents as appropriate, in an effort to harmonize the goal of protecting the public health with First-Amendment interests.

Question 2a. Before you began your current position at FDA, you advocated publicly for changes to certain regulations. For example, you gave a presentation in 2014 in which you called regulation a "barrier to disruptive innovation," and, in 2013, you wrote in the *New England Journal of Medicine* about inefficiencies in the requirements for clinical trials and safety monitoring for approved drugs.

What are the three biggest ways in which FDA poses a barrier to innovation? If confirmed, how would you address these problems?

Answer 2a. I think you are referring to a slide I have used in multiple lectures that characterizes regulation as a barrier to disruptive innovation.

This issue is a very important one for people proposing to develop new medical therapies. Throughout my career, I have benefited from a close relationship with the Fuqua School of Business at Duke and the many contacts it brings in the field of health economics and health management. Among the many brilliant people I have met is Clayton Christensen ("The Innovators Dilemma"), who developed the concept of "disruptive innovation."

This concept is derived from the study of the transformation of industries with the base case being the conversion of radios from the vacuum tube to the transistor. The concept is that the new product or method initially is inferior but lower priced so there is a market for it. This enables innovators to iteratively improve their prod-

uct until it becomes better and supplants the old product or method. My purpose in showing this slide in multiple lectures is to explain to audiences that often include students, trainees in fellowship and scientists who are not involved in development of medical products, why the risk and investment in biotechnology is higher than most other industries, i.e., because it is a highly regulated industry, which is in fact a necessary barrier to protect public health, as discussed below. The amount of capital needed is lower and the time to return on investment is shorter in many other industries.

I have never stated, implied, or argued that the barrier should be lowered or removed. In fact, I do not believe that we should be putting inferior medical products on the market, nor do the American people want inferior products to be used in medical practice. The belief that we should have evidence of benefits and risks *before* marketing in health care has been a driving force in my career and a motivation to develop more effective, efficient and unbiased ways of conducting generalizable clinical trials and implementing quality systems for learning in health care as a focus of my academic and practical work.

In summary, the purpose of the slide is to point out an issue that is motivational for people who want to develop medical products that prevent death and reduce disability: there is a requirement to demonstrate that your product is safe and effective before you market it and that it does not put people at risk, compared to the clinical care that is currently accessible. This is a good thing and forms the basis for the benefit of a strong FDA to make these determinations, and it places a special responsibility on innovators to develop the evidence base that can ensure the FDA (on behalf of the American public) that the product is safe and effective.

With these requirements (i.e., appropriate barriers) in place, it is reasonable to ask the question, what can FDA do to enable innovators to develop new approaches and technologies, maintaining the same standards, but reducing the cost and time so that Americans can get access to new technologies that are safe and effective and so that investors continue to invest in this enterprise, which is essential to our health and vital to our economy? Among a longer list, my top three responses would be:

- Reform the clinical trials system, using the principle of Quality by Design, so that a combination of small, focused trials for precision medicine and very large trials using electronic health records for inclusion of important populations can be conducted at a dramatically lower cost per unit of knowledge. The small precision medicine trials are lower cost because of lower sample size and the very large, inclusive trials will be lower cost because they will take advantage of data already collected and the novel methods of community-based research. FDA's Sentinel project is an excellent building block with claims data on over 170 million Americans available to evaluate the safety of drugs and biologics, but the same system with modifications could be used to dramatically reduce the cost of data collection in clinical trials. Direct involvement of patients will also enable us to streamline, because a more involved public, together with more trials relevant to the needs of patients will lead to faster enrollment.
- A second key approach is to continue to improve the communication between FDA and the scientific community. In every case where FDA has offered more meetings with sponsors, the opportunity has been over-subscribed. In addition, public-private partnerships have been highly successful in promoting multi-sector dialog and developing a common view of key issues in medical product development, including the Medical Device Innovation Consortium and the Clinical Trials Transformation Initiative.
- Finally, effective interactions between FDA and its Federal partners can be an important factor in maintaining the appropriate standard while reducing the cost of medical product development. The FDA-National Institutes of Health (NIH) Leadership Council is a successful collaboration between FDA and NIH, focused on clarifying the biomarker-surrogate-clinical outcome continuum and streamlining clinical trials.

There are many other measures to achieve the goal of optimizing the efficiency of the effort to produce useful, safe, and effective medical products based on high-quality evidence.

Question 2b. In your academic work, you have argued for expanding the size of certain clinical trials. What impact would larger clinical trials have on the cost and speed at which innovative new treatments come to market? Are there specific policies you would promote that would affect the size of future trials, and would those policies be tailored to particular types of trials?

Answer 2b. As discussed above, the principle of Quality by Design, an initiative that FDA is already undertaking, will lead to some trials that are "targeted," when

the therapy is expected to have a large effect in a small subpopulation, and others that will need to be much larger to ensure that the treatment is safe and effective across the spectrum of patients likely to be treated. The targeted trials are made possible by the dramatic advances in molecular biology and precision medicine methods, and the larger trials are made possible by the ubiquity of electronic health records and social media. Quality by Design is a risk-based approach to pharmaceutical development and manufacturing that has been described in numerous FDA guidance documents. In recent years, this approach has been increasingly recognized as having significant applicability to the development of clinical trial protocols and is now included in an FDA guidance document on risk-based monitoring.

Another consideration is that rare diseases will continue to need special trial considerations, especially when there is no effective treatment. As information and communication technologies advance, however, we can also develop new methods to improve enrollment in these trials.

Question 3. Will you commit to requiring FDA staff to act through rulemaking, rather than through the guidance process, when (a) it intends to legally bind regulated parties or (b) it expects regulated parties to change their behavior in burdensome or costly ways?

Answer 3. The Federal Food, Drug, and Cosmetic Act (FD&C Act), and FDA's own regulations, set forth clear criteria for determining whether guidance is appropriate and provide for ample opportunity for public consideration of, and comment on, FDA guidances. I commit to working to ensure that the Agency continues to follow the requirements set forth in these authorities and issue guidance only where appropriate.[1]

When issuing guidance, FDA complies with the requirements set forth in the FD&C Act as well as its own good guidance practices (GGPs). Section 701(h)(1)(A) of the FD&C Act outlines the procedures that FDA must adopt when issuing guidance relating to its initial interpretations of a statute or regulation, changes in interpretation or policy, and existing practices or minor changes in policy. The FD&C Act requires that the Secretary develop guidance documents with public participation and makes clear that guidance documents "shall not create or confer any rights for or on any person."

FDA's GGP regulation provides greater detail regarding the circumstances when guidance is appropriate and the procedures that must be employed when the Agency issues guidance. The GGP regulation explains that guidance documents are intended to describe the Agency's interpretation of policy on a regulatory issue, but are not intended to be binding documents or establish legally enforceable rights or responsibilities that bind the public or FDA (21 CFR 10.115). Guidance documents contain a statement of this non-binding effect.[2]

FDA's guidance documents are a valued resource for many external stakeholders, including industry and patient advocacy groups, because they can serve as a means of conveying FDA's current thinking on important issues, such as the most current scientific practices related to product development. Often the Agency's guidance documents are issued in response to stakeholder requests. Guidance is a helpful tool that allows the Agency to inform stakeholders about its views on scientific and technical policy issues. Small businesses are often particularly interested in and reliant upon Agency guidances on such topics.

Question 4a. Food and medical products regulated by FDA increasingly are imported from other countries into the United States. Currently, FDA is not able to clear many time-critical and often temperature-sensitive shipments quickly enough for them to arrive at their destinations intact and when they are needed.

How do you think FDA can improve its ability to process time-sensitive shipments by commercial express carriers in a timely manner to minimize the expense and disruption that even short delays can cause?

---

[1] In addition, the Administrative Procedure Act (APA) (5 U.S.C. 551–59) prescribes procedures for an agency issuing a "rule," which is defined as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency" (5 USC 551(4)). For legislative and substantive rules that create a new law, rights or duties, the APA requires that agencies, among other things, provide the public with adequate notice of a proposed rule followed by a meaningful opportunity to comment on the rule's content.

[2] That said, in certain instances, FDA is expressly authorized by statute to promulgate guidances with binding effect. In such cases FDA clearly explains the extent to which such guidance is binding, based on the requirements in the statute, in the guidance document itself. See, e.g., *Guidance for Industry: Necessity of the Use of Food Product Categories in Food Facility Registrations and Updates to Food Product Categories* (October 2012), available at *http://www.fda.gov/RegulatoryInformation/Guidances/ucm324778.htm*.

Answer 4a. FDA continues work on streamlining, improving, standardizing, and clarifying import processes and has initiated a number of efforts designed to process imported shipments more efficiently. FDA is a Participating Government Agency (PGA) involved in the ACE/ITDS (Automated Commercial Environment/International Trade Data System) project, which is designed to provide the import community with a single window for importing into the United States, commonly referred to as "One U.S. Government at the Border," to streamline the entry process and provide improved messaging to the trade community.

FDA is currently running a Secure Supply Chain Pilot Program (SSCPP) for pharmaceuticals. The SSCPP is allowing FDA to assess the various entities and processes involved in a repetitive-type import chain; and if found acceptable and if all information is accurately submitted at the time of entry, it would allow for more and quicker system-based releases of shipments (as opposed to having to manually verify required information). If successful, the expansion of this program will help expedite the admissibility process for pharmaceuticals originating from known sources, destined for known U.S. entities.

In addition, FDA is participating with U.S. Customs and Border Protection (CBP) in a trusted Trader Program designed to facilitate the importation process for selected firms. CBP issued a *Federal Register* Notice announcing a test program on June 16, 2014. FDA has been involved in the review of applications. The pilot will begin after the applicant awardees have been notified and CBP receives confirmation of the intent to participate.

FDA is in the process of implementing the Voluntary Qualified Importer Program (VQIP) for human and animal food to help facilitate the import entry of products from importers who demonstrate a high level of control over the safety and security of their supply chains. VQIP importers must offer FDA various assurances of compliance, including facility certifications of their foreign suppliers of VQIP products, in exchange for the expedited release of entries of those products imported into the United States. FDA continues to work on the operational design of VQIP; currently, IT requirements are being addressed and importer user fees are under development.

To improve transparency, FDA developed and deployed the Import Trade Auxiliary Communication System (ITACS), which facilitates two-way communication with the import trade community. ITACS allows users to check the status of FDA-regulated entries and lines, to submit entry documentation, and to submit the location of goods availability for those lines targeted for FDA exam. The system is currently undergoing enhancements to allow for FDA notifications to be sent directly to regulated industry via electronic means, which will allow for more timely and efficient communications.

FDA has conducted a centralized entry review pilot for courier operations. The results of this pilot are currently under review as a possible model for centralized entry review and staffing for all couriers that could expand Agency operations and better mirror the courier business model.

FDA is evaluating a dashboard intended to allow real-time monitoring of all aspects of the import process to determine if backlogs are forming and if delays are occurring, so that resources can be allocated before an issue arises.

In addition, FDA has proposed a request for new authority to assess user fees on international express courier facilities (or "couriers") that import FDA-regulated products into the United States. These fees would support part of the cost of certain inspection-related activities at courier facilities, including processing, examining, sampling, and analysis of FDA-regulated products by FDA to improve timeliness of processing. The fees will be charged in accordance with U.S. obligations under applicable international agreements (i.e., General Agreement on Tariffs and Trade (GATT), North American Free Trade Agreement (NAFTA), etc.).

Question 4b. What will you do to improve FDA's ability to use its electronic import review system—the PREDICT system—in a risk-based manner that minimizes the burdens on compliant, non-harmful shipments so that resources are allocated efficiently to the shipments carrying the highest risk?

Answer 4b. Since December 2011, FDA has been utilizing the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) screening tool to provide a more dynamic and risk-based assessment of imported shipments. PREDICT is designed to calculate a customized risk score based on a wider variety of factors, including, but not limited to, inherent risk of the product, data anomalies, data quality, and the compliance history of firms (e.g., manufacturer, shipper, and consignee) and the product.

FDA is continuing to improve the capabilities of PREDICT to minimize the impact on imported shipments. For example, many shipments consist of multiple commodities. Line release is a recently implemented enhancement to PREDICT that will

allow FDA to evaluate a higher-risk commodity in a shipment, independent of other products that may be included in the same shipment but do not have the same level of risk.

FDA has modified the PREDICT risk evaluation process from a pool of all FDA-regulated products to a commodity-based approach in order to compare products with similar risk factors. This will improve targeting for medium- and higher-severity products and improve the "May Proceed" rate for lower-risk commodities. As of November 2015, this improvement has been implemented for medical devices and diagnostics, biologics, human foods, pharmaceuticals, radiation-emitting products, and animal foods and feeds. FDA continues to work on developing the same approach for a number of other commodities, including vitamins and supplements, cosmetics, food and color additives, infant foods, house wares, veterinary drugs, medicated feed, and tobacco products.

Question 5a. In recent months, FDA has sent warning letters to overseas drug manufacturing facilities, particularly in India and China, that detailed alarming violations of current good manufacturing practices. These violations include not only sanitary issues—such as bird and lizard infestations in processing facilities—but also a troubling number of instances in which data were falsified or obscured, including an instance in which an employee grabbed a memory stick and fled from FDA inspectors. While it is reassuring that FDA identified these violations, it also raises questions about the extent to which similar violations in other imports are going undetected.

Section 706 of the Food and Drug Administration Safety and Innovation Act, signed into law on July 9, 2012, enables FDA to request records in advance or in lieu of an inspection. This authority enables FDA to detect many data integrity issues without having to send inspectors onsite, thus improving FDA's ability to detect violations rapidly and efficiently. It is now more than 3 years since FDA was given this authority, but FDA still has not used it to request records from a particular manufacturer in advance or in lieu of an inspection. Why has FDA not exercised this important authority for improving its oversight of drug safety? When can we expect FDA to begin requesting records in advance or in lieu of an inspection?

Answer 5a. FDA recognizes that the authority to request records in advance or in lieu of inspection under the Food and Drug Administration Safety and Innovation Act (FDASIA) is a potentially powerful tool for enhancing FDA's ability to assess drug manufacturers' compliance with current good manufacturing practices, and has sought to plan the use of this broad authority carefully via the several work streams described in greater detail below.

FDA is actively engaged in projects to implement this authority, for example:

- *Public Health Incident:* Recognizing that FDASIA section 706 represented a broad statutory authority that could potentially be used in many inspection contexts, FDA sought to prioritize implementation of the authority based on public health risk. To that end, in October 2014, FDA finalized procedures in the Staff Manual Guide (SMG) for requesting records in advance or in lieu of inspection in the event of a public health incident. Although FDA has not yet encountered a situation warranting use of a 706 request under this SMG, we continue to monitor appropriate opportunities for doing so.
- *Pilot to Optimize On-Site Inspection:* FDA is planning to pilot the use of the authority in advance of a small number of already-planned inspections in 2016, and the Agency will use the results of that effort to inform its strategy on a broader implementation of the authority. FDA believes that use of 706 in advance of an inspection could lead to efficiencies by allowing FDA investigators to maximize the use of their time while onsite. FDA is seeking to assess the best use of this authority by gathering data through this pilot effort to evaluate, for example, the appropriate scope and volume of records to request, and the burden of producing and reviewing those records.
- *Quality Metrics:* The continued existence of product quality issues may point to increased complexities in the supply chain, a lack of innovation in manufacturing, a failure to adopt modern manufacturing technologies and robust quality management systems, or other factors. In the summer of 2015, FDA announced the availability of draft guidance for industry entitled "Request for Quality Metrics," and held a public meeting on the Agency's plans associated with a quality metrics reporting program. The draft guidance and public meeting were intended to gain stakeholders' perspectives on various aspects of the development and planned implementation of a quality metrics program launched under the new FDASIA authority. FDA expects that quality metrics calculated from the data we intend to collect through this program will provide objective measures that, when used with additional internal data, can provide the Agency with indicators of the effectiveness of

quality systems associated with pharmaceutical manufacturing. These indicators are expected to be a factor in risk-based inspection coverage, which will enable FDA to focus resources on facilities and products that present a greater risk to consumers.

In addition, FDA has implemented FDASIA section 707 and issued guidance related to this section. Section 707 deems adulterated any drug that is manufactured in an establishment that delays, limits, denies, or refuses to permit entry or inspection. In the FDA final guidance issued in October 2014, we specified that under circumstances delaying, denying, limiting, or refusing a request for records in advance or in lieu of an inspection under section 707 of FDASIA may also result in a drug being adulterated under the FD&C Act.[3] In such circumstances FDA may issue an import alert that notifies FDA's field staff that the Agency has enough evidence or other information to refuse admission of future shipments of that imported product.

Question 5b. At your confirmation hearing, you stated that you have "major concerns about reimportation" of drugs from other countries, including Canada. Would you please elaborate on these concerns?

Answer 5b. Drugs that are not FDA-approved nor manufactured in a facility inspected by FDA do not have the assurance of safety, effectiveness, and quality as do drugs subject to FDA oversight. There have been documented incidences of non-FDA-approved imported drugs found to be contaminated, counterfeit, containing varying amounts of active ingredients or none at all, or containing different ingredients than the FDA-approved product. Moreover, FDA would not be able to make safety and quality determinations for prescription drugs offered for import into the United States that have not gone through the U.S. regulatory process. In fact, FDA evaluation of non-FDA-approved imported drugs revealed that while nearly half of imported drugs claimed to be Canadian or from Canadian pharmacies, 85 percent of such drugs were actually from different countries. Typically, these products are smuggled into the United States after being transshipped to third-party countries in an effort to avoid detection and create an appearance of coming through countries that consumers may find trustworthy. Through FDASIA Title VII and the Drug Supply Chain Security Act, Congress has recognized the need to bolster this closed drug distribution system. Authorizing importation would compromise the closed drug distribution system in the United States and undermine these laws, thus making it easier for unapproved drugs, which may include counterfeit or other substandard drugs, to reach American patients putting their treatment at risk. FDA is concerned that the risks of unapproved products from foreign sources outweigh any potential cost savings. We are also concerned that adverse events flowing from importation of such unapproved products could lead to diminished confidence in FDA-approved products.

Question 6. The Food Safety Modernization Act was signed into law in January 2011. It took the agency over 4 years after the law was enacted to finalize five of the seven regulations required under the law. Congress intended this law to be flexible and risk-based, taking into account the very diverse food industry across our country. If confirmed, how will you ensure that as FDA implements this law, it focuses on and prioritizes high-risk activities in the food supply chain consistent with Congress's intent to introduce a risk-based framework that targets areas with a history of foodborne illness, is flexible, and is not overly burdensome?

Answer 6. Since the passage of the FDA Food Safety Modernization Act (FSMA), the Agency has pursued a transparent process, engaging all stakeholders, to allow FDA to craft final regulations that provide sufficient flexibility across the broad spectrum of food-producing operations. Throughout the rulemaking process, the Agency has been committed to developing final regulations that are practical for businesses and that help ensure food is safe. An unparalleled outreach effort followed the original proposal of the FSMA rules. As you know, in September 2014, FDA issued supplemental proposals with a number of revisions that would add flexibility and reduce burden in key areas. FDA proposed these changes based on extensive outreach and feedback received during meetings with the public, industry groups, and consumer groups, and in the comments submitted to the Agency on the proposed rules.

In September 2015, FDA finalized preventive controls rules for human and animal food, which require modern preventive practices in food processing and storage facilities. In November 2015, the Agency published additional final rules, which establish enforceable safety standards for produce farms and make importers accountable

[3] Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection. *http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf.*

for verifying that imported food meets the same food safety standards as domestic products. The Agency also issued a rule establishing a program for the accreditation of third-party certification bodies, also known as auditors, to conduct food safety audits and issue certifications of foreign food facilities and their foods. These rules will work together to systematically strengthen the food safety system and better protect public health.

The final rules recognize the importance of providing for flexibility within the requirements. For example, the final produce safety rule enables a State, tribe, or country to request variances if it concludes that meeting one or more of the rule's requirements would be problematic in light of local growing conditions. The State, tribe, or foreign country must demonstrate that the requested variance is reasonably likely to ensure that the produce is not adulterated and provides the same level of public health protection as the corresponding requirement(s) in the rule.

Through our sustained engagement with stakeholders, the Agency has been laying the foundation for effective, efficient, and collaborative implementation of the new standards. The Agency intends to provide guidance and technical assistance to industry so that they know what is expected and are supported in carrying out their responsibilities. For example, FDA, in cooperation with the Illinois Institute of Technology's Institute for Food Safety and Health, has established the Food Safety Preventive Controls Alliance, which is developing training courses and materials on preventing hazards for both human and animal food during production.[4] These materials will help industry—particularly small- and medium-sized companies—comply with the new preventive controls rules. Our implementation strategy also calls for re-orienting and retraining the FDA inspection and compliance workforce, as well as our State food safety partners, so that we can provide consistent, high-quality oversight within the more preventive, systems-based and technically sophisticated FSMA framework.

Going forward, FDA is committed to continuing to ensure that its FSMA efforts are risk-based and targeted in order to achieve the greatest health benefit, without placing an unnecessary burden on the regulated industry.

Question 7a. In your role as Deputy Commissioner for Medical Products and Tobacco, you have overseen activities within the Center for Tobacco Products (CTP), including work to finalize a proposed rule to deem additional tobacco products subject to regulation. If that proposed rule is finalized and applies the same "grandfather date" that was written into statute for cigarettes, it will force cigars and other tobacco products, including most if not all electronic cigarettes and e-vapor products, to go through FDA's lengthy premarket tobacco application (PMTA) process in order to stay on or enter the market. Only recently has FDA acted for the first time to authorize the marketing of new tobacco products through the PMTA pathway, which means that the agency does not have an established track record of acting quickly on PMTAs. As a result, this rule, if finalized, is expected to create significant regulatory burdens on small businesses.

If confirmed, will you commit to ensuring that FDA reviews product submissions in a timely manner to prevent a delay of innovative and novel tobacco products from entering the market and limiting consumer choice, which could cause citizens to lose access to products they have been using as less harmful alternatives to traditional smoking? As part of this commitment, will you agree to dedicate as much funding as necessary from user fees to ensure that (a) FDA acts upon PMTAs within the statutory timeframe, and (b) adequate resources to assist applicants who previously have not been subject to FDA regulation?

Answer 7a. FDA is committed to continuing to strengthen the process for reviewing tobacco products to determine if they meet the statutory standard for marketing, including acting on applications in a timely way and working with applicants who have not previously been regulated.

As you indicated, FDA recently authorized the marketing of eight new tobacco products under the PMTA pathway. This action shows that the PMTA process is a viable pathway to market for new products, if they meet the statutory standard, which includes the requirement that permitting the product to be marketed would be "appropriate for the protection of the public health." It took FDA 8 months to issue decisions on these applications. Currently, the Agency does not have any pending PMTAs.

FDA has made significant progress in reviewing substantial equivalence (SE) applications for currently regulated products and this momentum will continue. The Agency has increased staffing, taken steps to streamline the SE review process, and established performance goals that include timeframes for review of regular SE re-

[4] *http://www.iit.edu/ifsh/alliance/*.

ports[5] and review of exemption from SE requests for currently regulated products. FDA has been able to develop these performance goals because of increased capacity, efficiency, and knowledge of the scientific evidence needed to adequately review SE applications.

As of November 1, nearly 70 percent of full regular SE reports had been resolved by a final decision, either because FDA issued an Order letter, issued a Refuse-to-Accept letter, or because the submission was withdrawn.

FDA continues to improve the tobacco product review program, including hiring and training new staff and addressing the scientific policy issues that result from developing a new regulatory review program. We will continue to advance our efforts to review and act on SE reports while preparing for the PMTAs that may be submitted to FDA once the deeming rule is finalized.

FDA recognizes that manufacturers of newly deemed products will need assistance in complying with FDA regulations. The Agency is committed to providing this assistance. For example, the Agency intends to issue guidance, hold training webinars, meet with companies at their request, and increase staffing in the Center for Tobacco Product's (CTP) Office of Small Business Assistance.

Question 7b. If FDA finalizes this rule, it will result in an increased workload not only for tobacco-specific offices within CTP, but also for other FDA components, such as the Office of Regulatory Affairs, which oversees inspections and other enforcement activity, and the Office of Chief Counsel. Will you commit to ensuring that the increased workload attributable to deeming does not require FDA to shift resources away from non-tobacco program areas? What specific steps will you take to ensure that such a shift in resources does not occur?

Answer 7b. The workload that will result after the tobacco deeming rule is final will not shift resources from non-tobacco program areas. The TCA states that tobacco user fees are the only funds available for FDA activities related to tobacco regulation. The TCA specifically prohibits the use of funds other than tobacco user fees for tobacco regulation activities. The TCA user fees are used to hire the necessary staff in other parts of the Agency that assist CTP in the implementation and enforcement of the law.

Question 8. FDA's Office of External Affairs engages in a variety of patient outreach programs, often through the Office of Health and Constituent Affairs. One such program involves a partnership with the National Forum for Heart Disease and Stroke Prevention to educate patients about heart disease and stroke, and to encourage them to follow their doctors' advice about lifestyle changes—such as improvements in diet and exercise. Although doctors' advice regarding lifestyle changes may be beneficial to the public health, it is not clear why FDA—which regulates the safety and effectiveness of medical products, but not the practice of medicine—is the right agency to be engaging in such efforts.

Do you believe that FDA's statutory mission includes encouraging patients to follow their doctors' advice regarding lifestyle changes, such as eating better or exercising more? Or are such efforts better left to other public health agencies, such as the Centers for Disease Control?

What do you see as FDA's proper role in the doctor-patient relationship?

Answer 8. FDA believes it is important for the Agency to keep our many stakeholders, including health care professionals and patients, informed as appropriate, when we approve important products, issue safety announcements, and take public health actions. Occasionally these communications may touch on lifestyle issues. For example, when FDA announced its approval of a medical device to treat obesity, our press release pointed out that patients who use the product must follow a medically supervised diet and exercise plan to augment their weight loss; this information is contained in the product labeling approved by FDA. We recognize that while many people learn about FDA's products and announcements from their health care providers, others learn through FDA's website, the news media, social media, or from family or friends, so we make sure that our communications include a recommendation that patients and consumers continue to follow their doctor's advice or to consult their doctor if they have any questions.

---

[5] SE applications submitted to the Agency are divided into two types: "provisional" and "regular." Products that are the subject of provisional applications were received prior to March 22, 2011, and may stay on the market unless FDA issues an order finding them not substantially equivalent, or NSE. Products that are the subject of regular applications cannot be legally marketed unless FDA issues an order that they are substantially equivalent to a valid predicate product chosen by the company.

SENATOR ENZI

Question. Dr. Califf, labeling of menus for chain restaurants and similar retail food establishments will take effect on December 1, 2016. What steps is the FDA taking to ensure that the new uniform labeling standards will not be eroded by additional labeling requirements being added across the Nation?

Answer. Federal law includes an express preemption provision that preempts

> "any requirement for nutrition labeling of food that is not identical to the requirement of section 403(q) [of the FD&C Act] [21 U.S.C. 343(q)],"

except that this provision does not apply

> "to food that is offered for sale in a restaurant or similar retail food establishment that is not part of a chain with 20 or more locations doing business under the same name (regardless of the type of ownership of the locations) and offering for sale substantially the same menu items unless such restaurant or similar retail food establishment complies with the voluntary provision of nutrition information requirements under section 403(q)(5)(H)(ix) [of the FD&C Act]."

Therefore, State or local governments cannot have nutrition labeling requirements for foods sold in establishments covered by the final rule, unless such requirements are identical to the Federal requirements.

Under the rule, consumers will have consistent nutrition information available to them, whenever they eat out in covered establishments. In addition, companies that are covered by the requirements won't have to display different nutrition labeling, depending on the geographical location.

Restaurants and similar retail food establishments that are not covered under the Federal requirements would remain subject to applicable State or local nutrition labeling requirements, unless they choose to voluntarily register with FDA to comply with the Federal nutrition labeling requirements.

FDA intends to work with State and local authorities, as appropriate, to ensure that the menu labeling requirements are uniformly applied.

SENATOR BURR

Question 1. The field of cellular therapies continues to show promise for a variety of diseases, and is moving at a rapid pace. If you are confirmed, how would you ensure that the potential of these therapies are fulfilled and that their regulation by the FDA strikes an appropriate balance which reflects their unique characteristics in this rapidly advancing area of medicine?

Answer 1. Cellular therapies are rapidly evolving and show great promise. Advances in molecular and cellular biology, combined with developments in biomedical engineering, have made the concept of in vitro production of tissues, and even organs, a reality. An example of success in this field is the artificial trachea, which consists of live cells layered on a scaffold.

Due to the breadth of product types, as well as their potentially inherent complexity, FDA is working with stakeholders to ensure that regulation of these products is appropriate. Appropriate regulation should encourage innovation and provide Americans with timely access to safe and effective cellular therapies. FDA recently announced a 1-day public hearing to obtain input on four recently issued draft guidance documents relating to the regulation of HCT/Ps. These draft guidance documents were issued by FDA in response to stakeholders' requests for guidance on FDA's current views about how manufacturers, establishments, and distributors of HCT/Ps and health care professionals can meet the criteria under the Agency's regulations that apply to HCT/Ps. The comment period for all of these guidances will remain open between now and 2 weeks following the public hearing. FDA will carefully consider information it obtains from responses submitted to the docket and from the public hearing as it works to finalize these four guidance documents.

Question 2. The FDA is in the midst of initial discussions with industry and stakeholders for the 2017 User Fee Agreements. The Agency is funded by both significant taxpayer dollars through the appropriations process as well as the user fees collected by the agency. The Agency is always eager for more resources. However, additional funding does not always translate into a more predictable and timely review process, or a decrease in the total time it takes for products to reach patients. Any agreement submitted to Congress will be heavily scrutinized.

The Agency has a responsibility to balance the priorities set forth in these agreements as well as those set forth in law by Congress. The requirements and priorities that Congress sets forth are not optional. The agency needs to satisfy its commitments from the last agreements, before making any additional promises. How would you ensure the FDA fulfills its current commitments?

Answer 2. The Agency takes its responsibilities under its user fee agreements, as well as those set forth in law by Congress, very seriously. We are working toward implementing each commitment, including through specific implementation steering committees that have been established for each user fee program. FDASIA requires annual reports to Congress, which describe the Agency's progress in achieving the goals of the agreement. The most recent reports can be found from the main User Fee site here: *http://www.fda.gov/forindustry/userfees/default.htm*. Please refer to the legend on the left-hand side of the website to find reports and plans for program-specific user fees.

Question 3. You stated during the nomination hearing that you are committed to working with the whole ecosystem of regulation for Laboratory Developed Tests (LDTs). If confirmed as Commissioner, how would you ensure that FDA regulation of LDTs does not cause the unintended stifling of innovative test development at research and public health labs? Is the FDA working with CMS to ensure that CMS policies are updated before any new policy from FDA is effective to avoid duplicative regulation? If so, what role does FDA see CMS's CLIA office keeping and what sections of CLIA's current regulation does FDA intend to overtake?

Answer 3. FDA is committed to developing a final policy for oversight of LDTs that encourages innovation, improves patient outcomes, and strengthens patient confidence in the reliability of these products. Under the proposed LDT framework, FDA would phase in enforcement of premarket review requirements and the quality system regulation for some LDTs, with a risk-based approach. We proposed a framework that prioritizes attention on those tests that have the potential to pose the greatest risk to patients and the public health if they do not work as intended.

FDA's premarket review is necessary to determine if IVDs generally, including LDTs, are analytically and clinically valid—that they will perform as claimed, and that patients and their physicians can rely upon their results to make major medical decisions. When conventional IVD manufacturers comply with FDA regulations and labs developing similar tests do not, this creates a lack of consistency across the diagnostic market. Inconsistent oversight also puts patients at considerable risk. Because most LDTs have not undergone premarket review for analytical or clinical validity, it is possible that patients may receive incorrect results from those LDTs. This could mean patients receive incorrect treatment recommendations if their physician or hospital is using an LDT. In addition to patient harm, incorrect treatment recommendations may increase our health care system costs through coverage of unnecessary treatments or more expensive treatments.

This inconsistency also creates a disincentive to develop new and innovative tests. Conventional diagnostic manufacturers who have invested in the development of an IVD generally obtain premarket approval or clearance before packaging their tests into kits for use in multiple labs or health care facilities. They also register with FDA, list their devices, report adverse events and comply with good manufacturing practices. They are concerned that their laboratory competitors are currently not doing any of this, yet offer immediate competition to their own FDA-authorized tests.

FDA and CMS have complementary, non-duplicative roles, and FDA does not intend to take over any of CMS's current responsibilities. CMS, under CLIA, focuses on the labs' overall performance, whereas FDA regulates lab tests. CLIA does not require premarket review of tests or a showing that a test is clinically valid.

When FDA finalizes and implements its framework, both FDA and CMS will play a role in ensuring that LDTs are high quality—CMS through CLIA by continuing to focus on laboratory operations, and FDA by using its authority and expertise to ensure the analytical and clinical validity of the laboratory tests.

Although the roles of the agencies are different, FDA and CMS share an interest in ensuring effective and efficient oversight of LDTs so that laboratories can offer tests to the American public with confidence that are accurate and provide clinically meaningful information, without unnecessary or duplicative agency oversight.

To coordinate efforts across the Department, FDA, and CMS established an interagency task force this past April that will continue and expand on our collaboration related to the oversight of LDTs. The task force, comprised of leaders and subject matter experts from each agency, will work to address a range of issues, including those involving quality requirements for LDTs.

Question 4. From 2010–14, the FDA spent almost $2 billion on external IT contracts. What are the results of these investments? Have these investments translated into more timely or faster review periods and/or resulted in an increase in the number of FDA-approved products? As Commissioner, how would you ensure that investments like these are effectively utilizing taxpayer and industry dollars?

Answer 4. FDA is committed to securing, supporting and enhancing its technological capabilities in furtherance of FDA's mission to protect the public health, support scientific excellence, and promote innovation and collaboration.

By investing and improving our information technology infrastructure, FDA has deployed state-of-the-art IT functionality through new systems and upgrades to existing systems to facilitate and improve the review of drugs and medical devices. These capabilities include electronic submissions processing, advanced search engines, and business intelligence capabilities. We are supporting "media-less," electronic-only submissions through dedicated client and web portal software for premarket and post-market information, enhanced search and database functionality with the use of search engines and NoSQL databases, and upgraded data mining and reporting for signal detection and trend identification.

As FDA continuously seeks new and innovative technological solutions to fulfill its mission, we are working to implement state-of-the-art technologies and technological improvements that would further support and enhance the Agency's initiatives. These innovative capabilities include increased automation in the development, deployment and maintenance of FDA's information systems, using modern technology approaches which will allow for reduced cost and more rapid deployments of new systems. In addition we are expanding our data network capacity to provide the improved ability to transfer very large data files between industry and FDA, as well as internally within HHS. The need for expanded network infrastructure is to support and manage the very large data sets that enter FDA and allow us to continue to expand on our scientific research capabilities.

Investments such as the FDA Electronic Submissions Gateway (ESG) and the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) allow FDA to receive and review a significantly increased volume of applications. Without these investments, FDA would be unable to respond to the increased volume in a timely fashion; for example, within the goal timeframes outlined in FDA's user fee performance commitments. Additionally, through FDA's Adverse Event Reporting System (FAERS) and the Safety Reporting Portal (SRP), FDA is able to more efficiently and effectively monitor and report on safety issues in accordance with our mission to protect the public health. FDA will continue the regular review of the performance of these investments. We will review and prioritize funding for IT investments to prevent waste and ensure emerging needs are met. Further, we will closely monitor IT systems, such as ESG, to safeguard the confidentiality of industry's sensitive and protected data.

Question 5. As you stated during your nomination hearing, the FDA is committed to reviewing applications in the Center for Tobacco Products according to the agreed upon timelines, which are set forth in the Family Smoking Prevention and Tobacco Control Act and require the agency to act within 180 days of receiving an application. Communication between the agency and the industry it regulates is also an important component of a timely review and approval process. As Commissioner, how would you ensure that the CTP maintains adequate lines of communication with the entities it regulates?

Answer 5. FDA is committed to communicating with regulated entities and reviewing tobacco product applications in a timely manner. The only application review timeframe specified in the TCA is for Premarket Tobacco Applications. That timeframe is 180 days. We agree that it is important for FDA to make tobacco product review decisions in a timely manner. It is absolutely critical that these decisions are sound ones, grounded in the best-available science, and made in accordance with applicable public health standards.

In 2009, as a new regulatory entity, FDA's CTP needed to establish and develop processes for the review of tobacco products that manufacturers wanted to bring to market. This had never been done by any regulatory body anywhere in the world, and initial review times were not as short as we would expect them to be with a more established program.

FDA has made significant progress in reviewing SE applications for currently regulated products and this momentum will continue. The Agency has increased staffing, taken steps to streamline the SE review process, and established performance goals that include timeframes for review of regular SE applications and review of exemption from SE requests for currently regulated products. FDA has been able to develop these performance goals because of increased capacity, efficiency, and knowledge of the scientific evidence needed to adequately review SE applications.

The ability to communicate with regulated entities is critical to the success of FDA's program to review tobacco product applications. FDA has provided many educational materials to help manufacturers complete quality product applications that the Agency will be able to review in a timely manner. In addition, the Agency as-

sists manufacturers on an individual basis at their request. To demonstrate FDA's commitment to be responsive to industry and other external stakeholders, in October 2014, CTP implemented a performance measure for fiscal year 2015 to respond to 80 percent of meeting requests from industry and other external stakeholders within 21 calendar days. This performance measure increases to 90 percent in fiscal year 2017.[6]

The Agency also communicates with regulated entities by regularly attending their conferences and public meetings. Since spring 2014, the Director of CTP has spoken at the Tobacco Merchants Association, the Global Tobacco Network Forum, the National Association of Tobacco Outlets, the Smoke-Free Trade Association, and the National Association of Convenience Stores. This is in addition to numerous meetings held with industry at their request.

FDA also looks for opportunities to proactively communicate with regulated entities. This will be especially important for manufacturers of newly deemed products who will need assistance in complying with FDA regulations. The Agency is committed to providing this assistance. For example, the Agency intends to issue guidance, hold training webinars, meet with companies at their request, and increase staffing in CTP's Office of Small Business Assistance.

SENATOR ISAKSON

Question 1. I appreciate all the work that the FDA has done to implement the Drug Quality Safety Act (DQSA), and the numerous work streams that the Agency has had to initiate to make this important legislation work. However, I am concerned that the Agency's implementation efforts may cause some unintended consequences outside of the parameters that Congress intended be regulated by the law. For example, several months ago FDA issued a draft guidance addressing repackaging under the authority of the DQSA. I understand that the Agency's draft is sweeping in scope, and is very broad in its application. More specifically, I understand that the draft guidance, if implemented, would fundamentally and negatively change the way in which prescription medications are distributed to nursing home residents by specialized long-term care pharmacies. As you may be aware, long-term care pharmacies that serve nursing home residents are obligated by law to dispense individual patient prescriptions in unit-dose packaging and through emergency kits that can be prepositioned in the home in the case of emergencies. Yet, I am told the draft guidance may prevent these pharmacies from providing the needed medications to residents in unit dose packaging and emergency kits to meet other requirements of both Federal and State laws.

What assurance can you give that the FDA will promptly address and correct this seemingly unintended consequence of its draft guidance, and how can the Agency improve stakeholder engagement before such Guidance is ever issued?

Answer 1. Title I of the Drug Quality and Security Act (DQSA), the Compounding Quality Act, amended the FD&C Act concerning compounded human drugs. However, the legislation did not address repackaged drugs, which are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs. Therefore, on February 13, 2015, FDA published draft guidance, *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*, to describe the conditions under which FDA does not intend to take action regarding violations of certain requirements of the FD&C Act, if a State-licensed pharmacy, a Federal facility, or an outsourcing facility repackages human drug products.

In June and July 2014, prior to issuance of the draft guidance, FDA engaged with approximately 40 stakeholder groups during listening sessions regarding compounding and related activities, including repackaging. FDA then published the guidance in draft form to seek input and feedback from stakeholders regarding its proposed policies. The Agency received approximately 625 comments on the draft guidance, mostly concerning its implications for long-term care pharmacies and the facilities they serve. Since publishing the draft guidance, FDA has held listening sessions with members of approximately 60 stakeholder groups, including long-term care organizations, to hear their views regarding the draft guidance and other issues related to compounding and repackaging. FDA is considering all of the issues raised in the comments as well as the input we received during the listening sessions, before finalizing the draft guidance.

Question 2a. CBER, or the Center for Biologics Research and Evaluation, has issued a series of Untitled Letters related to product classification of tissue products. FDA's Regulatory Procedures Manual explains that an Untitled Letter

[6] *http://www.fda.gov/tobaccoproducts/newsevents/ucm393894.htm*.

"cites violations that do not meet the threshold of regulatory significance for a Warning Letter. Therefore, the format and content of an Untitled Letter should clearly distinguish it from a Warning Letter."

Unfortunately, several of these recent CBER Untitled Letters are not distinguishable at all from Warning Letters. Because CBER posts these documents on its website and they are read exactly like Warning letters, these Untitled Letters have caused great disruptions and uncertainty for industry including damage to companies.

Why has FDA begun issuing Untitled Letters rather than trying to have a dialog with the company first about the product classification?

Answer 2a. FDA's Untitled Letters often serve as the initial communication with regulated industry concerning regulatory violations. But, FDA also uses other means to communicate and resolve questions with manufacturers.

For example, the Center for Biologics Evaluation and Research (CBER) formed the Tissue Reference Group (TRG) to assist stakeholders on questions regarding human cell tissues and cellular and tissue-based products (HCT/Ps). The purpose of the TRG is to provide a single reference point for product-specific questions received by FDA concerning jurisdiction and applicable regulation of HCT/Ps. FDA has publicly posted information on how manufacturers can submit inquiries to the TRG and publicly discloses information related to TRG recommendations on the CBER website.

If FDA issued an Untitled Letter subsequent to an establishment inspection, the FDA investigator may have already informally discussed the situation, though they are not required to do so. In determining whether to issue an Untitled Letter, FDA officials generally consider whether evidence shows that a firm, product, and/or individual is in violation of the law or regulations. Such evidence may have been obtained during a routine or directed inspection, or other means of surveillance, such as Internet website surveillance.

Untitled Letters should be clearly distinguishable from Warning Letters in their format and content. For example:

- The letter is not titled.
- The letter does not include a statement that FDA will advise other Federal agencies of the issuance of the letter so that they may take this information into account when considering the awards of contracts.
- The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.
- The letter does not evoke a mandated district followup.
- The letter requests (rather than requires) a written response from the firm within a reasonable amount of time (e.g., "Please respond within 30 days"), unless more specific instructions are provided in a relevant compliance program.

Untitled Letters are not limited to potential product classification issues, but are generally a mechanism to communicate and provide notice of a violation. These letters ordinarily provide the factual basis regarding the violation and serve to communicate the concern without committing FDA to enforcement action, if the violation is not corrected.

Question 2b. Why is FDA insistent that such letters must be posted on their website? FDA has Center-specific policies as to whether to post Untitled Letters, except to the extent that it overlaps with FDA's approach to proactive posting under the Freedom of Information Act (FOIA).

Answer 2b. FDA's posting approach under FOIA requires the posting of any FDA record subject to the FOIA, such as an Untitled Letter if:

1. FDA has received three or more FOIA requests for a copy of the record, or
2. If the content related to is a matter of significant public interest and we expect to receive multiple FOIA requests for it.

This approach is consistent with Federal law, guidelines from the Department of Justice, President Obama's January 21, 2009, FOIA Memorandum, and Attorney General Holder's March 19, 2009, Memorandum (5 U.S.C. § 552(a)(2)(D)).

Question 2c. In light of the above, are you willing to review your process for Untitled Letters, especially as it relates to product reclassifications, and examine ways to make issuance of these letters fairer, more effective and more consistent?

What are some procedural protections the agency might consider in this space?

At the hearing, you said that FDA will "do everything we can to produce a more even template across the FDA so that the standards are the same." Do you believe that it is important to have consistent and predictable standards across the FDA

governing the use of Untitled Letters? What specific steps will you take to improve consistency and predictability in this area?

Answer 2c. We are currently reviewing processes for issuing and posting Untitled Letters for FDA and each of our Centers. Specifically, we are reviewing ways that Agency and Center policies could be made more accessible and transparent.

FDA believes in transparency and consistency in our procedures. We recognize that some stakeholders want greater uniformity in FDA's practices related to posting Untitled Letters. We also recognize that our product centers need to maintain some specific procedures to address the particulars of the products they regulate.

Question 3a. The American Association of Tissue Banks (AATB) made CBER aware on numerous occasions that it was preparing a homologous use guidance proposal for FDA's consideration. That AATB proposal was to be discussed at the AATB–FDA liaison meeting on October 29, 2015. Given the exchange of agendas and meeting materials in the weeks leading up to the meeting, the agency was well aware of this scheduled discussion. However, around 5 p.m. on October 28, FDA posted its own homologous use draft guidance. This had the effect of rendering any substantive conversation about the AATB guidance impossible, as the subject matter was now part of an open docket which FDA cannot discuss while the comment period remains open.

Why did FDA choose to release this guidance just hours before the scheduled discussion with AATB, which limited the ability to have the ability to have a meaningful discussion?

Answer 3a. It was FDA's intention to have this guidance released well in advance of this meeting with AATB. The guidance was released as soon as the clearance process was completed. Unfortunately, AATB did not have enough time to review prior to the meeting. FDA was receptive to the comments from AATB regarding their proposed guidance, and looks forward to AATB's contributions through written comments on the guidance at the upcoming public meeting.

Question 3b. Will FDA evaluate AATB's proposed guidance document during the comment period?

Answer 3b. FDA will evaluate all comments received regarding this guidance, including AATB's proposed guidance, which FDA encouraged AATB to submit to the docket.

Question 3c. In what area is there alignment between the AATB proposed guidance and FDA's draft guidance?

Answer 3c. Both AATB's and FDA's documents share the goal of developing better clarity to help facilitate the development of HCT/Ps. FDA will carefully review the AATB proposal, as well as other comments received. In addition, FDA is having an open public meeting in April 2016, and this has been announced in the *Federal Register*.

Question 4a. The medical device industry continues to strive for the best quality and safety record possible, and believes inspections are an important part of this. However, there have been a growing number of challenges with the lack of consistency, transparency, and predictability in the FDA post-market inspection process. I understand FDA is engaging a number of efforts to reorganize their inspections program, such as Program Alignment.

Can you provide me with an update on the progress of these initiatives?

Answer 4a. Work continues to advance the transition to a commodity-based and vertically integrated regulatory program (specialization of our inspection and compliance staffs). The Office of Regulatory Affairs (ORA) and the Center for Devices and Radiological Health (CDRH) are actively working on the action plan for the second year of Program Alignment (Fiscal Year 2016). The fiscal year 2016 action plan includes development of a medical device and radiological health curriculum to ensure that inspection and compliance staffs have the requisite knowledge and training for their commodity-specific duties. Fiscal year 2016 is a transition year for ORA—operating in our current regional and district geographic structure, while planning for the implementation of program-based operations. Contingent upon appropriate approvals, standup is expected early in fiscal year 2017.

Question 4b. Has FDA included industry's perspective in developing these initiatives?

Answer 4b. The device program has multiple ongoing initiatives, and the device industry is engaged in many of these initiatives. The Agency has met, and will continue working with, industry to enhance communication channels and to assist us with identifying device program specialties and overall program enhancements. For

example, we plan to share the medical device and radiological health curriculum with our stakeholders to ensure comprehension and identify current and emerging gaps. ORA and CDRH plan to work with our stakeholders to identify and leverage state-of-the-art training opportunities. We also welcome additional approaches to better engage with industry.

Question 4c. How best can industry be a partner in addressing these challenges?

Answer 4c. All medical device and radiological health stakeholder organizations (e.g., AdvaMed, MITA, MDIC, MDMA, etc.) should engage in regular dialog with ORA's program director for medical devices, as well as the device management teams in the device divisions.

Question 4d. What other opportunities do you see for further improvements in the FDA post-market inspection process to address these challenges?

Answer 4d. ORA will continue to work with its stakeholders to ensure awareness of advances in manufacturing technology and development of corresponding training for inspection staff.

ORA also will continue to communicate with industry stakeholders about the inspection process; expectations, engagement opportunities, etc. ORA and CDRH, together with our stakeholders, will continue to identify opportunities to enhance and optimize the inspection method used for medical devices, and we will continue to develop feedback opportunities to use in process improvement.

SENATOR ISAKSON AND SENATOR MURKOWSKI

Question. We believe that pregnant women should have access to the latest science-based nutrition advice that empowers them to make healthy nutrition decisions during pregnancy. The FDA's draft guidance has been pending since June 2014, and at that point, the release was 3 years past the date of when Secretary Sebelius told us it would be issued. In April, we wrote to the current Commissioner along with many of our colleagues asking FDA to finalize this guidance in order to ensure that women have the best advice that reflecting the latest nutrition science about the types of seafood that is healthy and safe to eat during pregnancy. In addition to FDA's 2014 draft guidance on seafood nutrition advice to pregnant women, the agency also issued a comprehensive scientific study of the effects of consuming seafood during pregnancy, called the Net Effects Report. It is our understanding that FDA may be moving away from the findings of the Net Effects Report in order to finalize the advice, yet it is not clear to me why the agency would be shifting away from their most recent scientific study and contradicting its own scientific findings.

If the agency is not consulting its own Net Effects Report, what new scientific study is FDA using as the basis for finalizing its current thinking on seafood advice for pregnant women?

Furthermore, if FDA is using a different study, can you provide the source of funding for this new study or studies?

If confirmed, will you ensure that pregnant women receive final guidance on nutrition advice for what seafood is safe and healthy to consume that is consistent, understandable, and based on FDA's latest scientific review of the net effects of seafood consumption?

Answer. FDA shares your interest in ensuring that pregnant women have access to sound, science-driven, and clearly understandable recommendations that enable them to make informed decisions about their diets. The final seafood consumption advice for pregnant women is undergoing interagency review. We will continue to take steps to ensure that it is reflective of the latest nutrition science.

In response to our 2014 draft advice, we received many comments on science related to the draft advice. FDA has not initiated any additional studies on this topic, but we have looked carefully at the comments, the scientific literature cited in the comments, and the scientific literature that continues to surface relevant to this topic. Based on the totality of the scientific evidence, we remain confident that pregnant women, breast feeding women, and women considering becoming pregnant should eat more fish, particularly fish lower in mercury. Completing the updated advice remains a priority for the Agency.

SENATOR ISAKSON AND SENATOR MURPHY

Question. Every day over 1 million Americans are treated with medical gases. In 2012, this Committee and FDA worked together to enact historic reforms that we drafted, governing how this unique class of drugs are approved and regulated by FDA. The FDA is considerably behind in its rulemaking to implement this law, resulting in unnecessary confusion and disruption to the provision of medical gas. In

fact, there have been recent enforcement actions in Iowa, New Jersey, Ohio and Florida trying to apply FDA regulations that the agency has acknowledged should not apply to medical gases, such as expiration dating. And as communicated by both Houses in the Appropriates Bill Report Language, guidance and inspector training alone is not adequate.

If confirmed, will you commit to updating FDA's regulations to address the long-standing enforcement issues as to medical gas?

Answer. As required in FDASIA, FDA reviewed Federal drug regulations that apply to medical gases, and submitted a Report to Congress in June 2015. During that process, FDA sought public comments through meetings and a public docket.

As described in that report, FDA has determined that the current regulatory framework is adequate and flexible enough to appropriately regulate medical gases, with regard to most issues. FDA can work within the existing regulatory framework to regulate the production and distribution of medical gases without rulemaking, for example, through publication of revised guidance to industry and revisions to FDA's medical gas inspection program and related inspection training.

FDA is currently engaged in a number of activities intended to reduce any regulatory uncertainty and clarify expectations for industry and the public, including additional training of inspectors, issuing an updated compliance guide inspection program, and updating the 2003 draft guidance to industry on CGMPs for medical gases, with input from stakeholders, including industry.

Also, as stated in FDA's Report to Congress on the regulation review, FDA has determined that certain regulation changes regarding warning label statements and adverse event reporting are or may be needed, and FDA will continue to evaluate the need for regulatory changes on an ongoing basis. FDA expects to maintain open communication with industry, Members of Congress, and other stakeholders as appropriate, and will continue to evaluate and address medical gas issues as needed.

SENATOR COLLINS

Question 1. I am concerned about the sudden, aggressive price hikes in certain off-patent drugs where there is just one supplier. This to me represents a market failure that hurts patients and providers and increases costs for Federal and State programs too. Do you have any initial thoughts of what the FDA could do to bring to market generic or safe foreign drugs to compete with these prescriptions drugs to put pressure on costs?

Answer 1. I appreciate the concerns about drug costs. FDA works as quickly as possible to get safe and effective generic drugs to the market and will continue to evaluate other steps that may be able to be taken to address this concern. It is important to note, however, that FDA's role is to review drug applications for the statutory approval criteria but this authority does not extend to reviewing or approving drug costs or pricing, which are set by manufacturers and distributors. That said, FDA is concerned that the prices of drugs can interfere with patients' access to drugs, including lifesaving therapies. By making safe and effective generic drugs available, there is greater price competition with innovator drugs, resulting in significant drug cost savings to the American people.

Through GDUFA, the Agency has built up the infrastructure for a 21st-Century generic drug program. As part of this, FDA has established a review prioritization policy for generic drug applications determined to be a priority of the Agency.

Specifically, FDA considers certain types of ANDAs to be public health priorities, and expedites their review accordingly. In August 2014, FDA's Center for Drug Evaluation and Research (CDER) updated its Manual of Policies and Procedures (MAPP) entitled Prioritization of the Review of Original ANDAs, Amendments, and Supplements. This MAPP, which is publicly available, describes how the review of ANDAs, ANDA amendments, and ANDA supplements are prioritized.

For example, FDA considers potential "first generic" ANDAs to be a public health priority. First generics are the first generic to enter the market for a given branded product. Potential first generics are about 15 percent of our workload. All of them have been tagged as priorities, and their review has been expedited. This is true regardless of when the ANDA was submitted. In the past 3 years, we have approved hundreds of first generics for more than 200 new drug products. FDA also considers shortage-related drugs a priority, and expedites their review, as well as other public health priorities.

It is important to note that regardless of FDA granting approval, the sponsor makes the ultimate decision whether to market the approved product. There are many instances of FDA granting approval and the sponsor, for one reason or another, deciding not to bring the product to the market. This has occurred even in the "first generics" space.

Drugs that are not FDA-approved nor manufactured in a facility inspected by FDA do not have the assurance of safety, effectiveness, and quality as do drugs subject to FDA oversight. There have been documented incidences of non-FDA-approved imported drugs found to be contaminated, counterfeit, containing varying amounts of active ingredients or none at all, or containing different ingredients than the FDA-approved product. Moreover, FDA would not be able to make safety and quality determinations for prescription drugs offered for import into the United States that have not gone through the U.S. regulatory process. In fact, FDA evaluation of non-FDA-approved imported drugs revealed that while nearly half of imported drugs claimed to be Canadian or from Canadian pharmacies, 85 percent of such drugs were actually from different countries. Typically, these products are smuggled into the United States after being transshipped to third-party countries in an effort to avoid detection and create an appearance of coming through countries that consumers may find trustworthy. Through FDASIA Title VII and the Drug Supply Chain Security Act, Congress has recognized the need to bolster this closed drug distribution system. Authorizing importation would compromise the closed drug distribution system in the United States and undermine these laws, thus making it easier for unapproved drugs, which may include counterfeit or other substandard drugs, to reach American patients putting their treatment at risk. FDA is concerned that the risks of unapproved products from foreign sources outweigh any potential cost savings. We are also concerned that adverse events flowing from importation of such unapproved products could lead to diminished confidence in FDA-approved products.

Question 2. Dr. Califf, I would like to relay some ongoing frustrations I am hearing from grocery stores regarding the FDA's handling of the menu labeling regulations. There are clear differences between chain restaurants with pre-printed menus and grocery stores with salad bars, yet the menu labeling rule does not reflect this fact and is a one-size-fits-all regulation.

Former Commissioner Margaret Hamburg, just days before she left office, told the Senate Agriculture Appropriations Subcommittee, on which I serve, that supermarkets had legitimate concerns that required additional guidance and flexibility. It then took more than 10-months for the agency to provide "draft" guidance, which confused the situation even more.

One point that illustrates the need for flexibility is with local and seasonal foods. In Maine, you will see salad bar offerings or other menu items that are made with local blueberries or seafood. These foods may be sold at one or two stores, under the same name as 20 or more other stores, but the ingredients or recipe may vary from store-to-store. Under FDA's rules, these would all be considered "standard menu items," and require a store manager to provide a calorie-count for each of these locally made foods before selling them to their customers. Concerns have been raised that this will cause a store manager to move away from offering truly fresh and local items and instead outsource them to a central kitchen or standardized, pre-packaged food offerings. The date for complying with this menu labeling rule has been pushed out until December 2016, however, I am concerned that the rule is still burdensome for many who will have to follow it.

Would you be willing to explore ways to provide additional flexibility for these grocery store settings before compliance begins?

Answer 2. The final menu labeling rule applies to standard menu items sold at covered establishments. There is flexibility built into the final rule. If a food is not routinely included on a menu or menu board or routinely offered as a self-service food or food on display at a covered establishment, it is not a standard menu item and, therefore, is not covered by this rule. Also, if a food's ingredients and recipe changes daily based on food available in the store, it is likely that the food would not be a standard menu item but rather a daily special, and thus exempt from the provisions of this rule. Also, temporary menu items or a self-service food and food on display that is offered for sale for less than a total of 60 days per calendar year are exempt.

Further, daily specials that are not listed regularly on the menu are also exempt from the provisions of this rule.

If a covered establishment offers salad bar offerings or other menu items prepared using local or seasonal foods, and these menu items are standard menu items, they would be covered under the menu labeling requirements, even if they are not sold at every location within the chain. We note, however, that covered establishments have several means that can be used to determine the calorie and other nutrition information, including existing databases and cookbooks.

FDA is committed to working collaboratively with establishments covered by the menu labeling final rule, including chain restaurants, covered grocery stores serving

restaurant-type food, and others, now and in the future, to answer questions. In addition, we will be providing educational and technical assistance for covered establishments and for our State, local, and tribal regulatory partners to support consistent compliance nationwide. We will work flexibly and cooperatively with individual companies making a good faith effort to comply. FDA believes that this cooperative approach helps to improve the dialog surrounding the requirements and facilitates successful implementation in a practical way.

Question 3. Dr. Califf, the Department of Health and Human Services Inspector General listed the cybersecurity of networked medical devices as a new priority for oversight in 2016, writing that they pose a growing threat to the security and privacy of personal health information. Moreover, the research technology firm Forrester has predicted that hackers will release ransomware for medical devices that would allow criminals to take control of a medical device and hold the power to hold that device's control ransom until the victims meet the attacker's demands.

I understand FDA has started to take steps to address this problem, including releasing final guidance last year on its expectation that cybersecurity will be baked into the design of future medical devices. Many networked medical devices in use today, however, were created before cybersecurity was even a consideration. Dr. Califf, what role do you see for FDA in helping to address vulnerabilities that exist in these legacy medical devices?

Answer 3. FDA is taking a proactive approach to mitigating any medical device cybersecurity vulnerabilities that could pose a threat to patient safety. The landscape of medical device cybersecurity is complex, and a commitment from multiple stakeholders—including device manufacturers, cybersecurity researchers, hospitals, and others—is necessary.

FDA's approach embraces the National Institute of Standards and Technology (NIST) framework of "identify, protect, detect, respond and recover" in assuring the safety and effectiveness of medical devices and in facilitating medical device manufacturers and other stakeholders in the Health and Public Health Critical Infrastructure Sector to engage, assess, and address cybersecurity vulnerabilities before they are exploited. To that end, FDA's 2014 guidance addresses the Agency's premarket expectations to address cybersecurity vulnerabilities. FDA has established a Cybersecurity Working Group within the Center for Devices and Radiological Health to focus on Agency activities related to device cybersecurity. The Agency also partners with other Federal entities, such as the Department of Homeland Security's Industrial Control Systems Cyber Emergency Response Team (ICS–CERT) to quickly address cybersecurity vulnerabilities when they are identified and to facilitate communication among relevant stakeholders.

FDA is currently working on, and plans to soon publish, draft guidance to address post-market concerns regarding the cybersecurity of medical devices. This includes "legacy medical devices," some of which have been on the market before present-day cybersecurity concerns existed. In particular, the draft guidance will State FDA's expectations with regard to cybersecurity risk management across the total product life cycle. It will emphasize the need for vigilance, continuous monitoring and ongoing cybersecurity risk management, not just before commercialization or procurement, but for the entire lifespan of the product.

Additionally, in the coming weeks, FDA will announce a medical device cybersecurity workshop to be scheduled for January 2016. As a followup to the previously held October 2014 workshop, this workshop will emphasize the total product life cycle and will bring diverse stakeholders together to present progress as well as persistent challenges in information-sharing, implementation of voluntary frameworks, vulnerability disclosure, and proactive vulnerability management.

Question 4. Dr. Califf, I am pleased with the continued progress toward strengthening the role and voice of the patient in the medical product development process and the leadership that the FDA has shown. The patient voice is critical in understanding what patients value and the risk they are willing to accept in exchange for any potential benefit from any medical product.

To ensure that patient-focused drug development tools are of a caliber appropriate for FDA reviewers, do you see a role for publicly reporting how such tools are being used in product reviews?

Answer 4. I certainly agree that patient engagement in the drug development process is critical, and I look forward to continuing FDA's leadership in this area. In the last several years especially, the Agency has made significant efforts to publicly involve the patient community in product development in a variety of ways. Given that our activities have been public, I do not believe that a formal reporting mechanism is needed and instead would commit to continuing the Agency's trans-

parency activities around these issues. Below are some examples of the work FDA has done to date on this important issue.

The engagement by Parent Project Muscular Dystrophy (PPMD) in submitting their proposed guidance is an example of how early input from patients and caregivers can contribute to drug development. For the first time, the development of FDA guidance was preceded by the submission on June 25, 2014, of a proposed draft guidance independently prepared by PPMD. FDA values PPMD's effort and input and appreciates the insights provided by PPMD. PPMD's proposed draft guidance was posted on the web for public comment. Both the proposed guidance and public comments submitted to FDA were carefully considered in developing FDA's draft guidance. This example of collaboration between engaged stakeholders and FDA highlights how input from patients and caregivers can contribute to drug development.

In addition, FDA has conducted a series of disease-specific public meetings to systematically gather patients' perspectives on their condition and available therapies to treat their condition. These meetings have been a rich source of information for the Agency, and we hope to continue them in the future. We also anticipate issuing guidances in the future to address scientific and methodological issues related to incorporating patients' perspectives in medical product development and subsequent regulatory review, and look forward to receiving public comment on these guidances. In sum, we believe that it is especially appropriate for the Agency to be transparent regarding its activities related to patient engagement, and we will continue to involve the patient community and other interested stakeholders.

Question 5. Dr. Califf, we spoke last month about the FDA's proposed rule on electronic prescribing information and its implication for rural pharmacists. I continue to hear concerns that this rule, if finalized, would have an adverse effect on patient safety. This would be acutely felt by rural Americans who live in areas with limited Internet access. It would also affect patients and health care providers when electronic technologies are unavailable, including during a power outage or in the wake of a natural disaster or terrorist attack.

Given that 96 percent of the public comments were in opposition to the proposal, are you willing to carefully evaluate the concerns before proceeding any further with this rulemaking?

Answer 5. We encouraged patients, health care providers, and other stakeholders to submit comments to the docket for this proposed rule, with information or data supporting their concerns. In addition, in the preamble to the proposed rule, FDA specifically requested public comments on aspects of the proposal, including whether alternatives to request a paper copy of the prescribing information are adequate, and on alternative distribution systems in which both paper and electronic prescribing information would be available. As you know, FDA granted a request to extend the comment period for 60 days, until May 18, 2015. The Agency will consider all comments submitted in response to the proposal as we work to finalize the rule.

Question 6. Dr. Califf, I want to switch gears for a minute to an issue of growing interest to many Americans, personal care products. The average consumer uses 10 personal care products every day, yet the laws governing the cosmetics and personal care products industry haven't been updated since 1938, and States have been acting on their own in the absence of a national standard. I have been working with Senator Feinstein on legislation that would modernize cosmetic safety laws and provide greater transparency for consumers and regulatory certainty for manufacturers.

Would you agree that it is time to update the laws to better ensure the safety of personal care products?

Answer 6. The Administration believes that the United States needs a modern and effective system of safety oversight for cosmetics. The President's fiscal year 2016 budget requests authority to require cosmetic firms to register their establishments and products with FDA and to pay a user fee. The product, ingredient, and facility information submitted with registration would expand FDA's information about the industry and better enable the Agency to develop necessary guidance and safety standards. With additional funding resources, FDA would be able to conduct priority activities that meet public health and industry goals. This authority would be an important step toward improving FDA's capacity to promote greater safety and understanding of cosmetic products. We would be pleased to work with you and your colleagues on the HELP Committee to achieve these and other meaningful enhancements to our cosmetics safety program.

SENATOR HATCH

Question 1a. One issue that significantly affects many entities in my home State is the FDA's October 2014 proposed guidance on the regulation of laboratory-developed tests (LDTs).

FDA's proposal to regulate LDTs is a significant change that would impose considerable new burdens on regulated parties. Why was this proposed by guidance, when rulemaking would be more transparent, provide clear and binding rules, and include a better cost assessment?

Answer 1a. The draft guidances describe FDA's proposed new enforcement policy for LDTs. Issuing the proposed enforcement policy for LDTs via guidance, rather than regulation, is appropriate because FDA is communicating a change in its enforcement of applicable requirements that already exist in statute and regulations.

FDA is committed to a transparent and evidence-based process in the development of its guidance. In 2007, FDA issued a draft guidance proposing to no longer exercise enforcement discretion over a certain category of LDTs (in vitro diagnostic multivariate index assays), but the lab community urged FDA to address LDTs generally, rather than take a piecemeal approach in order to provide for greater predictability. In 2010, FDA held a public meeting to discuss FDA oversight of LDTs and also opened a public docket providing additional opportunity for public comment. In developing the draft guidances, FDA considered and incorporated many of the suggestions provided by stakeholders. In addition, upon issuing the draft guidances, FDA provided an extended comment period and provided additional opportunity for comment at a 2-day public meeting. FDA has received 300 public comments, has met with numerous stakeholders, and is working to incorporate suggested changes into the final guidances, as appropriate.

FDA oversight is needed to ensure that LDTs used in making major medical decisions are safe and effective. Due to advances in technology and business models, LDTs have evolved from being relatively simple tests that were generally only available on a limited basis to complex tests that have a nationwide reach and have higher risk uses, such as predicting breast cancer risk and directing critical treatment decisions, similar to those of other IVDs that have undergone FDA premarket review. Patients and physicians should be able to rely on the results of these tests to make major medical decisions.

It is also important to note that other entities, including NIH and the Department of Energy in the 1990s and two advisory committees to the HHS Secretary after the 1990s, have been talking about the need for greater FDA oversight of LDTs. More recently, the Institute of Medicine (IOM) reinforced this as well.[7]

Question 1b. Many stakeholders in my State and around the country have shared with me concerns on the impact of this proposed guidance. If the FDA finalizes it, how would the agency respond to potential non-compliance from those impacted, given that FDA guidance documents do not have the force of law and are non-binding on FDA and regulated parties?

Answer 1b. FDA is committed to developing a final policy for oversight of LDTs that encourages innovation, improves patient outcomes, and strengthens patient confidence in the reliability of these products. The Agency's premarket review is necessary to determine if IVDs generally, including LDTs, are analytically and clinically valid—that they will perform as claimed, regardless of where they are developed, and that patients and their physicians can rely upon their results to make major medical decisions.

Under the proposed LDT framework, FDA would phase in enforcement of premarket review requirements and the quality system regulation for some LDTs using a risk-based approach. This approach will allow for a clear and transparent process for those clinical laboratories complying with premarket review requirements. We appreciate concerns from laboratories and others about the FDA oversight proposal, and have proposed a framework that prioritizes attention on those tests that have

---

[7] National Human Genome Research Institute (1997). *Promoting Safe and Effective Genetic Testing in the United States*. See *http://www.genome.gov/10001733*.

Secretary's Advisory Committee on Genetic Testing (2000). *Enhancing the Oversight of Genetic Tests: Recommendations of SACGT*. See *http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf*. Accessed September 16, 2010.

Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services. Washington, DC: Department of Health & Human Services; 2008 Apr. 276 p. Also available at *http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS*.

Institute of Medicine. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington, DC: The National Academies Press, 2012.

the potential to pose the greatest risk to patients and the public health, if they do not work as intended.

Question 2. Many entities are engaging in criminal activity by manufacturing and marketing products that masquerade as "dietary supplements" but contain anabolic steroids, active pharmaceutical ingredients (APIs), or analogues of APIs. With the large number of legitimate dietary supplement companies who manufacture and market safe products to consumers, it is imperative that illegal manufacturers and marketers be removed to protect the public health. I was very pleased to see the FDA join with the Department of Justice (DOJ) and other Federal agencies in announcing a sweep of criminal and civil actions on Tuesday, November 17, 2015.

Should you be confirmed, will you make it a priority for FDA to develop a plan, in conjunction with the DOJ, to take more aggressive action, including pursuit of both felony and misdemeanor convictions, against these bad actors who are threatening the public health of American consumers?

During your hearing before the Senate HELP Committee, I asked whether you believe that the Dietary Supplement Health and Education Act (DSHEA) provides adequate authority to regulate the dietary supplement industry and protect consumers from unsafe products. In response, you stated that you are "fully aware of [your] authorities and plan to use them as Congress has directed." In light of the sweeping enforcement actions announced by the FDA together with the DOJ and other agencies later that same day, it seems apparent to me that the FDA does have ample authority to take action in this space. Given these points, can you elaborate beyond your statement cited above whether you believe, as prior FDA commissioners have, that DSHEA provides adequate authority to regulate the dietary supplement industry and protect consumers from unsafe products?

Answer 2. FDA is committed to fully enforcing DSHEA as vigorously as possible to protect the public health. Using these authorities, FDA has been able to take significant steps to protect the public, including recent Warning Letter initiatives related to products containing BMPEA, DMBA, DMAA and pure powdered caffeine.

The Agency is continuing to work on better focusing our resources to quickly identify and act against unsafe dietary supplements. For instance, over the past 5 years, we have emphasized inspections and enforcement of our current Good Manufacturing Practice regulations across the entire industry, and that is helping to ensure that dietary supplements are manufactured safely. Also, we have implemented the serious adverse event reporting law for dietary supplements passed in 2007. As we receive adverse event information under this system, our ability to recognize trends and patterns in adverse events is helping us target dangerous products or categories of products.

As you know, DSHEA puts the burden on FDA to develop the evidence necessary to take action against unsafe dietary supplements. In addition, dietary supplement manufacturers and distributors are not required to inform the Agency of most products they sell prior to marketing. This creates enforcement challenges for FDA in discovering violations within a huge universe of dietary supplements, proving the violation, and effectively deterring future bad actors.

FDA's dietary supplement program office is currently undergoing a strategic review of its structure and practices, including a review of the underlying statutory and regulatory authority for dietary supplements and how the Agency has traditionally used this authority. This effort is intended to ensure that we are using our full authorities in the most effective way possible.

FDA works with DOJ on civil and criminal actions, such as injunction or seizure. For those firms demonstrating repeated or significant non-compliance with dietary supplement regulations, we will continue to pursue the most appropriate action to assure public health, which may include, but not be limited to, such joint actions with DOJ.

Question 3. In September of this year, FDA's Division on Dietary Supplement Programs provided a Declaration to certain State attorneys general in response to concerns on whether a certain substance is a legal dietary ingredient under the Federal Food, Drug, and Cosmetic Act. This Declaration was then used in State enforcement activities by State AGs as primary evidence in cease and desist efforts against retailers.

Can you shed any light on why the FDA chose to engage with State enforcement actions and proceed with such a Declaration, and more importantly why FDA took this action instead of following the usual transparent process, such as issuing a public statement, a warning letter, consumer advisory, or requesting a voluntary recall on the ingredient?

I am concerned that FDA's approach of providing a Declaration privately to a State law enforcement agency on an issue never raised by the agency in a public forum or with industry could set a dangerous precedent. Should you be confirmed as Commissioner, will you commit to engaging in a more public and transparent process? Do you believe that FDA should clarify its position on this issue, if so, how will you ensure clarification? Do you believe it is appropriate and good regulatory practice to issue warning letters or consumer advisories when taking action in the future on such ingredients of concern?

Answer 3. FDA prioritizes its enforcement actions based on available resources and the level of safety concern identified. The Agency faces the challenge of having limited resources to monitor the ever growing marketplace for potentially harmful dietary supplements and dietary ingredients. As a way of leveraging those limited resources, we work with outside partners, such as other Federal and State agencies, as well as industry stakeholders, to encourage full compliance with applicable statutes and regulations.

In responding to requests from certain State attorneys general, FDA recognized the opportunity to work cooperatively in providing an Agency determination as to the validity of the purported dietary ingredient. This would not only assist these State agencies in exercising their jurisdiction over such products, but also help to conserve limited FDA resources while protecting the public health. FDA continues to investigate the marketing of products containing the ingredient in question, and will exercise our authority as warranted.

FDA is committed to protecting public health through a variety of avenues.

Question 4. In fiscal year 2015, FDA received around $1.9 billion in user fees from industry and others, and about $2.5 billion in appropriated funds. For the user fees, members of this committee receive annual financial and performance reports that are quite granular on the reporting of how those dollars are spent. My concern is that congressional dollars are not tracked as thoroughly. Programs without fees seem to suffer from delayed or ineffective implementation, including the over-the-counter drug program and food safety law. Can you comment to how you all currently track resources for programs outside of the user fee agreements, and commit to tracking taxpayer dollars to the same level of detail you track dollars from industry?

Answer 4. FDA tracks the spending of all of its resources to include appropriated budget authority and user fees. FDA has set up its financial system of record to enable the Agency to track and report on spending by the source of funds (i.e., budget authority or user fee) as well as by the organization doing the spending (i.e., Center and Office).

Question 5a. One of the hallmarks of the Hatch-Waxman framework governing generic drugs is that each generic version of a brand-name drug must have the same labeling as its brand-name equivalent. This requirement protects patients by ensuring that they have the same FDA-approved information no matter which version of a drug is dispensed and helps promote the use of lower cost generic drugs by providing public assurance that the products are identical. In November 2013, however, FDA proposed to require generic manufacturers to change the safety information on their drugs' labeling without prior FDA approval. If finalized, this proposed rule would lead to situations in which there are three or more different versions of the labeling of the same drug, with patients receiving different information depending on which version of the drug their pharmacists dispense.

The labeling for a generic drug is required by statute to be "the same as the labeling approved for" its brand name equivalent. Under this longstanding policy, a generic drug's labeling must match the brand-name labeling at the time of approval, and the generic drugmaker must update its labeling to follow changes made by the brand-name manufacturer. FDA's proposal, however, would allow a generic drugmaker to change a drug's labeling to be different from the labeling approved for its brand-name equivalent. What do you believe the word "same" means in this context?

Answer 5a. In the current marketplace, approximately 80 percent of drugs dispensed are generic and, as we have learned, brand drug manufacturers may discontinue marketing after generic drug entry. The proposed rule, if finalized, would provide abbreviated new drug application (ANDA) holders with the means to update product labeling to reflect data obtained through post-market surveillance, even though this may result in temporary labeling differences among products, while FDA reviews the proposed labeling change. During its review of a generic drug manufacturer's changes being effected (CBE–0) supplement, FDA would consider submissions by the brand drug manufacturer and other generic drug manufacturers re-

lated to the safety issue, and determine whether the labeling update is justified and whether modifications are needed. FDA would make an approval decision on proposed labeling changes for the generic drug and the corresponding brand drug at the same time, so that brand and generic drug products have the same FDA-approved labeling.

The proposed rule would likely reduce the variation between brand and generic drug labeling that currently takes place. Under current regulations, only brand drug manufacturers can independently update product labeling with certain newly acquired safety information and distribute revised labeling, before FDA reviews or approves the labeling change, by submitting a CBE–0 supplement. Under the current regulation, FDA generally has advised that a generic drug manufacturer may use the CBE–0 supplement process only to update its product labeling to conform to the FDA-approved labeling for the corresponding brand drug or to respond to FDA's specific request to submit a labeling change through the CBE–0 process. Accordingly, while FDA reviews a brand drug manufacturer's CBE–0 supplement, there currently is a difference between the brand drug labeling and generic drug labeling. Once FDA approves a change to the brand drug labeling, the generic drug manufacturer is required to revise its product labeling to conform to the approved labeling of the corresponding brand drug. FDA advises that this update should occur at the very earliest time possible; however, FDA has determined that there is often a delay, of varying lengths, between the date on which revised brand drug labeling is approved and the date on which the generic drug manufacturer submits such labeling updates. The proposed rule, if finalized, generally would reduce the time in which all generic drug manufacturers make safety-related labeling changes by requiring generic drug manufacturers to submit conforming labeling changes within a 30-day timeframe.

Question 5b. Will you commit to considering carefully, before taking further action on this proposal, what impact it will have on public perceptions regarding the sameness of generic and brand-name equivalents?

Answer 5b. The proposed rule is intended to improve the communication of important drug safety information to health care professionals and patients. FDA has received a great deal of public input from stakeholders during the comment period on the proposed rule regarding the best way to accomplish this important public health objective.

FDA is carefully considering comments submitted to the public docket, established for the proposed rule from a diverse group of stakeholders including: consumers and consumer groups, academia (including economists), health care associations, drug and pharmacy associations, brand and generic drug companies, law firms, State governments, and Congress, including comments on how the proposed rule, if finalized, may affect public confidence in generic drugs and comments proposing alternative approaches to communicating newly acquired, safety-related information in a multisource environment. FDA also met with the Generic Pharmaceutical Association (GPhA) on September 8, 2014, to listen to their comments and views regarding the proposed rule, and a summary of this meeting has been posted to the public docket (FDA–2013-N–0500). In addition, FDA held a public meeting at which any stakeholder had the opportunity to present or comment on the proposed rule, or on any alternative proposals intended to improve communication of important, newly acquired drug safety information to health care professionals and the public. In the February 18, 2015, notice announcing the public meeting, FDA also reopened the docket for the proposed rule until April 27, 2015, to allow the submissions of written comments concerning proposals advanced during the public meeting. FDA will determine next steps based on our analysis of comments on the proposed rule and additional information submitted as part of the public meeting.

Question 5c. Under current Supreme Court precedent, FDA's proposal could expand generic drugmakers' potential exposure to tort lawsuits under State law. To what extent do you believe it is appropriate for FDA to consider this potential impact on the proposal's (a) cost assessment, and (b) policy merits?

Answer 5c. It is appropriate for FDA to consider whether the proposed rule, if finalized, would result in higher costs to generic drug manufacturers, and also to consider information from commenters who support an alternative to the regulatory changes proposed by FDA in the proposed rule.

SENATOR ROBERTS

Question 1. Congress was clear when it passed the Food Safety Modernization Act that FDA was to clearly distinguish in its regulations the difference between animal foods and human foods. Can you please explain why these rules are so similar and

how the agency accounted for Congress' intended risk-based approach to regulating the supply chain for both human and animal foods? If confirmed, will you commit to working with inspectors to ensure the nuances between the animal food industry and the human food industry are taken into account?

Answer 1. In the final preventive controls for animal food (PCAF) rule, FDA finalized baseline CGMP requirements for producing safe animal food. FDA recognizes that the CGMPs have to take into consideration the unique aspects of the animal food industry and provide flexibility for the wide diversity in types of animal food facilities. From our original proposed rule in 2013 to the supplemental proposal in 2014, we significantly revised the CGMPs based on feedback from the regulated industry. We received a number of comments from industry that supported the revised CGMPs in the supplemental proposal, but additional modifications were also requested. For the final rule, we revised the CGMPs, based on the comments received and existing industry standards. These modifications provide clarity, additional flexibility, and decreased prescriptiveness, while still maintaining a baseline to protect against animal food contamination that would be harmful to public health.

FDA developed the rule with risk-based processes in mind to ensure that, where appropriate, the requirements for hazard analysis and risk-based preventive controls were the same for both the preventive controls for human food and the PCAF rules. Consistency in the regulations is beneficial for industry, especially those that manufacture raw material and other ingredients that may be used in both human food and animal food. Although the regulations are similar, the flexibility provided allows for the application of the regulations to reflect the type of facility and the type of food being processed. We expect the application to look different between human food facilities and animal food facilities, based on the expected hazards and types of food being processed.

Application of the regulations will also differ across the animal food industry, given the great diversity of facilities, ranging from a small feed mill to a large pet food facility. We are committed to training our workforce and our State, local, and tribal regulatory partners to understand the flexibility built into the final rule and the nuances of how they may see it being applied in an animal food facility. We are working with both State regulatory partners and industry in the Food Safety Preventive Controls Alliance (FSPCA) to develop training that will be required for all investigators; both regulatory personnel and industry will receive the same base training. FDA is also working on development of training specific to regulators, which will include expectations of what one might expect to see in various animal food facilities. We are also working on the development of several guidance documents to support the final rule and will be engaging with industry during the process to seek their input as the documents are intended to help them achieve compliance with the rule. FDA is committed to making implementation of the animal food preventive control rule a success, and we recognize it will take continued collaboration with our State and local regulatory partners and industry to achieve that goal.

Question 2. I understand the FDA is spending much of its food safety resources on training and education, in addition to utilizing State partnerships. It is also important that inspectors interact with those they are inspecting in a consistent manner, while also considering the diversity of the food industry. While some changes and improvements were made when the rules were finalized, the agency did not go nearly far enough in simplifying, ensuring consistency, and reducing unnecessary paperwork burdens. Now that five of the seven FSMA rules are final, will you commit to ensuring that the implementation and enforcement of the rules is consistent and as simple as possible if confirmed?

Answer 2. Yes. FDA is committed to implementing FSMA efficiently and effectively, in collaboration with our State and local regulatory partners and industry. As part of this effort, we have developed a new inspection paradigm and enforcement strategies that reflect the flexible, systems-based approach of the new FSMA rules. This new paradigm involves a major re-orientation and retraining of more than 2,000 FDA inspectors, compliance officers, and other staff involved in food safety activities, as well as thousands of State, local, and tribal inspectors. The training emphasizes that inspections under the FSMA regulations must be performed consistently from one region to another, and by both Federal and State officials.

We are also working on the development of several guidance documents to support the final rules and will be engaging with industry during the process to seek their input as the documents are intended to help them achieve compliance with the rule. Through guidance and technical assistance, we will continue to work together to ensure that firms can tailor their food safety systems to meet their particular needs and exercise a myriad of flexible options under the new FSMA rules.

In addition, FDA has funded and is working with three private-public, university-based alliances, which are responsible for providing standardized curricula and establishing mechanisms to train industry and regulators on the requirements of the produce safety and preventive controls rules.

Question 3. What are the existing tools the agency has, and if confirmed, how do you plan to use these existing hiring authorities to fill the 1,800 vacancies within the agency?

Answer 3. Addressing FDA's hiring needs is one of my top priorities during my time at FDA. I have already begun working with FDA's human resources staff to help ensure that our internal processes are working as efficiently as possible.

FDA primarily uses title 5 and title 42 hiring authorities to fill positions. These authorities include various flexibilities facilitating the inclusion of veterans, disabled persons, students, minorities, and others, as applicable. To ensure that the 1,800 vacancies are filled in the Agency, we are working to implement a corporate recruitment strategy to identify and recruit for mission-critical scientific and professional positions in an expedited manner. This includes targeted outreach to professional and scientific organizations/communities, academia, and industry, to further support FDA's goals and objectives. Outreach efforts involve announcing vacant positions through various sources such as USAJOBS, social media, paid advertisements, professional and scientific organizations, among others. In addition, FDA is working to utilize all available hiring and compensation authorities to assist with recruiting and retaining hard-to-fill scientific and medical staff.

FDA and industry agree on the importance of the Agency having highly qualified experts who can efficiently and expeditiously review cutting-edge products, and conduct post-market surveillance activities. We appreciate that Congress and industry have recognized the necessity of having a highly skilled FDA workforce, and I look forward to working with you to address the challenges that FDA faces in recruiting and retaining the talented individuals the Agency needs.

Question 4. Over the past 2 years, four studies, including two published in the *New England Journal of Medicine* and one from the Institute of Medicine (IOM), have found that diets too low in sodium (<2,300 mg/day) result in negative health outcomes. As a cardiologist, why do you believe the government continues to push for population wide reduction in sodium intake knowing that it might be associated with an increase in cardiovascular disease risks? And if confirmed, would you continue to support this position?

Answer 4. U.S. Government efforts focus on reducing the average sodium intake in the United States for those aged 2 years and older from the current 3,400 mg/day closer to 2,300 mg/day. The 2013 IOM report entitled "Sodium Intake in Populations, an Assessment of the Evidence" reaffirmed that sodium intake levels are too high and should be reduced to 2,300 mg/day. This recommendation is also supported by the Scientific Report of the 2015 Dietary Guidelines Advisory Committee, which thoroughly considered the 2013 IOM Sodium Report and other evidence in their review. The 2010 DGAs recommended a reduction in sodium intake to less than 2,300 mg/day and a further reduction to 1,500 mg/day among African Americans, individuals with hypertension, diabetes, or chronic kidney disease, and individuals ages 51 years or older. Again, the focus of FDA is on the general population recommendation with gradual reductions in intake levels for the general population toward the 2,300 mg/day mark.

A large body of evidence indicates that as sodium intake increases, so does blood pressure (Aburto, et al., 2013; Sacks, et al., 2001; He, et al., 2013; Mozzaffarian, et al., 2014). High blood pressure is a leading risk factor for heart disease and stroke (Stamler, et al., 1993; Kannel, et al., 1996; van den Hoogen, et al., 2000; O'Donnell, et al., 1997, Prospective Studies Collaboration, 2002). It is estimated that about 41–45 percent of deaths due to heart disease and stroke are attributed to high blood pressure (Yang, et al. 2012; Danai, et al, 2009). Heart disease is the No. 1 killer of men and women in the United States and stroke is No. 5 (CDC, 2015). One in three adults in the United States have high blood pressure, with only half having it under control (Nwankwo, et al., 2013; Egan, et al., 2010). Reducing average sodium intake in the U.S. population can reduce blood pressure and is projected to save tens of thousands of deaths and billions of health care dollars each year (Coxson, et al., 2013; Bibbins and Domingo, 2010), including among people whose blood pressure is above 120/80 (Huang, et al., 2014a). Average dietary sodium intake in the U.S. population, aged 2 years and older, is about 3,400 mg/day before salt is added at the table, compared to a recommended intake of less than 2,300 mg/day 2015 DGAC Report.) Because about 75 percent of sodium in the diet of the U.S. population is estimated to be added during the manufacturing of foods and

preparation of restaurant foods, it is challenging for consumers to reduce their sodium intake (Anderson, et al., 2010; Mattes and Donnelly, 1991).

Some recent observational studies (Stolarz-Skrzypek, et al., 2011; O'Donnell, et al., 2011; O'Donnell, et al., 2014; Graudal, et al., 2014) are inconsistent with a large body of evidence that consistently shows a dose-response relationship between sodium intake and blood pressure (Aburto, et al., 2013; Sacks, et al., 2001; He, et al., 2013; Mozaffarian, et al., 2014; Eckel, et al., 2014). Results of these recent observational studies suggest low- and high-sodium intakes are associated with cardiovascular disease (CVD) events or deaths, and are inconsistent with other observational studies showing lower sodium intake is associated with lower risk of CVD (Cook, et al., 2014; Poggio, et al., 2015). Expert review of these studies by FDA and CDC scientific experts indicate that they do not shift the weight of evidence.

Like other studies reviewed by IOM in 2013 and an American Heart Association Scientific Advisory Committee in 2014 (Cobb, et al., 2014), these studies have major limitations in the selection of participants and/or measurement of sodium intake. For example, a problem with some of these studies is the possibility for reverse causation. Reverse causation could occur if participants who have a major risk factor for CVD, such as chronic kidney disease, have lowered their sodium intake because of medical advice or because their illness reduces the amount of food consumed. Another major weakness is use of a measure of short-term sodium intake, like a single 24-hour urine collection or a spot urine specimen that does not accurately reflect an individual's long-term exposure. Many studies show a spot urine specimen can over or under-estimate individual daily sodium intake by as much as 3,000 mg or more (Mente, et al., 2013 and Cogswell, et al., 2015). This means people with high sodium intake are mis-classified as having low-estimated sodium intake and vice versa. This could result in people with low-estimated sodium intake falsely appearing to have an increased risk of CVD.

Question 5. I support encouraging industry to gradually lower sodium in the foods that are available to consumers, so that they will have more options if they choose to consume less sodium. The 2015 Dietary Guidelines Advisory Committee (DGAC) recommended that the FDA should modify the generally recognized as safe (GRAS) status of salt in processed foods to reduce the salt content of the food supply. Given the Dietary Guidelines Advisory Committee's stated research gaps, and the science that increasing finds adverse health outcomes at low-sodium intake levels, would you suspend any action in this regard until further research is conducted and a comprehensive review of all related science is concluded?

Answer 5. The Scientific Report of the 2015 Dietary Guidelines Advisory Committee referenced the 2010 IOM report on Strategies to Reduce Sodium Intake in the United States in their report. It was this 2010 IOM report that recommended the FDA should set mandatory national standards for the sodium content in foods by modifying the generally recognized as safe (GRAS) status of salt added to processed foods to reduce the salt content of the food supply.

Americans are consuming excess sodium, and this excess contributes to increased risk of hypertension, a primary contributor to stroke and heart disease. Encouraging industry to voluntarily reduce sodium in products so that consumers have more options does not require bringing consumers into an excessively low sodium intake range such as 1,500 mg/day. In fact, with average sodium intake at 3,400 mg/day there is considerable work to do to phase-down intake to the recommended level of 2,300 mg of sodium per day, which is consistent with the current State of the science.

We are in support of conducting well-designed research to add to the knowledge base on sodium intake in different population groups.

Question 6a. The 2015 Dietary Guidelines for Americans provides the basis of nutritional information for numerous Federal programs, including the Food and Drug Administration's Nutrition Facts label. The Dietary Guidelines are published jointly by the Department of Health and Human Services and the Department of Agriculture and are informed in part by an Advisory Committee, but most importantly are a source of nutritional and dietary information and guidelines. The 2015 Dietary Guidelines have not been finalized, yet the FDA is proposing to establish a new percent daily value (DV) for added sugars on the Nutrition Facts labels of packaged foods.

Is it appropriate for FDA to propose a policy change that is based on an unofficial Advisory Committee recommendation before the Departments of HHS and Agriculture finalize the 2015 Dietary Guidelines for Americans? And how will you ensure FDA upholds its use of scientific consensus standards when proposing a policy

change, such as proposing a change to the Daily Recommended Value for added sugars?

Answer 6a. In July 2015, FDA released a supplemental proposal to establish a Daily Reference Value (DRV) of 10 percent of total calorie intake from added sugars. The comment period for the proposal closed on October 23, 2015. The Agency is reviewing and considering the comments.

In developing the proposal, FDA did consider the scientific evidence underpinning the recommendations provided in the Dietary Guidelines Advisory Committee's report to set a DRV for added sugars. In considering any final proposal, I can assure you that FDA will continue to use the best available science and evidence.

Question 6b. Will you commit to ensuring that the agency's proposal to require the disclosure of added sugars per serving on the Nutrition Facts label is adequately understood by consumers and provide scientific evidence that supports such consumer comprehension before finalizing any new labeling requirement?

Answer 6b. FDA released the results of its consumer studies on added sugars in the Agency's supplemental rulemaking in July 2015. We initiated this research to explore consumers' potential interpretations of Nutrition Facts labels that include added sugars declarations. The Agency is considering and reviewing the comments on this consumer research. This research would inform any consumer education if added sugars are declared on the label. FDA believes that a multi-component, coordinated consumer education campaign should be implemented to make any new food label a successful tool in continuing to help consumers understand and use the label to assist them in making healthy food and beverage choices.

SENATOR CASSIDY

Question 1. Back in September I chaired a hearing where Dr. Woodcock spoke to the committee about implementation of the biosimilars pathway. She was, as always, very responsive and detailed in answering the many questions about the science and promise of biosimilars. However, she was repeatedly questioned about the timing of outstanding guidances, including those on labeling and interchangeability of biosimilars. She told the committee that those additional guidances are expected in 2015. Can you assure the committee that the outstanding biosimilars guidances will be published by the end of this year?

Answer 1. FDA has published the following final guidances related to biosimilars: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following draft guidances since 2012: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act; Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009; and Nonproprietary Naming for Biological Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above. Upcoming guidances are expected to include: Considerations in Demonstrating Interchangeability to a Reference Product; Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity; and Labeling for Biosimilar Biological Products.

FDA is diligently working to issue guidance on issues that have been identified by FDA and key stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide information to assist biological product developers—sponsors/companies—with bringing biosimilar and interchangeable products to market. FDA is continuing to clarify its approach to implementation of the BPCI Act to further facilitate sponsors' development of biosimilars and interchangeable biological products.

Question 2. Despite FDA reporting a decline in shortages in the last few years, we are still hearing that shortages are a substantial concern for providers. How do you reconcile the decline in shortages FDA is tracking with the continued struggles providers are reporting? What do you see as the key things that the agency still needs to do to better position itself to address shortages?

Answer 2. The Drug Shortage Staff in FDA's CDER is tracking numbers of new shortages annually, and this has greatly decreased since 2011. There were 44 new

shortages in both 2014 and 2013 compared to 117 new shortages in 2012. These numbers are significantly lower than the 251 new shortages recorded in 2011.

FDA is well-positioned to work with manufacturers to find ways to prevent or reduce a shortage's impact on patients, provided we are aware that there is a potential for a shortage. Early and timely notification by manufacturers has been aided importantly by Executive Order 13588 and by passage of FDASIA, and has enabled FDA and manufacturers to prevent 195 drug shortages in 2011; 282 drug shortages in 2012; 170 drug shortages in 2013; and 101 shortages in 2014. FDA has also used other tools to prevent or mitigate shortages, including expediting the review of shortage-related ANDAs. Since the enactment of FDASIA on July 9, 2012, through December 31, 2014, CDER's Office of Generic Drugs expedited the review of 298 applications, including 182 abbreviated new drug applications and 116 supplemental ANDAs, to prevent or mitigate drug shortages.

FDA also continues to improve its system for data tracking and analysis for drug shortages, with the Drug Shortage Data System (DSDS), which was put into place in 2014 and enhances the efficiency and consistency of drug shortage data entry. FDA is continuing to integrate DSDS with other CDER data systems to improve its drug shortage tracking and reporting capabilities. FDA works to find ways to mitigate drugs shortages; however, there are still shortages that persist for longer periods of time. There are a number of factors that can cause or contribute to drug shortages that are outside of the control of FDA. These factors include:

- Production delays at the manufacturer and delays companies have experienced receiving raw materials and components from suppliers;
- Discontinuations—for example, older drugs that are discontinued by companies in favor of newer, more profitable drugs;
- In the case of older sterile injectable drugs, limited production line capacity, which, combined with long lead times and complexity of the manufacturing process, results in vulnerability to shortage.

Drug shortages remain a top priority for FDA. Although FDA cannot directly affect many of the business and economic decisions that contribute to drug shortages, FDA is well-positioned to play a significant role as manufacturers work to restore lost production of lifesaving medications. While important progress has been made in preventing drug shortages from occurring, and decreases have been seen in the total numbers of new shortages, FDA continues to work to ensure that patients in the United States will have access to the medicines they need.

Question 3. Congress has made every effort to support the advancement of science, most notably giving FDA explicit flexibilities in FDASIA to review new drug applications under accelerated approval or via "breakthrough" status. What we intended—and in some cases FDA has embraced—is for the Agency to maintain the highest safety standards but to think creatively about what data can be provided where the traditional large, placebo-controlled clinical trial is simply infeasible or unethical due to the rarity and severity of a disease or the small patient population. We intended for FDA to re-evaluate the risk-benefit model and allow patients a voice in the process, where higher risk and greater uncertainty may be ok with them given the severity of their disease. For serious and life threatening diseases, particularly for children, we intended for some new drugs to move through the approval process more quickly, allowing a drug sponsor to submit post market data to confirm initial safety and efficacy data. And we intended for FDA to take a team approach on drug applications where the drug could be a "game changer," by allowing for additional communication between the Agency and the sponsor, including access to the senior management team.

Yet, despite our best intentions and FDA's best intentions in embracing FDASIA, I continue to hear from patients and innovators that there are significant inconsistencies across the review divisions. I understand the Oncology Division has a long track record of utilizing the accelerated approval pathway and as a result there are fewer death sentences from cancer. And I have been told recently the Metabolism and Endocrinology division has applied regulatory flexibility by allowing natural history data to serve as historical controls in support of at least 2 approvals in 2015 of rare disease treatments. Congress explicitly expanded the tools adapted in the battle against cancer and HIV/AIDS to other diseases and I applaud FDA for these examples of using them to the benefit of patients.

On the other hand, I have also been told that the Neurology Division continues to question that flexibility, seemingly resistant to approaches that are not traditional, placebo-controlled large scale trials that may be both infeasible and unethical for very sick patients, including children. This committee questioned Dr. Hamburg at a hearing about this very division in March 2014. And yet I am compelled to raise the same essential question with you again today.

This is not about whether you approve or deny drug applications. The question is about embracing the science, technology and approval pathways that allow new treatments to get to patients under the same high safety standards. It is about FDA adapting across the board to patient needs by allowing more and consistent regulatory flexibility, so all patients can benefit as they have in the case of cancer and HIV.

If confirmed, could you please share with me your ideas for improving the adoption of FDASIA's flexibilities across review divisions? How will you make flexibility the rule for rare diseases?

Answer 3. I share your interest in improving flexibilities across review divisions, including for rare diseases, building on FDA's efforts to date. We've improved the efficiency and predictability of clinical drug development by developing tools such as biomarkers and surrogate endpoints—markers of drug effect that do not directly represent an improvement in how a patient feels or functions, but are reasonably likely to predict a clinical benefit. In the early 1990s, only 5 percent of FDA's new drug approvals were for targeted therapies using biomarkers and in 2013, 45 percent of FDA's approvals were for targeted therapies using biomarkers. FDA has approved hundreds of drugs on the basis of validated surrogate endpoints using traditional approval. FDA has also frequently relied upon surrogate endpoints for accelerated approval. When a biomarker or surrogate endpoint is already validated, accelerated approval is not needed, because confirmatory post-approval studies generally are not necessary in this context to verify and describe the drug's clinical benefit. Whether accelerated approval can be utilized rests on the availability of biomarkers and surrogate endpoints applicable in a given disease. In some areas, like oncology, robust research has focused heavily on development of these, but that is not necessarily the case in other disease areas.

FDA published guidance in 2014 on our various programs to expedite the development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. FDA expects this guidance to help sponsors consider a range of possible endpoints that might support accelerated approval, and we are committed to working closely with them to facilitate the use of accelerated approval where appropriate to help bring needed drugs to patients. We know this cuts across many therapeutic areas and rare diseases offer some of the biggest challenges. In fact, CDER and OND have established a Rare Diseases Program to facilitate OND's review divisions strategic engagement in best utilizing tools like accelerated approval to make most efficient use of clinical trials and ensure the most creative approaches to product development.

For example, FDA used the accelerated approval pathway to approve Tysabri (natalizumab), a treatment for multiple sclerosis, based on a large therapeutic effect on relapse rate through approximately 13 months of treatment, despite uncertainty about the durability of the observed effect. As a condition of its accelerated approval, the sponsor was required to continue the existing trials into the post-marketing period to confirm durability of the observed effect at 2 years.

These are exciting times as we experience simultaneous revolutions in the biological and information sciences. We expect that the astounding increase in knowledge of biological systems enabled by whole genome sequencing, cloud computing, social media, and wearable devices to monitor physiology will create challenges to traditional thinking. And we are confident that this increased knowledge will continue to expand the pipeline of new therapies. We are prepared to deal with the product of this scientific investment by using regulatory paradigms that match the State of the science and by supporting dissemination of the latest knowledge applied to drug development.

In this paradigm that takes advantage of the depth of this new biomedical information, it will be critical to continue to support ongoing clinical trials and observational studies to ensure sufficient knowledge of the benefit-risk profile of therapies as they evolve into broad use. Even the best of the current surrogates such as systolic blood pressure cannot substitute for the entire cumulative effects of a drug on the intended biological target and for off-target effects.

FDA has in place standard operating procedures and guidance on good review practices for management of the review of marketing applications that are followed by all CDER review divisions. In addition, reviewers undergo rigorous training to ensure consistency in application of guidance, regulations, and best practices. However, like drug development strategies, review times can differ depending on the condition being treated and what is known about an individual product. Review times can be shorter for certain conditions, such as some cancers, since many cancer drugs qualify for one or more of our expedited review programs and may present a very favorable benefit-risk profile and a more limited amount of data that must be reviewed prior to making an approval decision. It is a misconception that speedy

reviews only occur in oncology, however. For example, approval of the first drug for cystic fibrosis was accomplished well ahead of the PDUFA goal date.

FDA's drug approval process—the final stage of drug development—is the fastest in the world, which means that Americans typically have first access to new drugs when they are demonstrated to be safe and effective. But even as our Agency has transformed the approval process—approving 51 new molecular entities and biological products last year alone, including more new orphan drugs for rare diseases than in any previous year—drug discovery and development is not keeping pace for many diseases (see 2014 Novel New Drugs Summary (January 2015), at *http://www.fda.gov/downloads/drugs/developmentapprovalprocess/druginnovation/ucm430299.pdf*).

Speeding the availability of safe and effective drugs that treat serious diseases is in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. To encourage innovation, we will continue to work with other government agencies and the health care community, including members of patient groups, academia, and industry. It will take a collaborative effort to improve our Nation's understanding of certain diseases and to translate any resulting scientific discoveries into cures.

SENATOR MURRAY

Question 1a. As we've discussed, FDA has jurisdiction over critical public health issues beyond the regulation of drugs and medical devices. The agency is also charged with protecting kids from the dangers posed by tobacco, giving Americans the nutrition information they need to make decisions about the foods they choose for themselves and their families, and ensuring the safety and nutritional soundness of our food supply, to name a few.

I'm particularly eager to see full implementation of two long-awaited FDA rules—the first to ensure menu labeling in restaurants and similar establishments, and the second expanding FDA regulation of tobacco products to include e-cigarettes and other products—a rule that urgently needs to be finalized.

Can you tell me more about what your priorities will be when it comes to these kinds of public health protections?

Answer 1a. Finalizing the tobacco deeming rule is of the highest priority for the Agency and the Administration. We share your sense of urgency on this important matter. We are working diligently to finalize the rule as soon as possible. The rule has undergone extensive internal review within FDA and HHS and is now under review at the Office of Management and Budget.

Once the proposed rule is finalized, some provisions (e.g., establishment registration, product listing, ingredient listing, and the adulteration and misbranding provisions of the statute) in the FD&C Act would automatically apply to all deemed tobacco products. In addition, other provisions of the proposed rule would apply to covered, newly deemed tobacco products—if included in the final rule—such as: minimum age and identification restrictions to prevent sales to underage youth; requirements to include health warnings; and a prohibition of vending machine sales, unless in a facility that never admits youth.

When the rule is final, FDA will prioritize implementation, including educating industry on how to comply with the requirements in the rule. In addition, FDA considers the deeming rule to be a foundational regulation, which, once finalized, will allow the Agency to take further actions regarding critical public health issues.

With respect to menu labeling, on September 11, 2015, FDA issued the draft guidance document titled "A Labeling Guide for Restaurants and Retail Establishments Selling Away-From-Home Foods—Part II (Menu Labeling Requirements in Accordance with 21 CFR 101.11." We currently anticipate issuing the final guidance in late spring 2016.

FDA will be focusing the first year of implementation on providing educational and technical assistance for persons and covered establishments, and for our State, local, and tribal regulatory partners to support consistent compliance nationwide. Since publication of the final rule, FDA has been very active in attending conferences as invited presenters, participating in industry-sponsored webinars and conference calls, and meeting with industry representatives to help them understand the provisions of the rule and how to implement the provisions. We will continue to be available for these types of activities. In addition, we have established a special mailbox for covered establishments (*CalorieLabeling@fda.hhs.gov*) to contact us with their questions.

Question 1b. Once FDA finally asserts their jurisdiction over additional tobacco products, what steps will you take to make sure the agency moves swiftly to fully

use its new authority and ensure that Americans—and especially kids—are protected from the full range of tobacco products?

Answer 1b. FDA has vigorously enforced the youth access and marketing restrictions for currently regulated tobacco products. This includes conducting more than 522,000 retail compliance checks nationwide to ensure retailers are complying with the law, initiating enforcement action when violations are observed, and providing compliance training and education to retailers so they understand the requirements under the law. These efforts will continue for newly deemed products, once the proposed rule is finalized.

As stated above, when the rule is final, FDA will prioritize implementation of all aspects of the rule and take further actions, when warranted, to protect the public health.

Question 1c. I know that limiting the amount of the sodium in the food supply is something the agency has been thinking about for a long time—and I'm guessing, as a cardiologist, as issue of personal interest to you. When do you think we might finally see action on this issue?

Answer 1c. I do have a strong interest in this issue and I can assure you that FDA is continuing to work diligently in this area, but we do not have a specified timeframe for issuing a proposal.

Question 2. In April 2015, Senator Isakson and I led a letter from a bipartisan group of 29 Senators to Acting Commissioner Stephen Ostroff stating,

> "Ensuring that women have the best advice that reflects the latest nutrition science about what to eat during pregnancy, for their health and the health of their children, is of the utmost importance."

If confirmed, will you ensure that pregnant women receive final nutrition advice that is clearly presented and consistent with the latest science?

Answer 2. FDA shares your interest in ensuring that pregnant women have access to sound, science-driven, and clearly understandable recommendations that enable them to make informed decisions about their diets. The final seafood consumption advice for pregnant women is undergoing interagency review. We will continue to take steps to ensure that it is reflective of the latest nutrition science. Completing the updated advice remains a priority for the Agency.

Question 3. One of the many responsibilities of the Food and Drug Administration is to consider aspects of food and nutrition labeling for Americans. As you are aware, the *Dietary Guidelines for Americans* are a set of recommendations that encourage Americans to eat healthy foods like fruits, vegetables, whole grains, lean meats, eggs, and nuts. Current FDA labeling regulations, however, do not allow some of these foods to be labeled as "healthy." Can you explain steps you would take to ensure FDA's approach to nutrient content claims—specifically the use of the term "healthy" to make a nutrient content claim—reflect current Federal dietary guidance and scientific evidence?

Answer 3. The Dietary Guidelines for Americans provide information and advice for choosing a healthy eating pattern. Included in this advice are food choices that are emphasized and encouraged to help Americans move toward healthful eating patterns. Healthful eating patterns can be achieved through a wide variety of foods, not just foods that are considered "healthy" individually. The recommendations include a wide variety of food choices which may not, individually, have nutrient profiles consistent with the definition of a "healthy" claim.

FDA's regulations provide a set of minimum nutrient content standards for individual foods to be considered "healthy" and bear a "healthy" claim. A "healthy" claim can generally be used if a food contains less than 3 grams of fat, 1 gram of saturated fat, 60 mg of cholesterol and 420 mg of sodium per reference amount customarily consumed.

It is possible that a food may not meet these minimum standards, yet may be able to contribute to an overall healthful eating pattern. To illustrate, a food can contribute an essential nutrient, such as calcium, to an overall healthful eating pattern, yet also contain nutrients that are recommended to be limited in the diet, such as saturated fat. This individual food could contribute to an overall healthful eating pattern, yet not be considered an overall "healthy" food by itself.

While we try to ensure that all regulations related to nutrition labeling are consistent with the Dietary Guidelines for Americans, it is important to understand that the focus of the Guidelines is healthful eating patterns. FDA will continue to monitor and assess the most recent science to update our nutrition and nutrition-related regulations as needed.

For example, we are currently working to update our requirements for the Nutrition Facts label.

Question 4. As you know, an increasing amount of manufacturing of both active pharmaceutical ingredients and finished pharmaceutical products, as well as testing for new drug applications, is occurring in foreign countries. How can we better ensure that drugs, devices, food, and other products regulated by the FDA—that are developed and made outside our borders—meet the quality and safety standards we require in this country to protect the public?

Answer 4. All drugs delivered to patients in the United States are subject to the same high standards, regardless of country of origin. Registered drug manufacturing facilities in foreign countries are subject to FDA inspection, with inspection frequency determined on the basis of risk to patients. FDA employs a highly trained global inspectorate, which is skilled in evaluating processes and uncovering manufacturing problems during inspections. Whenever FDA investigators find product quality issues that potentially implicate drug safety and efficacy, the Agency takes appropriate action, which could include issuing a Warning Letter or import alert, or taking other enforcement action. Because of resources made available under the Generic Drug User Fee Amendments of 2012 (GDUFA), FDA has been able to significantly increase the number of inspections (both surveillance and pre-approval) it conducts in foreign countries (e.g., India). Having in-country investigators allows FDA to be more responsive to high-priority public health and safety issues. FDA utilizes risk-based strategies and local intelligence in order to maximize its resources to conduct timely and high quality inspections. Such strategies may include the establishment's compliance, records, and recalls-related history, as well as the inherent risks of the drug produced at the facility.

Question 5. Please provide a description of the work that you performed in creating and leading the Duke Clinical Research Institute including what you believe is some of the most significant work you conducted or oversaw at DCRI.

Answer 5. The Duke Clinical Research Institute (DCRI) was established in 1996 by Duke University Medical Center (Duke) as an institutional resource for Duke faculty members conducting clinical research; including clinical trials, health services research and health policy research (*www.dcri.org*). I was appointed as the founding director of the DCRI in 1996 and served in this capacity until 2006. The DCRI operates as a multidisciplinary research unit within the Duke University School of Medicine. The mission of the DCRI is to "develop and share knowledge that improves the care of patients through innovative clinical research."

As part of their academic endeavors, Duke faculty members pursue grants and contracts for research studies based on their individual clinical and research interests. DCRI staff provide assistance to the faculty in preparing grant applications and proposals for potential studies sponsored by government agencies, non-profit organizations, and foundations and commercial entities.

When grants or contracts are awarded, the faculty member serves as the principal investigator of a study and a team of DCRI staff members and faculty (including statisticians, project managers, data managers, regulatory associates, etc.) is assigned to perform operational and regulatory activities required for the conduct of the study. Following completion of the study, the faculty member is responsible for conducting an independent analysis and interpretation of the study results, and disseminating the results through the peer-reviewed literature and presentations at scientific meetings.

In my role as director, my responsibilities included the following:

- Providing institutional leadership and a vision for directing the faculty toward the future of clinical research while meeting societal needs.
- Overseeing the work of faculty members and staff involved in research studies awarded to the DCRI.
- Overseeing the clinical, operational and financial performance and ensuring regulatory compliance of all research studies conducted at the DCRI.
- Ensuring the publication and dissemination of the results of studies conducted at the DCRI.
- Ensuring that DCRI operational capabilities are aligned with the research interests of the faculty.
- Developing a cadre of faculty members and staff who are experts in clinical research methods.
- Educating and training junior faculty, fellows, and students in clinical research.
- Ensuring a balanced portfolio of research studies by funding source to achieve financial self-sustainability and being a prudent steward of institutional resources.

Significant accomplishments:

• Developed a model for academic coordination of large scale research, including direct involvement in national policies on CMS reimbursement for clinical trials, conflict of interest reporting, and management and policies for sustaining independent voice for academics and clinicians in design and interpretation of clinical research.
• Expanded from a cardiology-focused research unit to include almost 20 therapeutic areas, ranging from pediatrics to obstetrics and gynecology, anesthesiology, infectious diseases, mental health, drug abuse prevention and treatment, and others. To date, DCRI has conducted studies at 37,000 research sites in 65 countries and enrolled over 1.2 million patients.
• Served as a major hub of clinical trial networks, with Federal funding from over 15 NIH Centers and Institutes.
• Established a nexus of patient registries in partnership with medical professional societies to improve healthcare quality and prevent medical errors. The registries in acute cardiac care and cardiac surgery have become national models with adoption of performance measures by CMS.
• Participated in multiple efforts on transparency of results of clinical research including major role in the development of *ClinicalTrials.gov* as a member of the Lister Hill Center (National Library of Medicine) Board and a contributor to the development of data fields and analytical efforts with the database.
• Developed one of the country's largest training programs for clinical research and expanded the program to an international reach.
• DCRI published over 800 manuscripts per year in the peer-reviewed literature.

Question 6. Please provide a description of the work that you performed in creating and leading the Duke Translational Medicine Institute including what you believe are some of the most significant work you conducted or oversaw at DTMI.

Answer 6. The Duke Translational Medicine Institute (DTMI) was established in 2006 to serve as an academic home for Duke's clinical and translational research community. I was appointed as the founding director of the DTMI in 2006 and served in this capacity until joining the FDA in February 2015. DTMI was created to expand the DCRI model to faculty across the entire translational research spectrum in concert with Duke's first Clinical and Translational Science Award from the NIH (the major translational research grant offered by the NIH at the institutional level). The mission of DTMI is to,

> "improve individual and population health by catalyzing translation across the continuum of scientific discovery, clinical research care delivery, and global health."

The DTMI serves as an umbrella organization including the Translational Research Institute (bench to bedside research), the Clinical Research Institute (described above) and the Duke Center for Community and Population Health Improvement. It functions as integrated support structure to facilitate the efforts of faculty members to accelerate the translation of basic science discoveries into new medical therapies to advance patient care and to develop methods of improving population health through community engaged research and the use of electronic records and analytics to improve access and effective implementation of health services. DTMI provides a continuum of resources and training, such as statistical expertise, degree-granting programs, regulatory affairs, project management, and biobanking.

In my role as DTMI director, my responsibilities mirrored those of my prior role as DCRI director, with the inclusion of a much broader scope of research ranging from pre-clinical translation to population health and community engaged research.

Significant accomplishments:

• Established the Duke Center for Community and Population Health Improvement to foster collaborations among community partners, researchers, and health system leaders with the goal of decreasing health inequities in the Southeast and across the country through studies designed to intervene at both the individual and community levels. This includes a CMS-funded project that uses geospatial mapping technology to identify residents in four counties in West Virginia, Mississippi, and North Carolina at greatest risk of poor health outcomes and implement interventions to achieve the "triple aim" of improved outcomes, better care and lower cost.
• Launched a major effort to develop innovative approaches for conducting pragmatic, patient-centered clinical trials. Served as the coordinating center for the NIH-funded Health Care Systems Research Collaboratory to increase the efficiency of clinical trials by using data from electronic health records; and the PCORI-funded National Patient-Centered Clinical Research Network to establish national networks of health systems, researchers, health care providers, and patients conducting clin-

ical trials that answer "real-world" questions most important to patients and their families.

• Created a regulatory affairs group to provide academic investigators with access to the regulatory expertise typically found in industry and assist them in navigating the regulatory process required to develop new diagnostic and therapeutic technologies. This group improved institutional compliance by creating a central database of regulatory submissions by Duke investigators and providing extensive training in regulatory requirements. This group is considered a model among other academic centers.

• Launched "The MURDOCK Study," a longitudinal health study involving the populations of Kannapolis/Cabarrus County, NC. The study aims to collect genetic and behavioral health profiles from 50,000 participants using participatory research methods to involve the entire community in the design and interpretation of the study. This has been described as a modern Framingham Study (a landmark study cardiovascular health). Over 11,000 participants have been enrolled to date.

• Developed a mechanism for all Duke investigators to access statistical expertise to improve research quality. The increased accessibility of these resources helped to facilitate a change in institutional culture regarding the value and importance of formal quantitative expertise, which is increasingly critical to ensure that research results are reproducible.

Question 7. In your hearing you testified that you were unable to undertake as much as 70 percent of the clinical trial work that was proposed because industry companies were not willing to agree to DCRI's requirements that all data from the trials be housed at DCRI. Why is it important that academic research centers maintain control of study data and why are some industry companies unwilling to agree to this requirement?

Answer 7. Under my leadership, the DCRI never and would never participate in coordinating a multi-site clinical trial without a contractual agreement that specifies the right to full access to the study data and to conduct its own analysis and interpretation of the data.

The independent role of the academic in the analysis and interpretation of the study data is an important element of the research enterprise. I have been a strong and consistent advocate for transparency through both *www.ClinicalTrials.gov* and the creation of access through independent coordinating centers. As discussed below, when industry controls the questions asked by the study, the data collection, and the analysis, there is significant bias because of the direct financial interest involved. Although academic investigators may have other biases, when they are conducting research in the context of their role as a faculty member in a university, there is a contract between the university and the industry sponsor, which includes the independent right to publish. This provides a balancing factor that I believe is important to ensure that the questions addressed by clinical trials are in the interest of patients, the data collected are not biased and the analyses have a perspective independent of the sponsor. The important role of patients and their advocates is discussed in the response to question 15.

Unfortunately, the majority of multi-site, industry-sponsored clinical trials do not have an academic coordinating center. Individual research sites that do not have coordinating center functionality do not have copies of the entire database, and if they did, they typically do not have the expertise to conduct the analyses. Thus, I believe that the role of academically based, not-for-profit coordinating centers is important to the clinical trials process.

While most major academic medical centers have some coordinating center function, there are only a limited number who are capable of conducting large multinational trials like the DCRI. The majority of multi-site, industry-sponsored clinical trials are coordinated in-house by the sponsor or outsourced by the sponsor to a for-profit contract research organization (CRO). In the early years of the DCRI's existence, it was common for industry sponsors to be highly resistant or even unwilling to allow full access to the study data because of their view that, in the event of a negative trial result, it would not be in their financial interest for findings to be made public.

It is now customary for medical journals to require that the authors of a manuscript attest that they had full access to the data and ability to analyze the data independent of the industry sponsor. The recommendations of the International Committee of Medical Journal Editors (ICMJE) now state that,

"we will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication." [8]

I have been a strong and consistent advocate for transparency through both[9] and the creation of access through independent coordinating centers.[10] The composite of all of these efforts has changed the landscape, and industry sponsors are now much more willing to agree to independent analysis.

Question 8. The 2011–14 conflict of interest statements filed by you that list the names of all private companies from whom you received consulting fees or other funds are publicly available on the Duke Clinical Research Institute website. Please explain the policy of DCRI regarding submission and posting of these conflict of interest disclosures, why that policy exists, and how long it has been in place.

Answer 8. The DCRI, as part of Duke University, abided by University policies. Like most major universities, Duke faculty members have the right to participate in private consulting 1 day per work week. All consulting must be reported to the University conflict-of-interest committee, and these consulting engagements are screened for the potential of conflict of interest and conflict of commitment by relevant committee members and institutional leaders. All of this information is kept within an institutional database to ensure followup.

I decided to begin publicly posting my interactions with industry to set an example for transparency, and DCRI created the venue for posting. Many DCRI faculty followed suit, but it was not a requirement of DCRI policy.

Question 9. Along with a number of other researchers at Duke University you receive consulting payments from industry companies through Faculty Connection, LLC. Please describe the purpose of Faculty Connection and the services that it performs for its consultant partners. Please include a description of the administrative fees and how excess administrative fees are used.

Answer 9. Faculty Connection, LLC was established by a group of Duke faculty members to provide administrative support for the faculty when they participate in consulting activities involving private industry. It has expanded over time to include faculty from several other institutions with similar needs.

It is designed to ease and consolidate the administrative burdens on individual faculty as they participate in consultation activities with industry on personal time and create greater efficiency for their work. Among the support it provides is:

- filing administrative paperwork required by the University, including summaries to facilitate accurate reporting to university conflict-of-interest oversight committees,
- ensuring compliance with legal and ethical requirements,
- negotiating contracts and ensuring that the contracts are in compliance with university policy and protect the rights of academic faculty to remain independent, and
- billing and accounting.

Payments for consulting activity are made directly to Faculty Connection, which retains 20 percent of the fees for administrative overhead (primarily to cover staff salaries), and the faculty member receives the remaining 80 percent. Since its inception, Faculty Connection has donated the proceeds not consumed by administrative costs to Duke University (and Stanford University beginning in 2013) to fund research and education activities for trainees.

In 2014, the following contributions were made by Faculty Connection to Duke University and Stanford University:

- $15,000 to the Stanford University Department of Medicine Residency Program for house staff research;

---

[8] International Committee of Medical Journal Editors. Sponsorship, Authorship, and Accountability (2007). Available at *http://www.icmje.org/news-and-editorials/update__spon__sep2001.html*.

[9] *Characteristics of clinical trials registered in ClinicalTrials.gov*, 2007–10. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. *JAMA*. 2012 May 2;307(17):1838–47. doi: 10.1001/*Jama*.2012.3424. PMID:22550198. *Compliance with results reporting at Clinical Trials.gov*. Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. N Engl J Med. 2015 Mar 12; 372(11):1031–9. doi: 10.1056/NEJMsa1409364. PMID:25760355.

[10] *Eur Heart J.* 2010 Apr;31(8):911–7. doi: 10.1093/eurheartj/ehp550. Epub 2010 Feb 3. *Toward a new order in cardiovascular medicine: re-engineering through global collaboration.*

Califf RM, Armstrong PW, Granger CB, Harrington RA, Lee K, Simes RJ, Van de Werf F, Wallentin L, White HD; Virtual Coordinating Centre for Global Collaborative Cardiovascular Research Organization.

• $30,000 to the Duke Clinical Research Institute (DCRI) fellowship fund to support current and future fellows including the adult cardiology fellows;
• $24,000 to the Duke Department of Medicine for research and pilot projects performed by residents and/or house-staff. The main purpose of the donation is to help the department encourage and support residents as they start their research careers;
• $15,000 to the Duke Department of Pediatrics for research and pilot projects performed by residents, house-staff, and trainees to support research careers; and
• $4,000 to the Duke Cancer Institute to train and provide research opportunities for the residents and or house-staff.

2013 Contributions to Duke and Stanford Universities totaled $115,000.
2012 Contributions to Duke University totaled $154,000.
2011 Contributions to Duke University totaled $100,000.
2010 Contributions to Duke University totaled $ 75,000.

Question 10. At your hearing you stated that you have a personal policy of donating all consulting fees received from industry to charitable organizations of your choosing. Is it correct that, not including funds paid toward clinical trial work conducted at Duke, all consulting fees you have received from industry have been paid to you through Faculty Connections and subsequently donated according to your long-standing practice?

Answer 10. Yes, this is correct.

Question 11. Please list any additional measures that you have taken to ensure that the scientific integrity of the clinical trial work you have undertaken in your career it is not compromised as a result of industry sponsorship and funding.

Answer 11. In addition to publishing the results of all clinical trials I have conducted throughout my career, I have publicly posted my Duke conflict-of-interest information since 2006, and donated all consulting fees to charity. I have been intimately involved in the development of structural and policy changes in the global research enterprise to increase transparency and reduce bias in the conduct, analysis, and reporting of clinical trials.

For the past three decades, I have worked with global colleagues who are experts in medicine, clinical research methodology, and medical ethics to develop new mechanisms to ensure that the data obtained from individuals who consent to participate in a human experiment (i.e., a clinical trial) are evaluated by parties who do not have a financial interest in the success or failure of the treatment under study, and who, by virtue of their employment as a faculty member in a university, are guaranteed the right to academic freedom. I do not use the term "human experiment" lightly, because asking someone to volunteer for a study carries with it a responsibility to do the best job possible to ensure that the trial is conducted properly and that the result of the trial will contribute to generalizable knowledge to help future patients.

One such mechanism is the establishment of steering committees for an individual clinical trial, comprised of academic investigators from multiple institutions and countries, to serve as a collective body to interact with the industry sponsor in developing the protocol and overseeing the operational conduct of the trial. This approach minimizes the influence of any given individual, ensures inclusion of a wide range of perspectives and opinions, and provides a formal structure for decision-making. The steering committee does not include representation from the sponsor but may have one or two sponsor representatives to ensure effective communication.

Another mechanism is the use of an independent academically based analytical center which is responsible for receiving data collected during a trial, ensuring the accuracy of the data, and analyzing the data following the conclusion of the trial. These are often referred to as Data and Statistical Coordinating Centers. This structure allows the database to be maintained by a party external to the industry sponsor and for the data to be fully analyzed before the results are shared with the industry sponsor.

A third mechanism is the formation of data monitoring committees, comprised of independent experts who oversee the conduct of the trial and have access to the data to protect the safety and interests of the research participants. I have published significant papers with colleagues to improve the function and scientific basis for data monitoring committees.[11]

[11] *Independent data monitoring committees: preparing a path for the future.* Hess CN, Roe MT, Gibson CM, Temple RJ, Pencina MJ, Zarin DA, Anstrom KJ, Alexander JH, Sherman RE,

Continued

Finally, the formation of a publication committee, which is now standard practice at the DCRI and other academic coordinating centers, serves as another extremely valuable mechanism for ensuring independent decisionmaking in the interpretation and publication of trial results. As is the case with steering committees, publication committees provide a formal organizing structure for decisions regarding both primary and secondary manuscripts, as well as a transparent and inclusive process for any investigator to propose an idea for a manuscript and to access the data in order to perform the proposed analysis. A representative of the industry sponsor is allowed to serve as a member of the committee, however, the majority of members must be academic investigators and decisions require a majority vote.

Question 12. Earlier this year, after joining the FDA you removed your name from three journal articles published in the Journal of Clinical trials that discussed pragmatic cluster randomized trials (PCRT). You have previously advocated for using more pragmatic cluster randomized trials or pragmatic clinical trials in research. Have you previously expressed the theme and ideas contained in these articles in published articles and speeches?

Answer 12. The depiction of my actions with regard to these issues was inaccurate. The articles in question were part of a major joint project between the NIH Health Care Systems Research Collaboratory ("the Collaboratory") and PCORnet, PCORI's large national network for clinical research. I was Principal Investigator (PI) of the Collaboratory and co-PI of PCORnet. Together with Professor Jeremy Sugarman, distinguished Chair of Medical Ethics at Johns Hopkins University, we organized 10 writing teams from the two projects, in addition to some outside experts to address ethics and regulatory issues that need to be better understood as the United States moves toward a "learning health system" model. Each team was assigned to work on a specific manuscript, all 11 of which (plus one capstone summary article) were to appear together in a special issue of *Clinical Trials* (published by the Society of Clinical Trials).

At the time of my transition to FDA in February 2015, the 11 manuscripts were moving along nicely, but they were not substantially complete. For three of the 11, I had done enough work personally to be on the author list. However, upon moving to FDA, it was clear that I could no longer devote the effort needed to be acknowledged as an author. The rules governing criteria for authorship, which include substantive participation throughout the process of revision as well as final approval of the manuscript prior to submission, are clearly delineated in guidelines published by the ICMJE, to which most peer-reviewed medical journals (including *Clinical Trials*) conform. (Please see *http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html#two* for details).

Realizing that I was unable to devote the time needed to represent responsibility for the full content of the articles, I worked with the co-authors to acknowledge my contribution in writing in each of the three articles up until the time I joined FDA—these acknowledgements are contained within the respective manuscripts. My commitment to the project and the general direction of the body of work is clearly stated in the introduction to the series, which I authored along with Dr. Sugarman.[12]

In summary, my contributions to the articles are clearly stated in the articles themselves, and I am deeply committed to the development of appropriate methods for pragmatic clinical trials and fully support the body of work represented by the articles. The details of the final recommendations are the work of the authors of the manuscripts, and as editor of the series it was not my role to agree or disagree with all detailed recommendations.

Fiedorek FT, Mahaffey KW, Lee KL, Chow SC, Armstrong PW, Califf RM. Am Heart J. 2014 Aug;168(2):135–41.e1. doi: 10.1016/j.ahj.2014.05.003.

Data and safety monitoring boards: academic credit where credit is due? Armstrong PW, Califf RM. JAMA. 2013 Oct 16;310(15):1563–4. doi: 10.1001/jama.2013.280383. No abstract available. PMID: 24129461

Issues in regulatory guidelines for data monitoring committees. DeMets D, Califf R, Dixon D, Ellenberg S, Fleming T, Held P, Julian D, Kaplan R, Levine R, Neaton J, Packer M, Pocock S, Rockhold F, Seto B, Siegel J, Snapinn S, Stump D, Temple R, Whitley R. Clin Trials. 2004;1(2):162–9. Review.

Liability issues for data monitoring committee members. DeMets DL, Fleming TR, Rockhold F, Massie B, Merchant T, Meisel A, Mishkin B, Wittes J, Stump D, Califf R. Clin Trials. 2004;1(6):525–31. PMID:16279293.

Monitoring and ensuring safety during clinical research. Morse MA, Califf RM, Sugarman J. JAMA. 2001 Mar 7;285(9):1201–5. PMID:11231751.

[12] Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015;12(5):436–41.

Question 13. It has been reported that in 2014 you gave a speech to healthcare and pharmaceutical stakeholders in which you characterized some regulations as a "barrier" to innovation in medicine. Please provide additional details regarding the speech and explain what you meant by this statement.

Answer 13. I think you are referring to a slide I have used in multiple lectures that characterizes regulation as a barrier to disruptive innovation.

This issue is a very important one for people proposing to develop new medical therapies. Throughout my career, I have benefited from a close relationship with the Fuqua School of Business at Duke and the many contacts it brings in the field of health economics and health management. Among the many brilliant people I have met is Clayton Christensen ("The Innovators Dilemma"), who developed the concept of "disruptive innovation." This concept is derived from the study of the transformation of industries with the base case being the conversion of radios from the vacuum tube to the transistor. The concept is that the new product or method initially is inferior but lower priced so there is a market for it. This enables innovators to iteratively improve their product until it becomes better and supplants the old product or method. My purpose in showing this slide in multiple lectures is to explain to audiences that often include students, trainees in fellowship, and scientists who are not involved in development of medical products, why the risk and investment in biotechnology is higher than most other industries, i.e., because it is a highly regulated industry, which is in fact a necessary barrier to protect public health, as discussed below. The amount of capital needed is lower and the time to return on investment is shorter in many other industries.

I have never stated, implied, or argued that the barrier should be lowered or removed. In fact I do not believe that we should be putting inferior medical products on the market, nor do the American people want inferior products to be used in medical practice. The belief that we should have evidence of benefits and risks *before* marketing in health care has been a driving force in my career and a motivation to develop more effective, efficient and unbiased ways of conducting generalizable clinical trials and implementing quality systems for learning in health care as a focus of my academic and practical work.

In summary, the purpose of the slide is to point out an issue that is motivational for people who want to develop medical products that prevent death and reduce disability: there is a requirement to demonstrate that your product is safe and effective before you market it and that it does not put people at risk compared to the clinical care that is currently accessible. This is a good thing and forms the basis for the benefit of a strong FDA to make these determinations, and it places a special responsibility on innovators to develop the evidence base that can ensure the FDA (on behalf of the American public) that the product is safe and effective.

Question 14. Are there particular FDA regulations you believe should be modified so that clinical trials can be run more efficiently and effectively?

Answer 14. I do not believe that new FDA regulations are needed, but there is a major need for the U.S. system to organize around some key principles that can be enunciated through multiple venues, including FDA guidances. We are already making substantial progress in developing a more efficient and effective approach for the United States built on the solid foundation of, among others: FDA's Sentinel Initiative and the existing specifications, developed in consultation with industry and other stakeholders, for submission of drug and biologic applications using common data standards and terminology; NIH's HealthCare Systems Research Collaboratory and multiple clinical trial networks; the VA's networks and million veteran cohort; DOD's commitment to research in its vast health system; and ONC's progress on interoperability.

The Precision Medicine Initiative is playing a key role as a use-case to develop appropriate approaches to patient volunteers, provider participation, data standards, interoperability and ethics. My overall views on these issues are described in publications #1204,[13] #1162[14] and #1133[15] on my CV. Much of this work is proceeding through the work of the NIH–FDA Leadership Council.

---

[13] Anderson ML, Califf RM, Sugarman J, participants in the NIH Health Care Systems Research Collaboratory Cluster Randomized Trial Workshop. Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. Clin Trials. 2015 Jun;12(3):276–86. PMCID: PMC4498459.

[14] Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. JAMA. 2014 Jun 18;311(23):2381–82. PMID: 24810723.

[15] Califf RM, Platt R. Embedding cardiovascular research into practice. JAMA. 2013 Nov 20;310(19):2037–38. PMID: 24240926.

Question 15. What are your ideas about how we can improve the design of clinical trials to ensure we understand the effect of new drugs and devices on subpopulations of patients, including women, children, and racial and ethnic minorities?

Answer 15. A rational approach to medical product development would be to include the relevant populations for whom the product is intended to be used. This would include women, children, minorities and populations identified by biological, social, or preference characteristics.

Unfortunately, it is well-documented that clinical trial populations typically are not representative of the population intended to be treated, with particular deficits in the categories mentioned above. The solutions include consideration of the following approaches, and this issue is a high priority:

- The issue of designing, conducting, and analyzing clinical trials to produce results to give patients, caregivers, providers, and policymakers adequate information about benefits and risks of therapeutic interventions in specific individual patients and populations with similar characteristics is a major challenge. Improving the situation will require a comprehensive, multifaceted approach using a concept known as "quality by design."[16] The general tools consist of small focused trials in people with common characteristics using clinical and molecular markers and, on the other extreme, very large trials using electronic health records and quality registries to provide a low-cost data system. Each circumstance is somewhat different and carefully planned trials to most efficiently answer the important questions are needed. All of this needs to occur in the context of more efficient networks of research sites with standard procedures and common data standards and terminology.
- A major new advance is the direct involvement of patients, their caregivers, and advocates in every aspect of the clinical trials, including prioritization of questions, protocol design, quality oversight and analysis and dissemination. FDA is already committed to more inclusion of patients in the effort, and as it evolves, it is already clear that trials are improving as result. The rapid advance of social media is enabling inclusion of patients in a direct and interactive manner, which has the potential for enormous improvement in generalizable enrollment into studies.
- The use of biomarkers and other patient characteristics can enable small, focused trials to evaluate particular populations. When viewed in the overall context of product development this approach will be a critical tool, and the Precision Medicine Initiative will accelerate the potential.
- On the other hand, the use of integrated health systems, community clinics, and community engaged research in combination with electronic health records and registries built on informed consent and developed to improve quality offer the realistic opportunity to do much larger trials with more generalizability at a dramatically lower cost. Considerable work on this approach is already underway at FDA and it will accelerate in the upcoming year. Before joining FDA, I was the PI of the NIH-funded Healthcare Systems Research Collaboratory and Co-PI of the (PCORnet), both of which are developing the concepts and operations for this transformation of the clinical trials system (see *https://www.nihcollaboratory.org/about-us/Pages/default.aspx*).
- In conjunction with industry for drugs and biologics, there is an agreement to submit data using common data standard over the next several years. This will enable FDA to look at inclusion of relevant populations much more effectively. Similar approaches are underway for devices.
- Two special populations merit consideration: pregnant women and the elderly.
  - We know little about the proper dosing of drugs in pregnant women, and the success of the treatment of congenital disorders, serious genetically determined diseases and chronic diseases of childhood has dramatically increased the number of pregnant women who must be treated during pregnancy.
  - The elderly are the most rapidly growing segment of our population but little is known about medical products in people over age 80, for example. FDA can help by calling attention to these efforts and working with industry sponsors, investigators and NIH to improve their inclusion in trials.

Question 16. With respect to pediatric research, what else can be done to ensure that providers and parents have the information they need to help them better understand how a child will respond to a particular treatment? Do you have specific ideas about how new products can be developed to meet the unique needs of children?

---

[16] Please see *http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm* for further details about this approach.

Answer 16. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were passed by Congress to encourage the study of drugs and biological products in pediatric patients in order to provide adequate pediatric use information in drug and biological product labeling. FDASIA made permanent BPCA and PREA.

Prior to the passage of the laws, almost 80 percent of products contained no pediatric-specific information. Since the passage of these important laws, FDA has approved almost 600 labeling changes to incorporate pediatric information. In addition, under PREA, sponsors submit pediatric study plans early enough in development to minimize the time from approval of a drug in adults to the addition of pediatric information.

It should be noted that some products intended for treatment of rare disorders, including rare disorders in children, can receive designation under the Orphan Drug Act, and as such, not be required to comply with requirements under PREA. However, the Orphan Drug Act is also an important and successful law that provides separate incentives for the development of products used to treat rare diseases, including rare pediatric cancers.

Additionally, under BPCA, the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) was directed to evaluate, and to the extent practicable, prioritize new and emerging therapeutic alternatives to treat pediatric cancer. Products under development for use in adult cancers are brought forward for discussion by the Pediatric Subcommittee of the ODAC after consideration by pediatric experts within FDA; advice and recommendation of outside pediatric oncology experts; and pediatric oncology advocacy groups.

If you or your HELP Committee colleagues have particular ideas in mind to further advance therapies for pediatric populations, we would be happy to discuss them.

Question 17a. There have been media reports discussing concerns with the Rocket–AF trial you led while at Duke and that ultimately resulted in FDA approval of the anti-coagulent drug Xarelto in 2011.

Please describe the design process for the study, and the role of the Steering Committee in determining the once-a-day dosage of Xarelto for purposes of the Rocket–AF trial.

Answer 17a. Like other large, international Phase 3 trials in this field, the international Steering Committee and Executive Committee consisted of dozens of experts in cardiology, thrombosis, anticoagulation, and primary care. A large number of studies already had been conducted with rivaroxaban (Xarelto) when the design of the Phase 3 trial came into focus.

Question 17b. The Rocket–AF trial sought to determine if Xarelto (Rivaroxaban) once a day was non-inferior to Coumadin (Warfarin), a drug that has been on the market for many years. When the results of the trial are examined on a country-by-country basis is there any country where Xarelto was found to be inferior to Coumadin?

Answer 17b. There was no significant heterogeneity of treatment effect for the comparison of rivaroxaban and warfarin across countries included in the trial. This is assessed routinely in large international trials using standard methods and closely evaluated by FDA. The results for regions of the world are displayed in the Appendix to the primary publication in the NEJM (please see reference #1039[17] in the enclosed CV; the relevant data can be found in the figures on pages 21–23 of the appendix, available at *http://www.nejm.org/doi/suppl/10.1056/NEJMoa1009638/suppl_file/nejmoa1009638_appendix.pdf*).

Question 17c. Is data from the Rocket–AF trial publicly available?

Answer 17c. FDA review and sponsor submissions are available, and 27 publications are already available with another 12 in press or other stages of review/development, and several dozen more in the planning stage. The trial results are also reported in *www.ClinicalTrials.gov* (NCT #NCT00403767; *https://clinicaltrials.gov/ct2/show/NCT00403767?term=NCT00403767&rank=1*). These have extensive tables of baseline characteristics, outcomes, and adverse events. Study sponsor Johnson & Johnson is working with Yale University through an open-science project called YODA (*http://yoda.yale.edu/*) that will make the raw data available upon request in the future.

---

[17] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883–91. PMID: 21830957.

Question 17d. In the 4-years since Xarelto has been on the market have post-market surveillance studies been conducted, and what have they shown regarding the safety and efficacy of Xarelto?

Answer 17d. Over 190 clinical trials are now registered in *www.ClinicalTrials.gov* involving rivaroxaban. In addition, numerous registries and observational studies have been undertaken. Finally, FDA uses post-marketing surveillance, including its Sentinel Initiative, to monitor the safety of marketed drugs, but as noted in the article by Dr. Ellis Unger ("Atrial fibrillation, oral anticoagulant drugs, and their reversal agents" *http://www.fda.gov/Drugs/NewsEvents/ucm467203.htm*), the safety of rivaroxaban has been a special area of interest. No signals have been announced by FDA, and the article offers reassurance.

SENATOR SANDERS

Question 1. I believe that when 35 million Americans are unable to afford to fill their prescriptions, as is the case now in this country, that constitutes a public health crisis. And FDA is a public health agency; as you noted in your testimony, "a successful FDA is a critical factor for better public health." In order to address a public health crisis of this magnitude, we need to do far more to make sure medications are affordable for all Americans. The best drug in the world won't save someone if they cannot afford to take it.

In your testimony you said that the United States does have the capability to import prescription drugs but that it would add additional costs and systems would have to be put in place to make it work. Please elaborate on what you will do, as Commissioner, to work with President Obama and Secretary Burwell to implement current law and begin importing prescription drugs from Canada. In case you are not aware, President Obama said in 2011,

> "Canada and Mexico are bulk purchasers of—drugs, so they negotiate much cheaper drug prices with the drug companies. We still don't do that, and I actually think it's something we should do—it would save us money."

He added, "It may be that importation is still something we should look at in terms of further lowering the price of drugs."

If you will not commit to importing prescription drugs from Canada at this time, please explain how it is possible that FDA can safely oversee the importation of millions of food and cosmetic products including vegetables, seafood, and infant formula that Americans ingest every day from dozens of countries—and yet FDA cannot take steps to import any prescription drugs from Canada.

Answer 1. FDA oversees the products it regulates including food, drugs, and medical devices through the provisions in the FD&C Act, which includes a number of more recent congressional authorities, including FSMA, FDASIA, and DQSA. These authorities establish differing systems of oversight to monitor manufacturers, producers, and growers of FDA-regulated goods, depending on the FDA-regulated product. For example, prescription pharmaceuticals receive a facility inspection prior to marketing to ensure the product was manufactured in compliance with FDA's good manufacturing practice standards. Drugs from foreign sources that are not FDA-approved nor have such an inspection do not have the assurance of safety, effectiveness, and quality as drugs subject to FDA oversight.

Drugs that are not FDA-approved nor manufactured in a facility inspected by FDA do not have the assurance of safety, effectiveness, and quality as do drugs subject to FDA oversight. There have been documented incidences of non-FDA-approved imported drugs found to be contaminated, counterfeit, containing varying amounts of active ingredients or none at all, or containing different ingredients than the FDA-approved product. Moreover, FDA would not be able to make safety and quality determinations for prescription drugs offered for import into the United States that have not gone through the U.S. regulatory process. In fact, FDA evaluation of non-FDA-approved imported drugs revealed that while nearly half of imported drugs claimed to be Canadian or from Canadian pharmacies, 85 percent of such drugs were actually from different countries. Typically, these products are smuggled into the United States after being transshipped to third-party countries in an effort to avoid detection and create an appearance of coming through countries that consumers may find trustworthy. Through FDASIA Title VII and the Drug Supply Chain Security Act, Congress has recognized the need to bolster this closed drug distribution system. Authorizing importation would compromise the closed drug distribution system in the United States and undermine these laws, thus making it easier for unapproved drugs, which may include counterfeit or other substandard drugs, to reach American patients putting their treatment at risk. FDA is concerned that the risks of unapproved products from foreign sources outweigh any potential cost savings. We are also concerned that adverse events flowing from importation

of such unapproved products could lead to diminished confidence in FDA-approved products.

Question 2. According to a 2013 CDC study, about five million Americans import medication for personal use in order to reduce their drug costs. Will you continue FDA's current personal importation policy?

Answer 2. The policy referred to in the question is not based on considerations of whether the importation of drugs for personal use is to reduce drug costs. Congress charges FDA with ensuring the safety and effectiveness of drugs sold in the United States. The FD&C Act prohibits the interstate shipment (which includes importation) of unapproved new drugs. Unapproved new drugs are any drugs, including foreign-made versions of U.S.-approved drugs, which have not been approved by FDA for marketing in the United States. Certain Internet websites have stated that personal importation of up to a 90-day supply of prescription medications is legal. This statement is not true.

FDA drug approvals are manufacturer-specific, product-specific, and they include many requirements relating to the product, such as manufacturing location, formulation, source and specifications of active ingredients, processing methods, manufacturing controls, and container/closure system. The drugs must be produced in FDA-inspected facilities. These facilities, and the drugs produced in them, are currently covered by the U.S. regulatory system. When individuals import unapproved drugs directly from foreign sources, they bypass the protections provided by FDA's drug approval process.

We must emphasize that from a public health standpoint, importing unapproved prescription drugs for personal use is a potentially dangerous practice. Neither FDA nor the American public have any assurance that unapproved products from foreign sources are effective, safe, or produced under current Good Manufacturing Practices (cGMP). Unapproved products may not have been stored under proper conditions, or may not be the real product. Foreign unapproved drugs may be contaminated, sub-potent, super-potent or counterfeit. In addition, some foreign drug outlets offer to dispense prescription drugs without a physical examination, bypassing the traditional doctor/patient relationship. As a result, patients may receive inappropriate medications because of misdiagnoses, fail to receive appropriate medications or other medical care, or take a product that could be harmful or fatal if taken in combination with other medicines. The personal importation policy is explained in full on FDA's website at *http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/importsandexportscompliance/ucm297909.pdf*.

Question 3. If a drug company has evidence that a drug is more or less safe than what is indicated on the label, then that company should submit this new information to FDA and, if warranted, request a change in their label. However, FDA proposed a guidance last year on the distribution of medical publications that lets sales representatives for drug companies talk to doctors and hand out articles saying their drugs are less dangerous than FDA labeling says they are. Do you agree or disagree with this?

Under no circumstances should the pharmaceutical industry's financial interests come before patient safety. It is my hope that you believe—and will commit—to working with FDA to revise this draft guidance and reiterate that companies should not be able to promote drugs using different risk information than what they provided to the agency. When new scientific information about a drug's risk is determined, the company should inform FDA and, if appropriate, pursue a label change.

Answer 3. Under FDA's regulations, drug companies are responsible for updating their approved labeling, when new information becomes available that causes the labeling to become inaccurate, false, or misleading. Nothing in FDA's draft guidance, "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices," is intended to change companies' existing obligations to update their labeling to accurately reflect what is known about the safety profile of the drug, to ensure that the labeling is not false or misleading, or for other reasons.

As stated in the draft guidance, FDA recognizes that the safety profile of a drug evolves throughout its life cycle as the extent of exposure to the product increases, and that it can be helpful for health care practitioners to receive significant new information about a risk identified in the labeling of an approved product in a timely manner. Accordingly, FDA issued the draft guidance to provide recommendations for drug companies that choose to distribute new risk information in the form of a reprint or digital copy of a published study. FDA's proposed recommendations are intended to help ensure that new risk information meets appropriate standards for

reliability and is presented with appropriate disclosure of its limitations and with the approved labeling.

The guidance was issued in draft to enable public comment on the proposed recommendations. FDA reviews the comments it receives on draft guidances to inform preparation of final versions of guidance documents. I will work with FDA on these efforts, including efforts to revise the guidance as appropriate.

Question 4. On October 6, 2013, the *Washington Post* published an article, "Pharmaceutical firms paid to attend meetings of panel that advises FDA, e-mails show," documenting FDA's convening a panel (IMMPACT), on the clinical testing of painkillers, a multibillion market in the United States, and charging pharmaceutical companies $25,000 to participate ("pay-to-play"). Despite NIH's warning that these payments would give the appearance that the panel was "paid for by a few large pharmaceutical firms who are assumed to be influencing the outcomes," FDA proceeded with the private meeting. The opioid epidemic has only worsened since these meetings; *according to CDC*, the death rate from drug overdose in the United States has more than doubled since 1999. In light of FDA's history blurring conflict of interest lines, especially when it comes to relationships with the industries it regulates, and even in cases with significant public health ramifications such as a panel on opioids where transparency should have been maximal, will you commit to prohibiting any FDA participation in "pay-to-play" meetings in the future? If you decline to make this commitment, please explain why and provide examples of meetings FDA may convene where private, pay-to-play meetings are both necessary and justified.

Answer 4. Your question refers to FDA involvement in the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), a partnership between the University of Rochester, academia, FDA and other government agencies, industry, professional organizations, patient advocacy groups, foundations, and philanthropic organizations. Its goal is to streamline the development process for new analgesic drug products for the benefit of public health.

ACTTION is one example of the numerous public-private partnerships in which FDA participates. These partnerships bring together expertise from all areas of drug development, including academia, government agencies and pharmaceutical companies, for constructive dialog and information sharing. Collaborations such as these, including those falling under the Agency's Critical Path initiative, play important roles in identifying and addressing knowledge gaps, public health questions, and unmet medical needs that plague many therapeutic areas.

They provide a forum in which FDA representatives and external stakeholders can collaborate to share their considerable expertise and respective views, which can play an important role in streamlining and fostering innovation in drug development. Both the IOM and the President's Council of Advisors on Science and Technology have called for the development of additional consortia to address areas of unmet medical need.

FDA takes the concerns raised about IMMPACT and ACTTION and other public-private partnerships very seriously. The Agency has conducted in-depth reviews of those specific collaborations, and has not found evidence that FDA officials engaged in any inappropriate behavior. Although FDA's PPPs produce many scientific and public health benefits, the credibility of FDA's public health decisions related to PPP efforts depends on public confidence that those decisions are impartial and science-based. To maintain that credibility, FDA PPPs should not create an opportunity for unfair access to FDA, undue influence on the Agency's decisions, or their appearance. FDA is currently drafting procedures to ensure that such collaborations are not influenced by conflicts of interest or the appearance of such conflicts.

Question 5. Since your arrival at FDA in January[18] 2015, the transparency of FDA deliberations regarding approvals for cardiac drugs, your area of expertise, appears to have deteriorated. This year, FDA approved two new drugs for heart failure, Entresto and Corlanor (*Entresto approval letter*) (*Corlanor approval letter*) without exposing them to public scrutiny at advisory committee meetings despite both drugs having publicized suspicions of safety problems, e.g., Alzheimer's disease for Entresto (*Wall Street Journal*) and higher mortality for Corlanor (*Corlanor label*). While FDAAA requires the action packages for new drugs to be posted on the FDA website within 30 days, FDA did not post the *action package* for Corlanor—approved on April 15—until November 20, more than 6 months later. FDA did post the *action package* for another recently approved cardiac drug, Savaysa, but then the medical

[18] Original question stated "January," however, Dr. Califf actually arrived at FDA in February 2015.

reviews disappeared from the action package several months later and are still missing. For each of these cases, please explain why FDA did not comply with the laws under which it is supposed to operate and please describe your knowledge of or involvement with these cases.

ADVISORY COMMITTEES

Answer 5. Advisory Committee meetings are not required for all applications. By long-standing practice, FDA convenes Advisory Committees as warranted. For reasons explained below, FDA chose not to convene advisory committee meetings to consider these two new drug applications (NDAs).

Entresto is a combination of two drugs: sacubitril and valsartan. Sacubitril is a new molecular entity, whereas valsartan has been marketed for many years. The company provided a conventionally designed study with typical cardiovascular endpoints. The study was well-executed, and the clinical benefit was clear, with 20 percent reductions in both hospitalizations for heart failure and cardiovascular mortality, and a 16 percent reduction in all-cause mortality.

Sacubitril poses a theoretical risk for central nervous system toxicity, based on its mechanism of action. The drug was found to affect beta-amyloid protein levels in the spinal fluid of animals and humans. Beta-amyloid is the protein that builds up in the brains of patients with Alzheimer's disease, so the finding is noteworthy; however, the drug did not affect beta-amyloid in the brains of animals, and it is not known whether there would be any effect in humans over the long term. No toxicity was observed in the principal study supporting approval (8,442 subjects studied over more than 3 years). But given the theoretical concerns, the company was given a post-marketing requirement to assess the issue further. In light of the clear benefits of the drug and what is only a theoretical risk, the reviewing division and office deemed approval to be appropriate, without the need of convening an advisory committee for discussion.

The rationale for not convening an advisory committee to discuss Corlanor (ivabradine) was similar. In a 6,500-patient trial, Corlanor was shown to reduce the combination of hospitalization for heart failure and cardiovascular death by 18 percent. There was a trend in favor of a lower rate of cardiovascular death on Corlanor, although the difference was not statistically significant. As with Entresto, there were no controversial issues, and a decision was made not to delay approval in order to take the application before an advisory committee.

SAVAYSA AND CORLANOR

Savaysa was approved on January 8, 2015, and the action package for the NDA was posted on the web on February 13, 2015. In May 2015, we removed the medical officer review section of the action package from the web because we received a complaint related to the amount of information redacted from this review and needed to reassess the redactions. The medical review section of the action package included a review that had not been considered by the approving official when the approval action was taken. This review had not been considered because it was unexpected (filed to the application outside the normal review process). It had been written by a medical officer who had not been assigned to the Savaysa NDA and who had not collaborated with the review team. This unsolicited review was also included as an attachment to a review document that was part of the action package for Corlanor, which was approved on April 15, 2015. The posting of the Corlanor action package was held until the issues related to this unsolicited review could be resolved. Now that this unsolicited review has been considered and addressed by issuance of a supervisory review memo and the disclosure staff has confirmed that any information being withheld from these reviews is justified under the Freedom of Information Act, we have begun posting this information.

Question 6. You testified that it is not FDA's role to set the prices of drugs. However, FDA's actions can assist drug companies in securing high prices for their new drugs. One way that FDA's decisions can have an impact: if care in the control arms of trials is compromised, as may have occurred, for example, in the following five trials: ROCKET AF, CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX, and PLATO, (such as by delaying clopidogrel administration in the control arms of the PLATFORM and PHOENIX trials or POGO's finding that the device used in the control arm of the ROCKET AF trial was faulty), then the new drug will appear "superior" to the old drugs, although artificially so. For additional background, see the concerns raised by the FDA Medical Team Leader's review at: *http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM385234.pdf.*

A new drug that is "superior" to the old drugs may command a higher price, while the same drug that is "non-inferior" (or not much worse than) the old drugs may not. Please explain whether you believe this mechanism was active for the five trials and please provide the relevant data.

Answer 6. The labeling for the affected drugs—rivaroxaban (ROCKET), cangrelor (CHAMPION studies), and ticagrelor (PLATO)—appropriately describes the results of the five trials. These decisions and relevant data reviewed are documented in memos available on line at Drugs@FDA, a searchable website that contains official information about FDA-approved innovator and generic drugs and therapeutic biological products..

It is not clear or established what the relationship is between drug prices and efficacy or clinical impact. For example, for patients with atrial fibrillation, anticoagulants reduce the risk of stroke by some 60 percent. For patients with life-threatening infections, antibiotics can be lifesaving. Yet other types of new drugs, such as certain cancer treatments, may have relatively small effect sizes but be higher priced.

SENATOR CASEY

Question 1. I appreciate your answers during the hearing to questions about your ability to remain impartial as FDA Commissioner. In law, we say that lawyers must not only refrain from impropriety, but refrain from any appearance of impropriety. Similarly, as FDA Commissioner, how would you, both with respect to your own actions and with respect to the rest of the Agency's employees, ensure independence and also avoid the appearance of a lack of independence?

Answer 1. At Duke, I was honored to lead a team of researchers who were pioneers and advocates for the expansion of measures to enhance the transparency, disclosure, and public discussion of funding sources.

Prior to joining FDA, I went through a comprehensive screening process for conflicts of interest, working closely with HHS staff. I hold my FDA colleagues to the same standards to which I hold myself. The United States—indeed the entire world—depends on a strong, unbiased FDA that can work with industry to advance critical technologies, but still make independent determinations to ensure safe and effective products. But this activity must adhere to societal guidelines and expectations for governing conflict of interest. Developing new technologies that revolutionize patient care calls for a community of dedicated people across the health care ecosystem. I have first-hand experience appropriately collaborating across industry, academia, the patient community, and government, which is a critical skill in today's science-based regulatory environment.

Following my appointment as Deputy Commissioner for Medical Products and Tobacco, the Office of the Commissioner established a process for screening invitations that I receive for speaking engagements and other requests for my participation to identify potential situations which would require my recusal. A team of individuals was convened, including a representative of the Office of the Commissioner and the Office of Chief Counsel. These individuals have extensive knowledge of my ethics agreement and recusal obligations. This team meets on a regular basis (often as frequently as weekly) and on an ad hoc basis, as needed. A member of my staff submits detailed information regarding specific invitations/requests for my participation, and the team determines whether I should be recused. If the team has any questions as to whether something is covered by the recusal, the HHS Designated Agency Ethics Official's office is consulted. The team has a standing teleconference with a representative of this office in order to facilitate consultations and determinations.

If my nomination is confirmed, I understand that I will be subject to more extensive recusal obligations under the President's 2009 Executive order, and accordingly, that additional monitoring procedures may be needed.

Question 2. Fitting combination products, such as products with both drug and device components, into the current regulatory framework can sometimes be challenging. However, we do not want to miss opportunities to innovate with combination products that would advance the public health because of regulatory challenges. Dr. Califf, you mentioned that FDA would be able to develop a proposal within a year to address these challenges. What does FDA envision?

Answer 2. FDA has found that sponsors face the challenges you identify under the existing pathways for device-led combination products. Device-led combination products range from simple products that pose little risk and address relatively simple treatment needs (such as a drug-coated bandage for minor wounds) to complex, riskier products intended to address more significant medical needs (such as drug-eluting stents). The device program as currently structured, however, is sharply di-

vided between 510(k) and PMA pathways. The PMA pathway is more akin to the innovator drug and biologic pathways (NDA and BLA), generally requiring an independent showing of safety and effectiveness. Under the 510(k) pathway, on the other hand, FDA has faced challenges in obtaining information critical to evaluating a drug or biologic component, and also on ensuring reasonable use of the 510(k) predicate system.

FDA believes a new premarket pathway for device-led combination products could significantly improve certainty and predictability for these products while enabling both protection and promotion of the public health. A pathway to achieve these goals would:

- ensure FDA has the tools necessary to assess the risks and benefits of device-led combination products,
- direct FDA to base data requirements on the potential risks and benefits of the product and what is already known regarding the safety and effectiveness of its constituent parts, and
- grandfather combination products that have been cleared under 510(k) to date and allow combination products that include the same drugs and substantially equivalent devices to rely on these grandfathered products as predicates, unless FDA finds that review under the new pathway is needed to establish reasonable assurance of safety and effectiveness for the product.

Question 3a. Following up on my question during the hearing, I wanted to continue with a question about drug labeling for neonates. According to reports from the FDA, up to 90 percent of the drugs used in NICUs are used off-label. Independent research estimates that the percentage is even higher. As such, the labels for these drugs do not include information on dosing, safety or efficacy for neonates. This represents a serious gap in effective regulation.

What are the most commonly used drugs in the NICU and do they have FDA-approved pediatric labeling?

Answer 3a. The top 10 most commonly used drugs in the neonatal intensive care units (NICUs), based on a recent study by Hsieh, et al., from Duke University, published in the *American Journal of Perinatology* in 2014, include the following: ampicillin, gentamicin, caffeine citrate, vancomycin, beractant, furosemide, fentanyl, dopamine, midazolam, and calfactant.

Of these top 10 commonly used drugs in NICUs, gentamicin, caffeine citrate, vancomycin, beractant, calfactant, furosemide, and midazolam included dosing information for neonates. Gentamicin and vancomycin are antibiotics, beractant and calfactant are surfactant products used to treat respiratory distress syndrome, caffeine citrate is used to treat apnea of prematurity, midazolam is used for pre-operative/pre-procedural sedation, and furosemide is to treat edema, secondary to edema-forming states and acute pulmonary edema.

Pediatric dosing, but not neonatal dosing, is present for ampicillin, an antibiotic, and fetanyl, a short-acting analgesic used during anesthesia. Dopamine does not have specific pediatric or neonatal dosing information.

Of the most commonly reported medications identified in this study, only 35 percent are FDA-approved in the newborn (for more information, see the attached publication by Hsieh, et al.). Many of these drugs were approved years ago and without the same data to support approval, as are required today. For example, furosemide was approved in 1966. Of the 409 drugs with pediatric-specific labeling changes between 1997 and 2010, only 28 included information for use in neonates (7 percent). Even more recently, of the 156 drugs with pediatric-specific labeling changes since 2012, only nine products were approved for use in neonates (6 percent).

Question 3b. What percentage of drugs used in the NICU are off-patent versus on-patent? How has FDA worked with NIH through the BPCA NIH program to approve pediatric labeling for off-patent drugs used in neonates and what have we learned about the safety and efficacy of these drugs?

Answer 3b. FDA does not formally track the percentage of drugs used in the NICU and their current patent status. However, as stated above, many of the drugs most commonly used in NICUs were approved many years ago and would not be expected to have remaining patent protection. Implementation and coordination of the BPCA NIH activities is conducted by NICHD's Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB). FDA has worked closely with colleagues in NICHD through the BPCA NIH program to increase the information to support pediatric labeling for off-patent drugs in all appropriate pediatric populations. For example, recent pediatric-specific labeling changes, including dosing information in neonates, were approved for sodium nitroprusside, used to treat hypertensive crisis, and meropenem, an antibiotic, included dosing information in neonates. Addition-

ally, FDA meets with the NICHD monthly to review progress made toward increasing pediatric labeling for off-patent drugs.

Question 3c. If confirmed, what actions will you consider to ensure that therapeutics for neonates are studied in that population so they can be used with appropriate safety and effectiveness?

Answer 3c. FDA has clearly recognized the need to increase efforts to develop therapeutics for neonates. In October 2014, FDA convened the first Neonatal Scientific Workshop. This workshop was co-sponsored by the Critical Path Institute, Burroughs Wellcome, and FDA. The workshop, entitled "Roadmap for Applying Regulatory Science to Neonates," considered the feasibility of the development of a global neonatal research consortium, including discussions of the governance structure. In May 2015, as a result of discussions initiated at the FDA workshop, the International Neonatal Consortium (INC) was launched by Critical Path Institute. The INC includes global collaboration including FDA, EMA, NIH, neonatal advocacy groups, pharmaceutical companies, academic researchers and neonatal nurses. The mission of the INC is to accelerate the development of safe and effective therapies for neonates. The creation of a global neonatal consortium, dedicated to advancing the development of safe and effective therapies for neonates is a major achievement and FDA will continue to support this global effort.

In addition, FDA will continue to support increasing the availability of safe and effective therapies for neonates through efficient, effective implementation of BPCA and PREA.

Question 4. As you are aware, there has been increasing scrutiny over the last 2 years on the safety of certain medical devices. I understand from communications with your predecessor that one of the challenges FDA can face when the safety of a medical device is called into question include a fractured and still quite limited system for medical device surveillance. Following up on Senator Murray's question at the hearing, from your perspective, what would a robust, proactive surveillance system for devices look like to ensure that new safety indicators are quickly identified and addressed?

Answer 4. Medical device post-market surveillance presents unique challenges due to the greater diversity and complexity of medical devices, the iterative nature of medical product development, the learning curve associated with technology adoption, and the relatively short product life cycle.

Although the United States has a robust medical device post-market surveillance system, we believe it can be strengthened by developing a more integrated national system, now being referred to as the National Medical Device Evaluation System (NMDES). This system would not be owned or run by FDA; rather, it would be operated through an independent public-private partnership and governed by a board with representation from the primary medical device ecosystem communities, e.g., patients, providers, payers, industry, and government. The system would ensure the security and privacy of the information used but would not own the data. Data ownership would be retained by the original data holder, such as health care systems.

The FDA's plan to develop NMDES provides a pathway to realizing a national system that harnesses novel data sources, modern analytical techniques and the participation of all stakeholders to optimize patient care. The system is envisioned to be able to develop and communicate an evolving understanding of devices' benefits and risks throughout their marketed life using high-quality, linked electronic health information, identify potential safety signals in near real-time from a variety of privacy-protected data sources serving as a safety net, reduce burdens and costs of medical device post-market surveillance, and facilitate clearance and approval of new devices or new uses of existing devices.

The NMDES evolved out of a vision for a medical device post-market surveillance system described in two FDA white papers. The initial report, "Strengthening Our National System for Medical Device Post-Market Surveillance," was issued in 2012 and provides an overview of FDA's medical device post-market authorities and the current U.S. medical device post-market surveillance system. The update to the report, issued in 2013, details the concrete steps that will promote more efficient collection of better and more timely data, helping to identify issues more quickly. A multi-stakeholder planning board to promote this vision was convened by the Engelberg Center for Health Care Reform of the Brookings Institution. In February 2015 the planning board issued a report titled "Strengthening Patient Care: Building a National Post-Market Medical Device Surveillance System," which sets out the key steps to take toward development of a national system for development, regulation, and effective use of medical devices, while supporting improvements in patient safety and health outcomes. The system, which will support the needs of the entire

community of stakeholders, was renamed an "evaluation system" with the release of the report "Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge the Clinical Care and Research" in August 2015. MDEpiNet, a public-private partnership, produced this report and is working to build infrastructure for the national system and development.

Question 5. There is mounting evidence documenting the value of immunization to protect pregnant women and their newborns from infectious diseases, such as influenza and pertussis. In the coming years, new maternal vaccines are expected to be developed at a faster rate, and to present FDA with a range of new considerations to take into account. If confirmed, what will you do to encourage maternal vaccine development and ensure timely approval of safe and effective maternal vaccines?

Answer 5. FDA shares the goal of having vaccines available to protect pregnant women and their newborns from infectious diseases. To help facilitate more optimal development of such vaccines, on November 13, 2015, we sought advice from our Vaccines and Related Biological Products Advisory Committee on appropriate clinical study designs to support the safety and effectiveness of investigational vaccines, as well as study designs of licensed vaccines that are recommended for use during pregnancy to protect newborns in addition to their mothers. FDA received helpful advice from the Advisory Committee members on ways to advance the development of these vaccines, and is committed to working closely with sponsors in this important area.

Question 6. Specialized nutrition and medical foods are critically important to patients with conditions such as phenylketonuria (PKU) as well as many other conditions. In this rapidly changing and evolving field, what are your goals and priorities for specialized nutrition and medical foods? Additionally, while there has been growing level of interest and innovation, coverage and reimbursement for these products often lag behind new developments. To what extent can FDA work more closely with agencies such as CMS to help patients gain better access to specialized nutritional solutions?

Answer 6. FDA recognizes the critical role of medical foods in the lives of patients with inherited metabolic disorders such as phenylketonuria (PKU). The Agency's goals for medical foods include staying abreast of the science in this rapidly evolving field; working to ensure the availability of safe and appropriately labeled products for patients with inherited metabolic disorders; and providing sound guidance to patients, health care providers, and industry.

For example, a current FDA medical food priority is to address stakeholder requests for updated medical foods guidance. FDA incorporated the most recent available science in its updated Draft Medical Foods Guidance, published in August 2013. We are currently considering the comments we received on the draft guidance, along with the latest science, as we work to finalize the Medical Foods Guidance.

FDA also prioritizes communication and collaboration with medical food stakeholders on scientific issues. For example, a recent NIH study revealed that a medical food intended for a single specific metabolic disorder was being inappropriately used to treat patients with a combination metabolic disorder, resulting in adverse effects. FDA, NIH, and a manufacturer of one such product collaborated on the matter, which led to the manufacturer changing their labeling to warn health care practitioners against its use for the specific combination disorder at issue. The manufacturer and NIH have agreed to continue working in partnership to further study the disorder (and other related metabolic disorders), with FDA providing any needed regulatory knowledge and guidance.

The advances in medical food research that are critical to patients with inborn errors of metabolism are also an important part of FDA's Office of Orphan Products Development (OOPD) goals and priorities to advance promising products for rare disease patients. OOPD provides funding support for clinical studies that advance the development of promising medical products for rare diseases, including medical foods to manage rare diseases such as PKU. For example, OOPD is currently funding a 4-year, Phase 2 PKU medical food study conducted by the University of Wisconsin. The $1.5 million dollar study evaluates the glycomacropeptide diet with the amino acid diet for PKU patients. OOPD's priority on funding the best studies that can further the development of medical product for rare disease will advance medical food options for patients with inborn errors of metabolism.

Coverage and reimbursement of specialized nutrition and medical foods is outside the scope of FDA's authority, but the Agency is committed to work collaboratively with our Federal agency partners and with Congress, as appropriate, to help patients with specialized nutritional issues.

Question 7. As you may know, the issue of teens abusing the over-the-counter cough suppressant, dextromethorphan (DXM) or "dex," is an issue I have been working to address for several years now. Years ago, as many as 6 percent of teens aged 13–17 abused dex by drinking cough syrup, sometimes as much as a full bottle or more. Since then, many stakeholders in the retail, pharmacy and OTC pharmaceutical sectors have worked together to establish voluntary restrictions on the sale of dex to minors, and to educate parents, educators and medical professionals about this problem. These efforts have led to a significant decrease in dex abuse, to the current rate of 3.3 percent for teens aged 13–17. We know that FDA has long been concerned with this effort and held an advisory committee hearing in 2010 on the abuse of dex, at which time the Agency suggested the benefit of a statutory, nationwide minimum age of 18 for dex purchases. I would ask that you continue to work with me on this issue as I continue to pursue a legislative solution.

Answer 7. The Agency has been working with you and your staff, as well as your colleagues in the House, on this very important issue. We have recently provided updated technical assistance and will continue to work with you and your staff moving forward.

SENATOR BENNET

Question 1. Dr. Califf, in the last few years, there have been numerous reports on the public health threat of antibiotic resistance. Experts warn that unless we take action, we could find ourselves in a post-antibiotic era. In such an era, the risk of infection would make many elective surgeries too dangerous to justify, where a simple wound could turn deadly, or where patients with compromised immune systems—those being treated for cancer for example—would not have medicines to combat the infections to which they are highly susceptible. Senator Hatch and I have introduced the PATH Act, which would create a new regulatory pathway for antibiotics to treat potentially fatal infections for which there are few or no other options—in essence, the drugs we need the most. We have been working closely with the FDA and the HELP Committee as we finish our work on the legislation. Can you talk about how the PATH Act would work to help encourage the development of new, life-saving antibiotics?

Answer 1. Thank you for your leadership combating the public health threat of antibiotic resistance and on the "Promise for Antibiotics and Therapeutics for Health (PATH) Act". The PATH Act would establish in statute an approval pathway for "limited population" antibacterial drugs.

We understand that the objective of this pathway is to help expedite the development and approval of antibacterial drugs intended to treat a serious or life-threatening infection and meet unmet medical needs in limited subpopulations of patients. Drugs eligible for this proposed pathway could be approved based on streamlined clinical development programs showing that the risk-benefit profiles of those drugs are appropriate for limited subpopulations of patients with unmet medical need, such as patients with serious infections caused by multi-drug-resistant organisms, even if the risk-benefit profile would not support approval for a broader population.

A statutory "limited population" pathway as proposed would provide FDA tools (e.g., a "limited population" designation on the label, pre-review of promotional materials) to ensure appropriate post-approval use of these antibacterial drugs in the indicated sub-population and focus on establishing a consistent and predictable program for drug sponsors.

However, it is critical that any legislation be carefully crafted so as not to undermine FDA's ability to approve drugs under our existing authorities. FDA is focused on balancing the need to encourage the development of critically needed antibacterial drugs while ensuring that the current FDA drug approval standard is maintained.

Question 2. What will you do as head of the FDA to ensure that medical device implants do not wear out prematurely and that patients are given verifiably accurate information on the life of their implant?

Answer 2. As a complement to its premarket review process, FDA's plan to develop a National Medical Device Evaluation System (NMDES) provides a pathway to realizing a national system that harnesses novel data sources, modern analytical techniques, and the participation of all stakeholders to optimize patient care. The system is envisioned to be able to develop and communicate an evolving understanding of devices' benefits and risks throughout their marketed life using high-quality, linked electronic health information, identify potential safety signals in near real-time from a variety of privacy-protected data sources serving as a safety net, reduce burdens and costs of medical device post-market surveillance, and facilitate clearance and approval of new devices or new uses of existing devices. A strong

NMDES will facilitate the ready availability of accurate information about implant lifespan and also support the rapid identification of problematic implants early in the market life of the device.

Question 3. As the FDA continues to issue draft guidance for comments, can you discuss your process of consulting with health care scientific experts? If commenters disagree with the science behind draft guidance after sending in a set of comments, are there any other opportunities to: (1) address these concerns with FDA directly; and (2) better understand why FDA disagrees with their position?

Answer 3. FDA's Good Guidance Practices (GGPs) regulations (21 CFR 10.115) lay out the ways in which affected parties may participate in the guidance development process and how the Agency goes about soliciting input from affected parties.

FDA has many ways to solicit and receive comments from outside stakeholders before, during, and after issuance of guidances. Before issuance of a draft guidance document, FDA can seek or accept early input from individuals or groups outside the Agency. When a draft guidance document is issued, FDA will publish a notice in the Federal Register and invite comments. FDA can also hold public meetings or workshops during this time and FDA can also present the draft guidance to an advisory committee for review at this time. FDA will then review any comments received and, when appropriate, incorporate the suggested changes into the final guidance document. FDA also can decide to issue a revised draft of the guidance document after reviewing comments on the draft guidance document. Even after a guidance is finalized, the docket remains open and comments can be submitted at any time.

If affected parties disagree with the science behind a draft or final guidance, they are able to suggest that FDA revise the guidance or withdraw an already existing guidance by submitting comments to the docket.

Question 4. Under the Biologics Price Competition and Innovation Act (BPCIA) of 2009, the FDA was given authority to review and approve biosimilars. While the FDA has approved the first biosimilar, many are still awaiting final guidance from the FDA on what biosimilars should be named, the makeup of their label, and interchangeability with the original biologic. When do you expect for this guidance to be released?

Answer 4. FDA has published the following final guidances related to biosimilars: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following draft guidances since 2012: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act; Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009; and Nonproprietary Naming for Biological Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above. Upcoming draft guidances are expected to include: Considerations in Demonstrating Interchangeability to a Reference Product; Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity; and Labeling for Biosimilar Biological Products.

FDA is diligently working to issue guidance on issues that have been identified by the FDA and key stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide information to assist biological product developers—sponsors/companies—with bringing biosimilar and interchangeable products to market. The FDA is continuing to clarify its approach to implementation of the BPCI Act to further facilitate sponsors' development of biosimilar and interchangeable biological products.

Question 5. Dr. Califf, as you know, there has been an ongoing concern about the rising cost of medicines. The Generic Drug User Fee Agreement enacted in 2012, gave FDA new resources to ensure the timely access to quality generic drugs. Unfortunately, there are estimated to be 4,000 generic drug applications still pending approval by the FDA. Can you please explain how the Agency is addressing and prioritizing these applications?

Answer 5. Pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA), "backlog" is a defined term. It means all Abbreviated New Drug Applica-

tions (ANDAs), ANDA amendments and ANDA supplements pending as of October 1, 2012 (the date of enactment). GDUFA was negotiated by FDA and Industry and passed by Congress as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).

Pursuant to GDUFA, Industry pays FDA certain agreed-upon fees, and in exchange FDA agrees to certain quantitative review performance goals. FDA's GDUFA goal for the backlog (as defined above) is for the Agency to take action on 90 percent of the legacy, pre-GDUFA "backlog" submissions by the end of fiscal year 2017. We have already taken action on 82 percent of the pre-GDUFA "backlog," well ahead of schedule to fulfill our negotiated commitment. There were approximately 2,866 ANDAs in the pre-GDUFA backlog. Many of these submissions were long pending when GDUFA started, providing one of the key reasons that Industry entered into GDUFA in the first place.

GDUFA explicitly assumed that Industry would send FDA approximately 750 new ANDAs each year of the program, an assumption upon which the Agency budgeted and planned accordingly. In fiscal years 2012, 2013 and 2014, Industry submitted 1,103; 968; and 1,473 ANDAs, respectively. Given that GDUFA assumed, and industry users fees reflect, a much smaller workload, the Agency is striving to take action on all of these submissions before the end of fiscal year 2017.

The status of our pre-fiscal year 2015 workload is detailed below. Of the 5,720 total ANDAs that the Agency has received:

- 1,316 ANDAs have been approved.
- The Agency "refused to receive" (RTR) 226 ANDAs—meaning we did not accept them for review because they were not "sufficiently complete to permit a substantive review."
- 422 ANDAs were withdrawn.
  Note: ANDAs that have been approved, RTR'd or withdrawn are no longer part of our review workload.
- 1,113 ANDAs are "pending industry." This includes:
  - 846 submissions where FDA issued a Complete Response (CR) Letter. A CR Letter lists deficiencies an applicant must fix to obtain approval. FDA cannot take further action on these 846 submissions until the applicant responds to the issues raised in the CR Letters.
  - It also includes 267 Tentative Approvals (TA). TAs reflect the fact that the patent or exclusivity on the new drug product hasn't expired, and thus the Agency is barred from issuing a final approval, the ANDA is otherwise approvable from a regulatory perspective.[19]
- 2,643 ANDAs are pending an FDA action.
  - 7 are pending a filing review to determine whether or not they will be accepted or RTR'd.
  - 498 have been successfully filed, but we have not communicated review deficiencies to the applicant concerning these ANDAs yet.
  - For the remaining 2,138 ANDAs, we have issued at least one review communication to applicants. In fiscal year 2015, we issued over 4,700 communications concerning ANDA review deficiencies to industry.

In summary, out of 5,720 submissions, over 90 percent have been approved, RTR'd, withdrawn, are pending industry, or are under active review. Applicants are still waiting to hear from FDA on less than 10 percent of our overall pre-fiscal year 2015 ANDA workload.

As for prioritization, in August 2014 the Agency's Center for Drug Evaluation and Research (CDER) updated its Manual of Policies and Procedures (MAPP) entitled *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. This MAPP, which is publicly available, describes how the review of ANDAs, ANDA amendments, and ANDA supplements are prioritized.

FDA considers certain types of ANDAs to be public health priorities, and expedites their review accordingly. Specifically, FDA considers potential "first generic" ANDAs to be public health priorities. First generics are the first generic to enter the market for a given branded product. Potential first generics are about 15 percent of our workload. All of them have been tagged as priorities, and their review has been expedited. This is true regardless of when the ANDA was submitted. In

[19] Pursuant to the Drug Price Competition and Patent Term Restoration Act, often referred to as the "Hatch-Waxman" Amendments, FDA generally cannot approve a generic until any relevant patents and statutory exclusivity on the new drug product expire. For many potential first generic ANDAs in our workload, expiry occurs at a future date and we cannot lawfully approve them at the time our review is complete, though some may be issued a Tentative Approval, as noted above.

the past 3 years, we have approved hundreds of first generics for more than 200 new drug products. FDA also considers shortage-related drugs a priority, and expedites their review.

Question 6a. Dr. Califf, we appreciate the FDA's efforts to diligently implement Title II of the Drug Supply Chain Security Act and are encourage that thus far, implementation of the law appears to be progressing across the supply chain. As this implementation moves forward, we have the following questions.

Currently, there are several guidances that are in development such as grandfathering, and licensures for 3pls and wholesale distributors. What is the status of these items and do you expect FDA will meet the statutory deadlines? If not, will FDA provide alternative deadline for supply chain stakeholders?

Answer 6a. As you know, FDA is tasked with developing many guidances and regulations to implement the Drug Supply Chain Security Act. We are focused on accomplishing these tasks as quickly as possible while simultaneously addressing the myriad, complicated issues raised by stakeholders and providing guidance to the industry as needed. Unfortunately, we have not been able to promulgate the required national standards and licensing rules as quickly as we would like owing to the complexity and magnitude of the drug supply chain business models, the procedural requirements associated with rulemaking, and the Agency's limited resources. However, the national standards and licensing rules are a priority and we continue to work on them and the guidances required by the Act, including the grandfathering guidance.

Question 6b. Regarding licensure of 3pls and wholesale distributors, does FDA have a plan in place for outreach and direction to States about: (1) how they should adopt the pending standards and (2) how their authority may change due to Federal preemption in this area under the Drug Supply Chain Security Act?

Answer 6b. FDA's outreach includes engagement of State officials, and FDA has presented at various meetings hosted by the National Associations of Boards of Pharmacy, a group that brings together the State Boards of Pharmacy and others responsible for States' licensure of wholesale distributors and third-party logistics provider (3PLs). Additionally, on November 18, 2015, FDA held an inter-governmental working meeting on the Drug Quality and Security Act. At this meeting, FDA hosted representatives from the State Boards of Pharmacy and other State Officials responsible for licensure of wholesale distributors and 3PLs. The following issues were discussed: timing and implementation issues for States related to the licensing of wholesale distributors and 3PLs, what issues State Officials felt clarification would be helpful, and how FDA and States can improve collaboration. FDA will continue to work with the States as it implements the licensing standards under the DSCSA.

Question 6c. Colorado and many other States run nonprofit drug donation programs across the United States, helping get donated drugs to uninsured or underinsured patients. In Colorado alone, a nonprofit organization called the Supporting Initiatives to Redistribute Unused Medicine (SIRUM) has already provided 8,900 prescriptions to needy patients. These nonprofits never take ownership or possession of the drug. However, current FDA guidance threatens the ability of nonprofit drug donation programs and organizations transfer donated medicines to affiliates. The Drug Supply Chain Security Act contemplates the idea of a nonprofit organization distributing donated medications to affiliates. In that case, the transfer of medicines is not considered a "transaction". Because these nonprofits have a unique structure that does not take ownership or possession of the drug product, would the FDA be willing to provide technical assistance to these programs to ensure that nonprofit drug donation programs around the country can continue to provide the thousands of medicines a year to the uninsured and the underinsured?

Answer 6c. FDA continues to conduct outreach and education to many stakeholders, in additional to hearing about specific issues related to different and complicated business models that present unique challenges in implementing the DSCSA. Congress enacted DSCSA to allow FDA to implement a robust system to better protect the quality of drugs throughout the pharmaceutical distribution supply chain. DSCSA exempts from the definition of "transaction" (section 581(24)(viii))

> "the sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization described in section 501(c)(3) of the Internal Revenue Code of 1986 to a nonprofit affiliate of the organization to the extent otherwise permitted by law."

DSCSA also exempts from the definition of "wholesale distribution,"—

"the distribution of a drug or an offer to distribute a drug by a charitable organization to a nonprofit affiliate of the organization to the extent otherwise permitted by law"

(section 503(3)(4)(F) of the FD&C Act). FDA is examining these issues and intends to provide information to stakeholders, as necessary, to clarify how charitable donations are treated under DSCSA.

SENATOR BALDWIN

Question 1a. It is imperative that consumers get the most up-to-date, accurate information about medical products to make the best health decisions and that the medicines they take are safe. I believe that more must be done to improve both transparency and the oversight of drug products after they reach the market to ensure safety. For example, in 2012, Ranbaxy Pharmaceuticals Inc. issued a voluntary recall of lots of their generic version of Lipitor because small glass particles were found in certain batches of the product. The company had already been under investigation—and later pleaded guilty—for failing to conduct proper safety and quality tests of several of its manufacturing plants in India since 2008. Further, once Ranbaxy announced the recall, the FDA initially issued conflicting public statements about the safety of these drug products, confusing patients and doctors.

This raises a number of important issues that I hope the next FDA Commissioner will address to fulfill the agency's mission of protecting the public health. Specifically:

Do you believe that FDA needs mandatory recall authority for drugs to guarantee that dangerous products are swiftly taken off the market?

Answer 1a. Yes, FDA needs mandatory recall authority and the Agency has repeatedly sought this authority. While it is true that drug companies typically issue a recall voluntarily when FDA determines it is necessary, absent clear authority for the Agency to require a company to issue a recall we often lose critical time negotiating the terms of the recall, during which patients continue to be exposed to dangerous or ineffective products. Under the current system, a company may disagree with FDA as to the need for a recall or the scope of a recall. While we work out those matters collaboratively, patients are left vulnerable to potentially dangerous products.

Question 1b. What steps has FDA taken, including with respect to internal protocols, to improve its communication to consumers and other stakeholders about voluntary drug recalls since 2012?

Answer 1b. As a matter of policy, FDA will promptly post or issue public notification in situations that present an imminent health risk to consumers.

Firms often also issue a public warning, typically in the form of a press release. Firms are requested to provide a draft of the press release for FDA to review and comment. FDA has developed recall press release templates for firms to follow which are posted on FDA's website under industry recall guidance: *http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm*. FDA may issue its own public warning in instances where a firm declines to issue public warning, where a firm's public warning is inadequate, or where FDA believes that additional warning is needed to inform the public.

In 2012, the enforcement report, where FDA publishes recall information, was automated thereby enhancing availability of recalls to the public. Further improvements to this automated process are expected in the near future to provide more timely and accurate data to the trade and public.

FDA constantly evaluates its processes to self-identify where improvements are needed that serve better the health of the public. As part of this process and FDA transparency, FDA created the FDA Track Web page where the Agency provides performance metrics on different programs the Agency administers.[20] One of the metrics available at the Web page is recall classification timeframes. This is the time it takes the Agency to classify a recall once a firm provides the Agency with a recall notification and all the pertinent information to evaluate the recall.

Data reported on the Web page shows how steps taken such as increasing the automation of recall classification process and hiring of employees, has helped decrease the classification timeframes and help maintain a consistent high level of performance. This consistent high level of performance allows the Agency to publish recall information soon after the recall is classified.

---

[20] See *http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&status=public&id=CDER-DQC-Percentage-of-recall-classification-meeting-timeframe&fy=All*.

FDA is conducting a pilot program seeking to expedite notifications of human drug product recalls to the public. In addition to the information about classified recalls found in the weekly Enforcement Report, the Agency will include actions that have been determined to be recalls, but that remain in the process of being classified as a Class I, II, or III recall.

Question 1c. Can you please provide an update on how many inspections FDA has conducted of domestic and foreign establishments and how many adverse findings that resulted in corrective actions, since the risk-based inspection schedule for drug facilities was enacted in the FDA Safety and Innovation Act of 2012?

Answer 1c. Following FDASIA passage in 2012, our fiscal year 2013 and 2014 domestic and foreign human drug inspectional data (GMP-related) is as follows.

Number of Inspections by Fiscal Year

	2013	2014
Domestic	1851	1869
Foreign	827	993
Total	2678	2862

Fiscal year 2015 data is not yet finalized.

FDA issues FDA-Form 483s to companies, and an overwhelming number of companies undertake satisfactory corrections to the cited objectionable conditions. An FDA-Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the FD&C Act and related acts.[21] These are confirmed during the next scheduled inspection, or in an accelerated re-inspection. While corrections to specific citations are routinely corrected, FDA at times finds that problems recur, and additional interventions are necessary. These firms are reflected in our Import Alert, Injunction, and Seizure data from fiscal year 2013, 2014, and 2015, which is as follows.

Data by Fiscal Year

	2013	2014	2015
Injunction	5	1	3
Seizure	1	2	1
Import Alerts	146	101	144
Warning Letters	86	94	Data not yet available

In addition, Warning Letter Closeout data is available at: *http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?qryStr=&sortColumn=12+desc&Go=Go&__1__issueDt=&__2__issueDt=&company=&subject=&office=&hasResponseLetter=Both&hasCloseoutLetter=Yes&recsPerPageDef=500.*

Question 2. Medical foods play an important role in meeting the distinct nutritional requirements for patients with certain diseases and conditions. For example, medical foods are medically necessary for children and adults living with phenylketonuria (PKU), an inherited metabolic disorder that is characterized by the inability of the body to process the essential amino acid phenylalanine. I am encouraged by the FDA's past work in recognizing medical foods and their role in managing disorders such as PKU, and it is critical that patients and providers continue to have access to the latest safe treatments.

What more can the FDA do to apply the most recent advances in nutrition science to improve health outcomes for patients with PKU and other diseases?

Answer 2. FDA recognizes the critical role of medical foods in the lives of patients with inherited metabolic disorders such as phenylketonuria (PKU). FDA continues to work to ensure medical food products are safe and appropriately labeled so that medical practitioners are able to make informed decisions about the best care of their patients, leading to overall improved health outcomes. We are committed to staying abreast of new science that emerges concerning these disorders and working with other stakeholders to improve health outcomes for affected patients.

As an example, a recent NIH study revealed that a medical food intended for a single specific metabolic disorder was being inappropriately used to treat patients

[21] *http://www.fda.gov/ICECI/Inspections/ucm256377.htm.*

with a combination metabolic disorder, resulting in adverse effects. FDA, NIH, and a manufacturer of one such product collaborated on the matter, which led to the manufacturer changing their labeling to warn healthcare practitioners against its use for the specific combination disorder at issue. The manufacturer and NIH have agreed to continue working in partnership to further study the disorder (and other related metabolic disorders), with FDA providing any needed regulatory knowledge and guidance.

FDA has also incorporated the most recent available science in its updated Draft Medical Foods Guidance published in August 2013. We are considering the comments we received on the draft guidance, along with the latest science as we work to finalize the Medical Foods Guidance.

Advances in medical food research are critical to patients with inborn errors of metabolism and an important part of FDA's Office of Orphan Products Development (OOPD) rare disease mission. OOPD provides funding support for clinical studies that advance the development of promising medical products for rare diseases, including medical foods to manage rare diseases such as phenylketonuria (PKU). For example, OOPD is currently funding a 4-year Phase 2 PKU medical food study conducted by the University of Wisconsin. The $1.5-million study evaluates the glycomacropeptide diet with the amino acid diet for PKU patients. We welcome competitive grant applications that will further the evaluation of recent medical food research to provide better medical food options for patients with inborn errors of metabolism.

Question 3. Routine screening for social and emotional distress, or "distress screening", is a key recommendation of the 2008 Institute of Medicine report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*.[22] According to the report, up to 43 percent of cancer patients experiences psychosocial distress, which negatively impacts both quality of life and long-term survivorship rates. Distress and lack of social support services also contributes to low clinical trial participation rates among eligible patients, as well as decreased retention once the trials begin.

What role can distress screening play in improving the efficiency of the clinical trials through recruitment and retention? In what ways can the FDA incentivize increased use of distress screening and support services for clinical trial participants, especially in oncology trials?

Answer 3. We support excellence in patient-centered clinical care, in standard practice as well as clinical trials. FDA agrees that psychosocial distress can be an important issue for cancer patients and that identifying and providing services for cancer patients with increased levels of psychosocial distress can be a valuable component of routine clinical practice.

If sponsors wish to pursue these services within the context of a clinical trial, these are issues relevant to an institutional review board's review of the informed consent process and we would be willing to work with stakeholders as appropriate.

SENATOR MURPHY

Question 1. The passage of the Food Safety Modernization Act (FSMA) shifted the focus of food safety regulations from a crisis-management approach to a preventative model that seeks to identify risks and put policies and procedures in place to mitigate those risks.

Following FSMA's passage, the FDA was required to release and subsequently implement a total of seven new food safety regulations. Two of these regulations are particularly important for Connecticut farmers—the preventive control for human food and the produce rule.

I commend the FDA for taking a collaborative, thoughtful, and thorough approach to finalizing regulations under FSMA. As we move forward, it is critical Congress fully fund the FDA's budget request, particularly the $109.5 million increase in dedicated funding this year to implement FSMA. Fully funding FSMA is not only important to ensure a reliable and safe food supply, it is critical for ensuring farmers, producers, processers, and stakeholders can depend on an engaged and responsive regulator.

Connecticut is not a big agricultural State, but since 1982 there has been a 60 percent increase in the number of farms in the State. Connecticut is now home to nearly 6,000 farms. Although the number of farms has increased dramatically, the acreage of farm land has not grown at nearly the same rate. As such, most of Con-

[22] Institute of Medicine (US) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting; *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, National Academies Press (US); 2008; *http://www.ncbi.nlm.nih.gov/books/NBK4015/*.

necticut farms are small and sell directly to consumers at farmers markets or through Community Supported Agriculture.

Dr. Califf, under your leadership, what type of education, training, and technical assistance can small farmers, State agencies, and other stakeholders, particularly those that will be subject to FSMA, expect from the FDA to support a transition to FSMA compliance?

Answer 1. Please be assured that I understand the importance in providing assistance to affected stakeholders, especially small farmers, to help them comply with the new requirements. As you may know, in October 2015, the Agency released a FSMA training strategy, which outlines training options and delivery formats as well as introduces the partners in government, industry, and academia who are working with FDA on the development and delivery of training to the global community of food suppliers.[23]

Industry training will be an important component of successful implementation of FSMA. The Agency recognizes that one-size-doesn't-fit-all, and that the most important goal that FDA expects of any training program is the outcome—that it advances knowledge among the food industry to meet FSMA requirements. The needs of small- and mid-sized farms and facilities are at the center of FSMA training development and will be met through multiple efforts.

The vision of FSMA training began in 2010 through 2012 with the creation of public-private alliances, funded in part by FDA, as a resource for industry and to facilitate widespread compliance with the new standards. The Produce Safety Alliance, Food Safety Preventive Controls Alliance, and Sprout Safety Alliance (Alliances) are developing training to help domestic and foreign food producers—including small and very small farms and facilities—meet the requirements of the preventive controls and produce safety rules. The curricula developed through the Alliances are designed to be standard curricula with training modules that can be added to meet unique needs.

In addition to working with the Alliances, FDA is collaborating with the U.S. Department of Agriculture's National Institute of Food and Agriculture (NIFA) to administer and manage the National Food Safety Training, Education, Extension, Outreach, and Technical Assistance Program, as mandated in Section 209 of FSMA. This competitive grant program will provide food safety training, education, extension, outreach, and technical assistance to owners and operators of farms, small food processors, and small fruit and vegetable merchant wholesalers.

Grants issued through this program will fund a National Coordination Center (NCC) and four Regional Centers (RCs), which will be involved in both key components of training—primarily facilitating training delivery but also, in certain situations, facilitating curricula development targeted to specific audiences. FDA has awarded the International Food Protection Training Institute a grant of up to $600,000 over 3 years to establish the NCC, which will lead coordination of curriculum development and delivery to those food businesses covered by the FSMA Section 209 mandate for implementation of FSMA. The NCC will coordinate and support the delivery of standardized and/or alternate training curricula through the RCs.

The RCs will be charged with understanding and communicating the landscape of training opportunities available to target businesses in their region. They will identify any need to develop or tailor curricula to meet specific unmet regional needs and/or to target a specific audience. Training programs may differ to meet those needs. The NCC will facilitate communication between the RCs, the Alliances, and other partnering groups about the development of such region- and/or audience-specific materials.

The RCs will be established in the Southern, Western, North Central, and Northeast regions of the country. These centers will work with representatives from nongovernmental and community-based organizations, as well as representatives from cooperative extension services, food hubs, local farm cooperatives, and other entities that can address specific needs of the communities they serve.

As these efforts indicate, we fully recognize and respect the importance of small farms and processors in our economy and our food safety system. We look forward to continuing to work with these communities throughout implementation of FSMA to facilitate the successful transition to the new preventive food safety framework.

Question 2. Biologics have provided major advances in the treatment of cancer, rheumatologic disease, and other conditions but they also come at great cost to our health care system due to the expense of developing and manufacturing a drug. For example, even though they account for less than 1 percent of all prescriptions dis-

[23] *http://www.fda.gov/Food/GuidanceRegulation/FSMA/ucm461513.htm.*

pensed in the United States, expenditures on biologics amount to 28 percent of prescription drug spending, and both their use and their cost are forecast to grow sharply. This increased cost is borne by our health care system as a whole but more specifically by patients as more and more insurance companies place higher cost-sharing burdens on biologics.

While we may never get close to the price reductions that are seen in the generic market, biosimilars will likely be 15–30 percent cheaper than the reference biologic. These reductions will result in significant savings to the health care system and patients as the biosimilar market matures. However, FDA still has not released draft guidance on such key issues as labeling and interchangeability.

Dr. Califf, do you expect draft guidance on biosimilar labeling and interchangeability to be issued before the end of the year as the Center for Drug Evaluation and Research 2015 Guidance Agenda suggests?

Answer 2. FDA has published the following final guidances with respect to biosimilars: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following draft guidances since 2012: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act; Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009; and Nonproprietary Naming for Biological Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above. Upcoming guidances are expected to include: Considerations in Demonstrating Interchangeability to a Reference Product; Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity; and Labeling for Biosimilar Biological Products.

FDA is diligently working to issue guidance on issues that have been identified by the FDA and key stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide information to assist biological product developers—sponsors/companies—with bringing biosimilar and interchangeable products to market. The FDA is continuing to clarify its approach to implementation of the BPCI Act to further facilitate sponsors' development of biosimilars and interchangeable biological products.

Question 3. As FDA Commissioner, you will be charged with regulating a number of prominent industries that you have interacted with in the past. Can you inform the committee on the steps that you have taken thus far to steer clear of any potential conflicts of interest and the ongoing monitoring that is planned as new matters arise before the FDA?

Answer 3. Following my appointment as Deputy Commissioner for Medical Products and Tobacco, the Office of the Commissioner established a process for screening invitations that I receive for speaking engagements and other requests for my participation to identify potential situations which would require my recusal. A team of individuals was convened including a representative of the Office of the Commissioner and the Office of Chief Counsel. These individuals have extensive knowledge of my ethics agreement and recusal obligations. This team meets on a regular basis (often as frequently as weekly) and on an ad hoc basis as needed. A member of my staff submits detailed information regarding specific invitations/requests for my participation and the team determines whether I should be recused. If the team has any questions as to whether something is covered by the recusal, the HHS Designated Agency Ethics Official's office is consulted. The team has a standing teleconference with a representative of this office in order to facilitate consultations and determinations.

I am recused from all particular government matters that would affect Duke's financial interests, any matter in which Duke is a party or which would have a special or distinct effect on Duke, or that potentially could include particular matters involving Duke-affiliated research. If a particular matter potentially implicates Duke-affiliated research, before participating, I will consult with HHS and FDA ethics officials to determine whether my recusal allows for participation.

If my nomination is confirmed, I understand that I will be subject to more extensive recusal obligations under the President's 2009 Executive order, and accordingly that additional monitoring procedures may be needed.

SENATOR WARREN

Input of Pharmaceutical Industry Sponsors on Clinical Trials Conducted at Duke Clinical Research Institute

Question 1a. For the clinical trials you conducted or oversaw while at the Duke University School of Medicine and the Duke University Medical Center, can you detail for us exactly what input pharmaceutical sponsors did and did not have in the:

- **design of the trials?**

Answer 1a. Pharmaceutical (and device) sponsors provided input into the design of trials including the intervention, control measures, eligibility criteria, randomization, study endpoints, blinding methods, and sample size. In order for Duke to conduct the trial as the coordinating center, agreement must be reached by the academic leaders and the industry sponsor. All aspects of the design are included in the protocol, which is subject to review and approval by FDA, and for international trials, by regulatory authorities from each involved country and the European Medicines Agency. Finally, any participating research site has a Principal Investigator and an Institutional Review Board (IRB) that must review and approve the protocol in order to proceed with enrollment.

- **analysis of trial data?**

Answer. Pharmaceutical sponsors provided input into the development of the statistical analysis plan. The plan is included in the protocol, which is subject to review and approval by FDA, by regulatory authorities in other countries, and the data monitoring committee (a committee of non-conflicted experts in the relevant medical specialty, clinical trial methodology, and ethics of human studies) Finally, as noted above, any participating research site has a Principal Investigator and an Institutional Review Board (IRB) that must review and approve the protocol with its included analysis plan in order to proceed with enrollment. The details of how the analyses are actually conducted are provided below.

- **publication of trial results?**

Answer. After a publication was written by the academic investigators (including Duke investigators and other participating academic leaders), the pharmaceutical sponsor was given the opportunity to review and comment on the publication within a period of time that is specified in the contract. Final decisions about publication are made by the trial executive committee (which is comprised of the academic leaders). The industry sponsor has the right to review and comment, but no right to censor or dictate content or verbiage.

Question 1b. For each of the activities listed above:

• Which group had the final decisionmaking authority if differences arose between Duke academics and industry sponsors?

Answer 1b. In situations in which the Duke academics were not in agreement with an industry sponsor regarding the design of a trial, the Duke academics did not participate in the trial. With regard to analysis of trial data and publication of trial results, the Duke academics always had the final decisionmaking authority per the terms in the contract regarding access to data and the right to publish. For example, the right to a copy of the database is what allows the academic group to perform an independent analysis and interpretation of the trial results.

• **Did industry sponsors have veto authority over decisions related to data analysis and the publication or presentation of trial results?**

Answer. In trials coordinated by the DCRI, or in which I participated as a lead investigator, industry sponsors never had veto authority over decisions related to data analysis and the publication or presentation of trial results. As noted above, the majority of industry-sponsored multi-site clinical trials do not have an independent academic coordinating center, so I believe the approach we developed at DCRI is best practice because it provides the independent voice in analysis and publication of results.

Question 1c. Referring to the input of pharmaceutical sponsors on the analysis of clinical trial data you said at the Senate HELP Committee hearing on November 17:

> "Typically we'll have an analysis done by the company and an analysis done by our statisticians, then we compare the results to see if they match up, and resolve any discrepancies. But in no case did we allow the company to do the analysis and we just were recipients of what they said the answer was."

Answer 1c. As a prelude to this series of questions, it is important to have some key background about industry-sponsored clinical trials:

• The majority of multi-site, industry-sponsored clinical trials do not have an academic coordinating center. They are coordinated by industry and for-profit contract research organizations. In cardiovascular medicine and many other highly evidence-driven specialties, the independent role of the academic is an important element to ensure that the results are not biased, given the industry-sponsor's direct financial interest in the outcome. While most major academic medical centers have some coordinating center function, a limited number can conduct multi-national large trials, like the DCRI.

• The role of coordinating center is distinctly different from the role of a research site. The coordinating center assures that the trial is being conducted as designed by participating sites, collects the data from the sites, monitors the conduct of the trial, and does the analyses. The research site enrolls the patients, conducts the study protocol, and submits the data to the coordinating center. The research sites do not have a copy of the aggregate trial data and for the most part are not capable of doing the overall trial analysis.

• **Why might discrepancies between statistical analyses arise?**

Answer. Data bases from large, international clinical trials are complex with hundreds of thousands of pages of data and millions of data items. The analytical code to actually perform the analysis takes hundreds of hours to write and it is checked multiple times. There is also an audit trail to assure that analytical steps are not altered after unblinding. Because of this enormous complexity, there is great value in redundant checking both within the academic coordinating center and on the industry side and in checking between the two entities. All of this is done before unblinding the trial.

Academically coordinated trials that are not intended for regulatory review often do not have this level of rigor, which has led to concern about reproducibility. At the DCRI the procedures of checking and redundancy are standard for both industry-funded and government-funded trials.

• **How often did these discrepancies arise?**

Answer. Because of the careful and extensive nature of this pre-unblinding work, it is very rare to have discrepancies that are significant, and, in fact, I'm not aware of any such instances. But small differences in coding and interpretation do occur, and it's critical to resolve these. Importantly, during this checking phase on the primary analysis, the statisticians are unblinded, but the clinical investigators and clinical development experts for the sponsor remain blinded.

• **Can you describe the process for "resolving discrepancies?"**

Answer. When discrepancies arise in primary analyses, as described above, they are resolved prior to unblinding to eliminate bias. For secondary analyses and subsequent manuscripts, the academic coordinating center performs the analyses used for the study. These analyses typically are planned out in less detail prior to unblinding, but statistical analysis plans are constructed. Industry is welcome to provide a perspective from their own analyses, but control of the interpretation and message resides with the academic authors of the manuscript.

• **What factors are involved in making a final determination related to the analysis?**

Answer. As stated above, the types of discrepancies encountered in the primary analysis are small and I have not encountered a situation in which a difference has occurred that would affect the interpretation of the trial.

• **Did Duke academics or the industry sponsor have the final decision over what analysis was submitted to the FDA?**

Answer. Sponsors have the responsibility for regulatory submissions, which involve not only FDA, but the European Medicines Agency and dozens of national authorities for countries in which the product will be marketed. Accordingly, the sponsor has primary responsibility for the FDA submission, but the key analyses are duplicated by the academic coordinating center.

• **Was the analysis published by Duke academics?**

Answer. Duke academics published in the context of the purview of the executive committee and the steering committee. The final decision was made by the executive committee of the trial. The sponsors, such as Johnson and Johnson and Bayer, had input into the primary manuscript, but no right to alter the decision of the executive committee.

• **Was results published by the industry sponsor?**

Answer. The industry sponsor is not charged with publishing key results of the trial independently of the academic coordinating center and steering committee. After the steering committee has published its primary manuscripts, the industry sponsor may make its data available for others to do analyses and publish the results.

Question 1d. How many publications have you authored or co-authored that report results from an industry-sponsored study regarding the safety or efficacy of that sponsor's product?

Answer 1d. Please see question E below.

Question 1e. Please list publications you have authored or co-authored that report a negative result from an industry-sponsored study regarding the safety or efficacy of that sponsor's product.

Answer 1e. The enclosed "Table A[24], Clinical Trials and Outcomes" contains a list of clinical trials in which I played a major role in the design, conduct, or oversight. The first column gives the acronym by which the trial was known.

The second column gives the publication reference. In cases in which I was an author, the manuscript is denoted by the number on my CV that was submitted to the committee. Some trials are listed in which I played a major role, but was acknowledged in the list of committees or in subsequent articles. In these cases the reference is given.

The third column gives the trial outcome:

• **Positive** means that the trial finding and interpretation favored benefit for the sponsor's product.

• **Negative** means that the trial finding was not beneficial for the sponsor's product.

• **Mixed** means that the finding was equivocal for the sponsor's product or more than one product was evaluated with mixed results.

• **Non-inferior** means that the sponsor's product was found to be non-inferior to the comparator, and the trial was designed for this purpose. So, a non-inferior trial should be considered a positive finding from the sponsor's perspective.

• **Neutral** means that trial did not reach a conclusion about the product.

Of the 55 trials in total, 28 (51 percent) were negative; 15 (27 percent) were positive; six (11 percent) were non-inferior; and six (11 percent) were either neutral (two) or mixed (four).

The fourth column identifies the medical product that was evaluated and the final column gives a brief summary of the finding.

As expected, the majority of trials did not show a positive outcome for the sponsor's product. From the perspective of an academic researcher, the desired outcome of a trial is that it answers an important clinical question (regardless of whether that finding was positive or negative). A review of all trials done by DCRI would have a similar distribution, reflecting the tremendous need for more trials to guide clinical practice. (See Table A. Clinical Trials and Outcomes).

Question 1f. How does the conduct of privately funded clinical trials (wholly or in part) at Duke Clinical Research Institute differ from the conduct of clinical trials at other major medical centers in the United States?

Answer 1f. To fully understand the response to this question, it is critical to know that clinical trials have 2 major organizational functions: the research site and the coordinating function. Most major academic medical centers and integrated health systems participate in hundreds of industry-sponsored clinical trials as one of many research sites in each trial. As a research site, after agreeing that the study is meritorious and after independent review by the Institutional Review Board, the site conducts the trial and submits its data to a coordinating center. The individual research site is not equipped to analyze the trial data and does not have a copy of the aggregate data, nor should it, since the multi-site trials are needed to provide adequate sample sizes representative of the population likely to be treated with the therapy under evaluation, so that a single site analysis would not provide a valid scientific conclusion for the trial as a whole.

The coordinating center oversees the overall study organization, distributes and collects regulatory and operational documents and takes responsibility for overseeing the quality of the trial through a combination of auditing and monitoring the

[24] The Table referred to may be found at the end of Senator Warren's Questions and Responses. Due to the high cost of printing, the listing of Peer-Reviewed Journal Publications of Mr. Califf are being retained in the committee files.

conduct of the trial and quality of the data. The coordinating center then does the analyses and manages the Steering Committee functions and interactions with the Data Monitoring Committee.

The Duke Clinical Research Institute (DCRI) is one of a small number of major academic medical centers in the United States with the capability of coordinating large global clinical trials. Most major medical centers participate in clinical trials in the role of a research site (i.e., enrolling patients at their institution in multi-site trials). So, DCRI performs many "coordinating center" functions which are not performed by most academic centers (such as clinical monitoring and safety surveillance). Coordinating center functions are also performed by commercial contract research organizations (CROs) which conduct this activity on a fee-for-service basis. Unlike academically based coordinating centers, however, CROs do not have requirements for independent access to data and publication rights. A growing number of institutions have developed coordinating functions similar to DCRI for the same reasons, but few have the global reach or capacity of the DCRI.

Question 1g. Are the standards for preserving academic independence in sponsored research at Duke more stringent, less stringent or similar to standards at other peer institutions?

Answer 1g. As noted above, an academic center may serve in the role of a coordinating center for a multi-site clinical trial or an individual research site responsible for enrolling patients at its institution in a multi-site trial.

The standards (i.e., contractual requirements) for preserving academic independence are different based on the institution's role in the study. For example, since a specified sample size is required to discern whether a treatment is more or less safe and effective compared to another treatment (or to a placebo), the analysis of data from an individual research site is not scientifically valid. An individual research site would not typically require the right to publish the results of its own data, but rather would require that the aggregated data from all sites be subject to an independent analysis, interpretation and publication by the academic leadership of the trial.

Accordingly, an assessment of the stringency of the standards for preserving academic independence in the setting of a coordinating center requires comparison with those of other academic coordinating centers, rather than with those of individual research sites. Because Duke's standards for independent access to data and publication rights as a coordinating center are absolute, there is no situation in which its standards for preserving academic independence in sponsored research are less stringent than those of any peer institution.

Post-market Surveillance of Medical Devices

Question 2a. In response to a question from Senator Murray regarding post-market surveillance of medical devices during the Senate HELP Committee hearing on November 17, you stated:

> "The Sentinel System . . . is a model in drugs; we have 170 million Americans' claims data so when there is a problem with a drug we can look almost in real time. We need the same system on the device side."

Unique Device Identifiers (UDI) will make post-market surveillance of devices possible, but only if they are captured in electronic health information.

What steps need to occur before the FDA can integrate UDIs and medical device information into the Sentinel System, as mandated by Congress in the 2012 Food and Drug Administration Safety and Innovation Act?

Answer 2a. FDA, the Office of the National Coordinator for Health IT (ONC), and the Centers for Medicare & Medicaid Services (CMS) are working closely on the shared goal of incorporating UDIs into electronic health records (EHRs), starting with implantable devices. The recently finalized rules on the 2015 HIT Certification Criteria (ONC) and Medicare and Medicaid Electronic Health Record Incentive Programs—Stage 3 and Modifications to Meaningful Use in 2015 Through 2017 are important steps in this process as both support the addition of UDIs for implantable medical devices to the Common Clinical Data Set which would be able to be exchanged and available to providers who care for the patient.

In addition, FDA and CMS look forward to continuing to explore options that would improve surveillance in a timely and effective manner. These agencies are committed to capturing appropriate data and sharing information transparently to improve the quality and safety of care delivered to people across the Nation. FDA and CMS also support the recommendation by the National Committee on Vital and Health Statistics to consider conducting voluntary pilot tests of the benefits, costs,

and feasibility of UDIs in claims reporting between providers and commercial payers.

Voluntary pilots should address key challenges to adding UDIs to claims, including significant technological hurdles and costs (for providers, payers and others), as well as difficulties in validating UDIs reported on claims.

Question 2b. As a cardiologist and clinical trials expert who has experience with real-world data sources, how do you understand that UDI information in medical claims could support the evaluation of medical devices after approval—such as through enhancements to registries like those operated by the American College of Cardiology and to expand the Sentinel system?

Answer 2b. The current Sentinel data model focuses on querying administrative and claims data maintained by partner organizations who share aggregated results with FDA. FDA does not receive or hold personally identifiable information, but can query privacy-protected data and receive aggregated data from local environments that together cover approximately 126 million patients.

These records generally lack manufacturer or brand-specific device identifiers and therefore cannot be leveraged to perform meaningful medical device post-market surveillance. While CDRH is actively engaged in promoting the integration of UDI into electronic health information, we are also undertaking complementary efforts to develop a more comprehensive evaluation system for medical devices. FDA is exploring the means to expand Sentinel by linking national device registries to these claims data. We are currently linking clinical registries to claims data to enable the evaluation of longitudinal data. Clinical registries collect information that uniquely identifies and provides curated clinical data in selected medical device areas. These activities, along with establishing linkages to electronic health records, are envisioned to be the building blocks of a broader National System for Medical Device Post-market Surveillance [*http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm*] that would use evidence from clinical experience in a network of existing electronic data systems to improve patient safety, enhance our understanding of device performance, and facilitate device innovation.

Question 2c. If UDI information is not included in claims data, what negative repercussions would that have for the Sentinel system to evaluate specific medical devices?

Answer 2c. The current Sentinel data model focuses on querying administrative and claims data maintained by partner organizations, who share aggregated results with the FDA. FDA does not receive or hold personally identifiable information, but can query privacy-protected data and receive aggregated data from local environments that together cover approximately 126 million patients. These records generally lack manufacturer or brand-specific device identifiers.

Question 2d. What are the benefits of the integration of UDIs into electronic health records?

Answer 2d. UDIs incorporated into electronic health information, especially electronic health records and medical device registries, can help create additional, more robust, and cost-effective post-market monitoring and surveillance data sources and support additional device research by leveraging real world clinical data. UDIs allow us to more easily link the use of a device with a patient's experience with that device.

UDIs incorporated into electronic health information will also help the FDA, the health care community, and industry to:

- More accurately report and analyze device-related adverse events by ensuring that devices associated with these events are correctly identified.
- More rapidly develop solutions to reported problems.
- More efficiently resolve device recalls, including the removal of potentially harmful devices from the market.
- Reduce medical errors by enabling health care professionals and others to rapidly and precisely identify a device, obtain important information concerning the device's characteristics, and improve the identification of the device through the distribution chain to the point of patient use.

The Unique Device Identifier (UDI) system is essential to transforming postmarket surveillance of medical devices; a critical cornerstone of FDA's strategy is the incorporation of UDIs into electronic health information, particularly electronic health records (EHRs) and device registries. In the 2012 Food and Drug Administration Safety and Improvement Act, Congress required FDA to expand Sentinel to include medical devices.

Question 2e. How do you plan to work with the Centers for Medicare and Medicaid Services, the Office of the National Health Coordinator for Health Information Technology, private payers, and the medical device industry to facilitate the integration of UDIs into multiple sources of electronic health information?

Answer 2e. FDA, the Office of the National Coordinator for Health IT (ONC), and the Centers for Medicare & Medicaid Services (CMS) are working closely on the shared goal of incorporating UDIs into EHRs, starting with implantable devices. The recently finalized rules on the HIT Certification Criteria (ONC) and Medicare and Medicaid Electronic Health Record Incentive Programs—Stage 3 and Modifications to Meaningful Use in 2015 Through 2017 are important steps in this process as both support the addition of UDIs for implantable medical devices to the Common Clinical Data Set which would be able to be exchanged and available to providers who care for the patient.

Antibiotic Resistance—Antibiotic Use in Animal Agriculture

Question 3a. While FDA policies (Guidance for Industry (GFI)#209 and #213 and the Veterinary Feed Directive Final Rule) make the use of antibiotics to promote animal growth illegal and subject all remaining uses of antibiotics to veterinary oversight, I remain very concerned that these policies leave the door open for dangerous antibiotic regimens to continue. FDA officials have previously communicated to me that they plan to monitor the removal of growth promotion from labels.[25] However, measuring how many companies make promised changes in their drug labels is not an adequate measure of whether the policies have been successful at ending the misuse and over-use of antibiotics in animal agriculture.

Additionally, FDA's policies will work only if veterinarians follow appropriate prescribing guidelines that take into account not only the health of the animals in front of them, but also consider the public health. GFI #213 describes principles that veterinarians should consider when determining the appropriateness of antibiotic use for disease prevention. FDA has stated that the agency "intends to work with veterinary and animal producer organizations to reinforce the importance of these principles."[26] However, representatives from many animal producer organizations have publically voiced doubts about the need to reduce antibiotic use and the impact that the FDA's policies will have on the amount of drugs used.[27]

Given documented disagreements among stakeholders, and given that veterinary adherence to appropriate antibiotic prescribing guidelines is a critical part of FDA's policies, how will you, as Commissioner, monitor, evaluate, and take necessary actions with regard to compliance with GFI #213's appropriate antibiotic prescribing guidelines?

Answer 3a. The Food and Drug Administration (FDA or the Agency) is confident that the changes under its judicious use policy, as outlined in Guidance for Industry (GFI) #209 and GFI #213, will be effectively implemented. FDA has received written commitments from all affected pharmaceutical companies to align their products with the GFI #213 recommendations. There has been positive engagement of key stakeholders, including the animal pharmaceutical industry, the animal feed industry, and veterinary and animal producer organizations. Furthermore, once the affected products are aligned, it will be illegal to use these medically important antibiotics for production purposes or to use these products for the remaining therapeutic purposes without the authorization of a licensed veterinarian. Veterinarians play a critical role in the diagnosis of disease and in the decisionmaking process related to instituting measures to treat, control, and prevent disease.

The President's National Action Plan calls on FDA to collaborate with veterinary organizations, animal producer organizations, the animal feed industry, and others to develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive the necessary information and training to support implementation of GFI #213. As part of these efforts, FDA is working with the U.S.

---

[25] Secretaries Burwell, Carter, and Vilsack to Senator Warren, Aug. 17, 2015.

[26] Kraus, Thomas A., Associate Commissioner for Legislation, FDA to Senators Warren, Feinstein and Gillibrand, Sept. 8, 2014; FDA, *Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*. December, 2013. (pg.7)

[27] Christine Hoang, American Veterinary Medical Association (AVMA), on "The Trouble with Antibiotics," PBS Frontline, October 2014; AVMA Antimicrobial Use and Antimicrobial Resistance FAQ; Ron Philips, Animal Health Institute, in Flynn, Dan (27 May 2011) "Ag Coalition Says Antibiotic Facts are on Its Side." *Food Safety News*; Coalition letter to David Hoffman, PBS Frontline Producer, August 2014; Juan Ramon Alaix, Zoetis in Loftus, Peter. (2013 Nov. 19). Zoetis Chief Leads Animal-Health Firm Following Split from Pfizer. The *Wall Street Journal*.

Department of Agriculture (USDA) to ensure that veterinarians have access to timely, updated information and training for the appropriate use of medically important antibiotics in the feed and water of food-producing animals. For example, FDA is developing guidance on the Veterinary Feed Directive (VFD) form, which veterinarians will use, as well as supporting changes to veterinary curricula, and leveraging many opportunities to provide necessary education via our partnerships with various stakeholders.

As part of its compliance efforts, FDA will utilize its authority to conduct inspections that will provide important information for determining compliance with GFI #213. For example, VFD records will be examined as part of inspections conducted at feed manufacturing facilities. Examination of such records is an important tool for determining whether these drugs are being appropriately authorized. In addition, as part of the recent revisions to the VFD regulation, FDA updated requirements for the establishment (by veterinarians) of a veterinary-client-patient relationship (VCPR) when a veterinarian authorizes the use of a VFD drug. Since veterinarians are licensed at the State level, FDA is working closely with the State boards of veterinary medicine on this issue.

Ongoing surveillance of antibiotic use and resistance is also a critical element of FDA's strategy for assessing the impact of FDA's GFI #213. FDA's data collection efforts include enhancements to the collection and reporting of data collected under the National Antimicrobial Resistance Monitoring System (NARMS), enhancements to the collection and reporting of Antimicrobial sales and distribution data, as well as ongoing collaboration with USDA to collect additional on-farm data on antibiotic use and resistance. FDA co-sponsored a public meeting with USDA and the Centers for Disease Control and Prevention (CDC) on September 30, 2015, to obtain input from the public on approaches for enhancing collection of data on antibiotic use and resistance in animal agricultural settings. These efforts will allow FDA to better assess the effects of antibiotic stewardship policies and analyze the association between antibiotic use and resistance.

The efforts that are currently underway represent a significant step forward in addressing antimicrobial resistance. We acknowledge that this is an ongoing effort and additional measures may be needed. In addition to effectively eliminating growth promotion use and instituting veterinary oversight, we recognize the importance of ensuring that meaningful stewardship principles are applied in conjunction with the use of medically important antimicrobial drugs for therapeutic purposes, including for disease prevention. FDA is committed to working in collaboration with USDA, CDC, veterinarians, animal producers, and other stakeholders on this important effort.

Questions 3b and c. As Commissioner, what currently available data sources will you use to measure the success of FDA's current antibiotic use in animal agriculture policies at addressing the overall public health threat?

How will you work with USDA to prioritize the development of additional data sources, including measures of how antibiotics are used on farms?

Answers 3b and c. Gathering information on the way medically important antibiotics are used is essential to assessing the impact of FDA's judicious use strategy. FDA has several data sources currently available to measure antibiotic use in animal agriculture.

Under section 105 of the 2008 Animal Drug User Fee Amendments (ADUFA 105), drug sponsors must report to FDA annually on all antimicrobials sold or distributed for use in food-producing animals. FDA collects, summarizes and reports this information annually in its ADUFA 105 report. In 2014, FDA enhanced the format of its annual summary report so that it now includes information on the importance of the drug in human medicine and provides aggregate data on the approved route of administration of antimicrobial drugs sold or distributed for use in food-producing animals, whether such drugs are available over-the-counter or require veterinary oversight, and whether they are approved for therapeutic indications, or both therapeutic and production indications.

FDA also reanalyzed previous years' reports in the same manner. In May 2015, FDA proposed revisions to the ADUFA 105 reporting requirements in order to obtain estimates of sales by major food-producing species (cattle, swine, chickens, and turkeys). The additional data would help FDA further target its efforts to ensure judicious use of medically important antimicrobials. The public comment period closed on August 18, 2015, with varying reactions from stakeholder groups. The final rule is an FDA priority, and we hope to publish it next May.

In addition, FDA collaborates with USDA and CDC to collect data on antimicrobial resistance among foodborne pathogens as part of NARMS. Recent enhancements to the NARMS program make the data more useful for measuring the

effects of GFI #213, particularly a new USDA Food Safety Inspection Service slaughter-sampling program, launched in March 2013, which increases national representativeness of the animal samples. FDA is also working with State partners to perform whole-genome sequencing on NARMS samples, which will provide unprecedented details on the traits of resistant strains of foodborne bacteria from animals and animal-derived foods. In August 2015, FDA released its 2012–13 NARMS Integrated Report, which overall reveals mostly encouraging findings, with some areas of concern.

On September 30, 2015, FDA, in collaboration with USDA and CDC, held a jointly sponsored public meeting to obtain public input on possible approaches for collecting additional on-farm antimicrobial drug use and resistance data. Information from the public meeting will help FDA determine the most efficient way to collect the additional on-farm use data needed to assess GFI #213's impact on antimicrobial resistance. Combined with existing sales data on antibiotic drugs sold for use in food-producing animals and the data from NARMS, the new on-farm data will provide a more comprehensive and science-based picture of antibiotic drug use and resistance in animal agriculture. This data collection plan is intended to provide the data needed to: (a) assess the rate of adoption of changes outlined in the FDA's GFI #213, (b) help gauge the success of antibiotic stewardship efforts and guide their continued evolution and optimization, and (c) assess associations between antibiotic use practices and resistance trends over time.

In addition, FDA and USDA are collaborating with a Cornell University researcher through the National Institute of Mathematical and Biological Synthesis (NIMBioS) to develop a new mathematical modeling methodology that would inform the approach to monitoring and assessing the impacts of GFI #213. The work of this group is still ongoing. The working group has so far met in September 2014 and February 2015 (meeting summaries are available at *http://www.nimbios.org/workinggroups/WG_amr*).

Question 3d. What result or results—based on those data sources—would indicate to you that the policies have been successful or unsuccessful?

Answer 3d. FDA believes it is important to assess progress in the context of five key components or phases of the overall effort. First, FDA focused on engaging the animal pharmaceutical industry and the animal agriculture community more broadly to work cooperatively with FDA to implement the changes outlined in FDA's judicious use strategy. FDA has been able to successfully gain commitments from all affected drug companies.

Second, FDA is focused on working with these affected drug companies to complete the transition from old labeling to new labeling, to remove all growth promotion indications, and bring the remaining therapeutic indications for these products under veterinary oversight. FDA is currently in the middle of the 3-year implementation period for implementing these label changes by the target date (end of December 2016). FDA expects all affected products to be aligned by this target date.

Third, FDA continues to engage consumer advocacy groups to ensure transparency of our efforts and that the appropriate public health risks related to antimicrobial use in food producing animals are identified and addressed.

Fourth, FDA is currently working with USDA and CDC to develop approaches for collecting additional on-farm data on antibiotic use. Having better data on actual antibiotic use practices at the farm level will enhance our ability to assess whether our policies are having the desired effect to align such antibiotic use practices with good stewardship/judicious use principles.

Finally, FDA is also working with USDA and CDC to develop approaches for collecting additional on-farm data on antibiotic resistance. This additional information, along with other sources of resistance information such as that provided by NARMS, will better enable us to assess whether our policies are having the desired effect to reduce resistance.

The additional data collection efforts described above will all play an important role in assessing the impact of current as well as future measures that are implemented to address this important public health issue.

MSM

Question 4a. Earlier this year, the FDA released the "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products: Draft Guidance for Industry" which, if finalized, would change the blood donation policy for men who have sex with men (MSM) from a lifetime deferral to a 1-year deferral from last sexual contact with another man. I am pleased that the FDA has finally taken this first step toward lifting the lifetime deferral. However, the 1-year deferral policy is still not based on science, not based

on an individual donor's risk of carrying a transfusion transmissible infection, still prevents many low-risk individuals from donating blood, continues to let higher risk individuals donate, and gives no signal from the FDA that the agency is committed to achieving a fully risk-based system for all donors. If you are confirmed Commissioner, are you committed to ending the lifetime deferral policy for MSM?

Answer 4a. The Food and Drug Administration (FDA) takes its responsibility to regulate the blood supply and to ensure its continued safety for patients who receive potentially lifesaving blood products very seriously, and also understands the need to update these policies to reflect current science. In collaboration with other government agencies, and considering input from advisory committees, the FDA has carefully examined the available scientific evidence relevant to the blood donor deferral policy for men who have sex with men (MSM) and recommended a change in the blood donor deferral period for MSM from indefinite deferral to 12 months since the last sexual contact with another man. We intend to issue final guidance in the near future. In addition, FDA is committed to continuing to work with stakeholders to develop the most optimal deferral strategies, including investigating individual risk assessment.

Question 4b. When the draft guidance is finalized, how do you plan to reach out to the MSM community to explain the change in the lifetime deferral policy and encourage these individuals to donate?

Answer 4b. FDA intends to reach out to stakeholders, including the LGBT community as part of the rollout for the final guidance, when it publishes. We will explain the changes to the policy and answer any questions regarding blood donation.

Question 4c. What is your plan to ensure that the 1-year deferral policy is only a first step toward implementing a risk-based blood donation policy for all blood donors, including MSM?

Answer 4c. FDA has examined the available scientific evidence relevant to the blood donor deferral policy for men who have sex with men (MSM) and recommended a change in the blood donor deferral period for MSM from indefinite deferral to 12 months since the last sexual contact with another man. We intend to issue final guidance in the near future. In addition, FDA is committed to continuing to work with stakeholders to develop the most optimal deferral strategies, including investigating individual risk assessment.

FDA has already taken steps to implement a national blood surveillance system that will help the agency monitor the effect of a policy change and further help ensure the continued safety of the blood supply and to develop scientific evidence potentially relevant to making further changes to the blood donor deferral policy in the future.

Implementation of the surveillance system is not contingent upon changing FDA's blood donor deferral policy for men who have sex with men. The system will monitor a majority of the blood collected in the United States for a number of different transfusion-transmitted viral infections, including HIV. We anticipate that the system will provide important information that will be helpful as we continue our efforts to further enhance the high level of safety of the U.S. blood supply and potentially support further revisions to our blood donor deferral policies.

Clinical Trial Data Sharing

Question 5a. A study entitled "Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012," published last week in the *British Medical Journal*, found that several major drug companies have not met the standards for clinical trial results reporting under the Food and Drug Administration Amendments Act (FDAAA) of 2007. FDAAA established civil monetary penalties of up to $10,000 per day for non-compliance, and yet the FDA has never been imposed.

What do you do you believe the impact of greater transparency of clinical trial data and results would be on: (a) Clinical trial efficiency; (b) The cost of drug development; (c) Drug safety; and (d) Biomedical innovation.

Answer 5a. FDA supports the view that transparency of clinical trial data and results is in the public interest. FDA is committed to increasing the transparency of information available regarding clinical trials and supports the principle of providing increased access to registration information and clinical trial data and results. The requirements in Title VIII of FDAAA have resulted in greater access to information for significant numbers of clinical trials. The public, and particularly clinical trial participants, benefit from access to these results. An additional benefit of the transparency provided by *ClinicalTrials.gov* is that it may provide FDA reviewers with a fuller picture of the trials under way in a particular area. Such infor-

mation could contribute to current efforts to improve the design and quality of clinical trials and provide additional analytical tools and methodologies for analyzing clinical trial data and results.

FDA's role in protecting and helping to ensure the safety and efficacy of medical products, however, does not depend on data reported to the *ClinicalTrials.gov* data bank. FDA's regulatory and surveillance mechanisms for identifying potential medical product problems and alerting patients and health care professionals are broad and continue to improve through programs such as the Sentinel Initiative. Dissemination of research results is a fundamental and long-standing principle of science and affords clinical trial participants the opportunity to know the value of their participation. Such access informs future research and can improve study design as well as prevent duplication of unsafe trials. Ultimately, greater transparency of clinical trials results will enhance public trust in clinical research. The additional impacts on safety as a result of this transparency and any effects such transparency may have on the costs of drug development.

Question 5b. If you are confirmed Commissioner:

(1) How do you plan to work with the NIH to finalize the Proposed Rule issued this spring to fully implement and clarify the FDAAA policy?

(2) How will you ensure compliance to the disclosure policy implemented by FDAAA? and

(3) Will you enforce the law using civil monetary penalties or by other means?

Answer 5b. FDA worked with NIH to issue the Proposed Rule (published in November 2014) and continues to work with NIH to develop a final rule to implement the FDAAA requirements. The comments made to the Proposed Rule were complex and raised a number of issues that FDA is reviewing carefully and cooperatively with NIH. Although NIH is the lead for developing and finalizing the regulations and for implementing the *ClinicalTrials.gov* data bank, FDA has the responsibility for enforcing the FDAAA *ClinicalTrials.gov* requirements. However, enforcement actions are not the only tools used by FDA to ensure compliance with the statutory requirements. FDA has undertaken significant compliance efforts with regard to the *ClinicalTrials.gov* requirements, even in the absence of a final rulemaking, and will continue to do so even after a final rule is effective. However, without a final rule explaining the statute's requirements, thus putting all affected parties on a level playing field, a full enforcement program cannot be implemented. When NIH finalizes the rule, FDA will be in a better position to increase its compliance/ enforcement actions. The use of civil money penalties will depend on each case and the applicability and appropriateness of seeking such penalties. It will be part of the enforcement "tool set."

Patient Medication Information

Question 6. While the FDA strictly regulates the prescribing information meant for doctors and requires the Drug Facts on over the counter medications, patient information about a medication and its potential risks is largely unregulated. The FDA has been working in collaboration with the Brookings Engelberg Center for Health Care Reform since May 2010 to engage in research and facilitate discussions among stakeholders regarding the design, implementation, and evaluation of a PMI document. Janet Woodcock testified before the Senate Aging Committee in December 2013 to discuss the FDAs ongoing work to develop consumer-friendly patient medication information (PMI) documents. I sent a letter asking about the FDAs timeline for implementation with Senators Gillibrand, Nelson, and Blumenthal in March 2014, but received no information in the agency's response. As Commissioner, are you committed to issuing regulations that will require consumer-friendly patient medication information to be provided with prescription medications before the end of this administration?

Answer 6. FDA is in the process of developing proposed rulemaking for PMI and regulations of this type require significant public input, consumer research, and economic analysis. In order to obtain information to determine the best path forward for patient medication information, FDA has conducted research and continues to engage with interested stakeholders including patients, industry, and others, on how to improve the content and availability of PMI. These meetings have included an open public hearing on PMI in September 2010, as well as four public workshops with the Engelberg Center for Health Care Reform at the Brookings Institution since 2010 that discussed optimizing, implementing, and evaluating the adoption of PMI, the last of which was held on July 1, 2014. In addition, RTI published the results from the qualitative portion of FDA's PMI study (75 FR 78252) on October 14,

2014, in an article entitled, "Preferences for Patient Medication Information: What Do Patients Want?"

FDA is in the process of developing proposed standards for PMI format and content, a central repository to serve as a source for PMI, and methods of distribution to patients and pharmacies.

FDA continues to be committed to the development of a PMI framework where the focus is on patient comprehension and issuing regulations in a timely manner.

Biosimilars

Question 7a. The Affordable Care Act established a pathway for the approval of biosimilar drugs that will create competition in the biologic drug market. Over 5 years since this pathway became law, FDA has still not established clear rules of the road for drugmakers, and many key guidance's, including those on naming, labeling, and interchangeability have not been finalized. If you are confirmed Commissioner, what timeline will you implement for finalizing the outstanding guidances?

Answer 7a. FDA has published the following final guidances related to biosimilars: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following draft guidances since 2012: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act; Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009; and Nonproprietary Naming for Biological Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above. Upcoming guidances are expected to include: considerations in demonstrating interchangeability to a reference product; statistical approaches to evaluation of analytical similarity data to support a demonstration of biosimilarity; and labeling for biosimilar biological products.

FDA is diligently working to issue guidance on issues that have been identified by the FDA and key stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide information to assist biological product developers—sponsors/companies—with bringing biosimilar and interchangeable products to market. The FDA is continuing to clarify its approach to implementation of the BPCI Act to further facilitate sponsors' development of biosimilars and interchangeable biological products.

Question 7b. How do you plan to work with the medical and patient community to educate them about biosimilars to avoid inaccurate perceptions—like those that are still prevalent about generic drugs over 30 years since Hatch-Waxman?

Answer 7b. FDA has a multi-phase plan for communicating with stakeholders about biosimilars. The first phase of communication is to lay a solid foundation with basic definitions and descriptions about biosimilars that health care professionals and consumers can easily understand and adopt. Concurrent with the approval of Zarxio, the first biosimilar licensed in the United States, FDA used a number of tools to help reach the medical and patient community, including working with stakeholder groups, including professional associations, to share the details on the new approval and encouraging them to disseminate to their memberships; updating the consumer tools on our website, including development of a user-friendly consumer update, and providing Web content that includes background information such as definitions of biosimilar products and interchangeable products, information on how these products are prescribed, and the differences between biosimilar products and generic drugs. FDA plans to communicate information in various formats to consumers as more biosimilar products are licensed and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability. In addition to developing communication materials, as part of its multi-phase plan, FDA is conducting research on prescriber's knowledge and perceptions of biosimilars. This research will help inform future outreach and education efforts to both health care professionals and consumers. Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to increase health care provider and consumer confidence in this new category of products.

Question 7c. How do you plan to work with CMS and private insurers to help inform their biosimilar policies to be sure that they are consistent with science, encourage market competition, and encourage innovation?

Answer 7c. While the FDA does not have a role in coverage and payment decisions by CMS or other insurers, however, FDA and CMS regularly communicate about pharmacovigilance.

FDA recognizes that healthcare providers have consistently indicated the importance of assurance that biosimilars will not have clinically meaningful differences from the originator, or reference product. FDA applies a scientifically rigorous review process and approval standard to earn and sustain confidence in biosimilar products and interchangeable products. We are committed to providing this assurance and recognize its importance to the acceptance of these products, and the future success of the biosimilars program.

Opioids

Question 8a. America is in the midst of an opioid epidemic. According to the Substance Abuse and Mental Health Services Administration, 4.3 million Americans reported use of prescription painkillers for non-medical reasons in the last month, and according to the Centers for Disease Control, 16 million Americans died of an opioid overdose in 2013. Congress has signaled an especially vested interest in reducing the impact opioids have on pregnant women by passing the Protecting Our Infants Act of 2015, championed by my colleague from Massachusetts, Representative Katherine Clark.

What role do you believe the FDA has in combating this epidemic?

Answer. 8a. Misuse, abuse, addiction, and overdose of opioid medications have become a public health crisis in this country. FDA plays an important role in helping to address this issue. Our work supporting the development of non-opioid pain medications, the development of abuse-deterrent formulations of opioid drugs (including generics), and improving prescriber education are Agency priorities.

I am committed to doing what we can to curb the abuse of these drugs. We also understand the need to balance efforts to address the abuse and misuse of prescription opioid medications with legitimate and safe use of pain medicines by patients who need them.

Our hope is that there will be alternative treatment options for pain management using non-opioid pain medications. We are actively encouraging and supporting the development of such products.

At the same time, FDA will continue to work to reduce the risks of opioid abuse and misuse, but we cannot solve this complex problem alone. A comprehensive and coordinated approach is needed; one that includes Federal, State and local governments, public health experts, health care professionals, addiction experts, researchers, industry, and patient organizations.

Question 8b. If you are confirmed as Commissioner, what FDA authorities could you use to help address the opioid crisis?

Answer 8b. FDA will act within its authorities, based on science, to address the opioid crisis. When appropriate, the Agency is using its expedited programs to speed the development of products like non-opioid pain medications, abuse-deterrent formulations and formulations of naloxone that are easier to use.

Also, FDA can require a risk evaluation and mitigation strategy (REMS) when necessary to ensure that the benefits of a drug outweigh the risks. In 2012, using this authority, FDA required manufacturers to make available continuing education programs on opioid prescribing practices for prescribers. Under the REMS for extended-release/long-acting (ER/LA) opioid analgesics, manufacturers have also developed a patient-friendly counseling tool for prescribers to give to every patient, when they write a prescription for an ER/LA opioid. The REMS also includes a product-specific Medication Guide to be provided to the patient when they pick up their prescriptions. Included in these materials is information on how to safely store medications, while still in use, and what to do with the leftover supply, when it is no longer needed. We are in the process of evaluating the effectiveness of the ER/LA opioid analgesics REMS and whether any changes are appropriate.

Additionally, FDA held a public meeting and opened a public docket in February 2013 to hear from researchers, patients, health providers about issues concerning opioids, including the approved labeling for opioid medications and how it is used in clinical practice.

We listened and reviewed the science. As a result, FDA required important changes to the labeling of all ER/LA opioid analgesics. In April 2014, we finalized these required changes to the labeling for these drugs, changing their indication to inform prescribers that these drugs should only be used for pain severe enough to

require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate to provide sufficient pain relief. At the same time FDA significantly strengthened the safety warnings for these opioids. We want prescribers to use these medicines with care, and today the labeling for ER/LA opioid medicines have some of the most serious warning language that can be found in drug labeling, including a boxed warning about their potential for abuse, and clear language that calls attention to their potentially life-threatening risks.

There are additional existing post-marketing requirements for all of the ER/LA opioid analgesics that include a requirement to conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products.[28] We are working with sponsors to develop this information and these studies are currently underway.

Question 8c. How do you plan to expand our knowledge base about the safety of all drugs in pregnant and lactating women?

Answer 8c. Understanding that adequate information on the use of medications in pregnant and lactating women is extremely sparse, the Agency supports efforts to spur greater research and development in these patient populations. Such efforts must focus on building a greater foundation for both the quality and quantity of research, such as basic pharmacokinetic data, as well as addressing key policy issues that hinder additional research on the use of drugs in pregnant and lactating women.

Of note, the Agency intends to publish two revised guidances to reflect the Agency's current thinking regarding expert/scientific opinions and to ethical issues surrounding clinical evaluation of drugs used in pregnancy and lactation. These revised policy documents, *DRAFT Guidance for Industry: Clinical Lactation Studies—Study Design, Data Analysis & Recommendations for Labeling, and DRAFT Guidance for Industry: Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling* are in the final stages of the drafting process. In addition, following the May 2014 Pregnancy Registry Public workshop, the Agency has been engaged in revision of the *Guidance for Industry: Establishing Pregnancy Exposure Registries* to reflect key conclusions from this public meeting.

The Agency is also focused on improving communication of known information on the use of prescription drug and biological products in pregnant and lactating women in the labeling of these products. On December 4, 2014, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling*" rule, also known as the Pregnancy and Lactation Labeling Rule (PLLR), was published in the Federal Register.[29] The rule went into effect on June 30, 2015. The rule amends the Physician Labeling Rule[30] requirements for how information is presented in the pregnancy and lactation subsections of labeling for prescription drugs and biological products. The rule replaces the product letter categories—A, B, C, D and X—used to classify the risks of using prescription drugs during pregnancy with a description of risks within the real-world context of caring for pregnant women who may need prescription drug and/or biological products. These changes in product labeling will help ensure labels more effectively communicate important health information where prescribing decisions during pregnancy and lactation are generally individualized and involve complex maternal, fetal and infant risk-benefit considerations. The PLLR content and formatting requirements provide a more consistent way to include relevant information about the risks and benefits of prescription drugs and biological products used during pregnancy and lactation based on available information.

There is a major need to invest in clinical research in pregnant women. The success of treatment of congenital and childhood diseases has dramatically increased the need for pharmacologic treatment of chronic diseases during pregnancy. Yet, we have only a fraction of the information that we have obtained in children, because very few studies have been done. Recent FDA rules have improved the labeling of drugs for pregnant women because the old pregnancy letter category system was overly simplistic and often misleading. The new format is structured to more clearly describe available data that can be used to aid in complex risk/benefit discussions between prescribers and their patients. However, in many cases there is still a lack of high-quality data to inform about the risks of a drug when used during preg-

---

[28] *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm*.

[29] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[30] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

nancy. In such cases, the new labeling format also includes required statements to communicate that data are lacking.

Comprehensive Clinical Trials

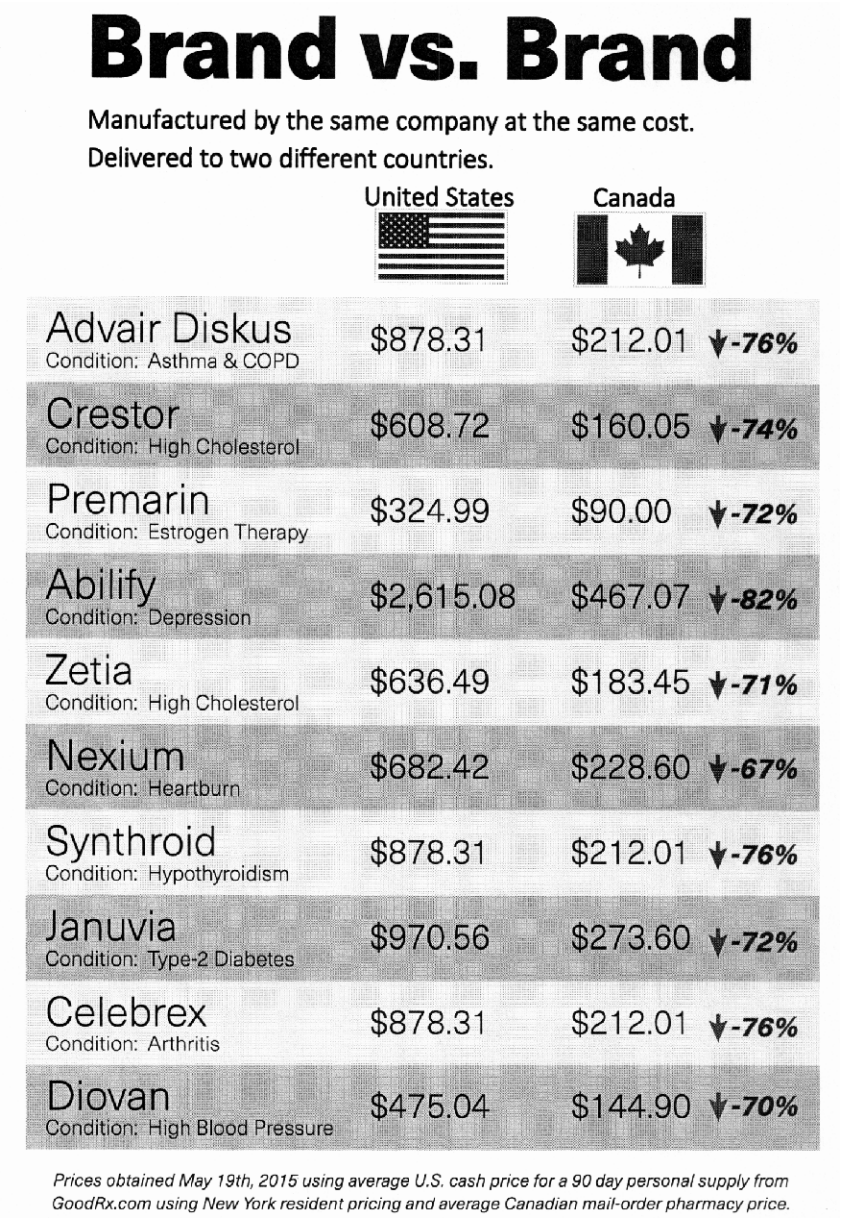
Trial	Publication #	Result	Product	Comment
TAMI 1	52	Negative	Angioplasty	Found that direct PCI did not improve outcomes after thrombolysis
TAMI 2	68	Negative	Urokinase	No improvement in Patency or LV function. Some secondary outcomes were promising
TAMI 3	79	Neutral	Heparin	Phase 2 trial did not reach conclusive result.
TAMI 4	97	Negative	Prostacyclin	No improvement in patency or LV function. Adverse to sponsor hopes for development.
TAMI 5	131	Positive	Urokinase	Reduction in reocclusion of arteries, but ultimately not enough effect to go forward to large trial
TAMI 6	155	Negative	Angioplasty	PCI beyond 12 hours from onset of symptoms did not improve LV function
TAMI 7	150	Positive	Dose-ranging study for accelerated tPA	Accelerated injection of tPA led to more rapid reperfusion
TAMI 8	176	Positive	Abciximab	Some improvement in reperfusion status
EPIC	191	Positive	Abciximab	First monoclonal antibody in cardiology; positive trial led to long, useful life cycle for abciximab
TAMI 9	201	Negative	Fluosol	No improvement in patency or LV function. Detrimental to hopes of sponsor.
CAVEAT	219	Negative	Directional Coronary Atherectomy	Direct atherectomy had more complications than PCI. Very adverse for the sponsor
PARADIGM	212	Positive for surrogate (platelet function)	Lamifiban	Early phase trial; not designed for clinical outcomes. Ultimately, the product was not fully developed
CAVEAT-2	233	Negative	Directional Coronary Atherectomy	Similar results to CAVEAT-1 In vein grafts. Very adverse to sponsor.

Trial	Publication #	Result	Product	Comment
DUCCS-2	259	Neutral	Aspirin dosing with APSAC	Could not distinguish the effect of one dose of aspirin over the other, but low dose looked better
IMPACT-AMI	306	Mixed	Integrilin and lysis	Faster lysis with integrilin, but no improvement in clinical outcomes
FIRST	324	Negative	Flolan (BW)	Stopped early for excess mortality; very adverse to sponsor
GUSTO-2	373	Mixed	Hirudin	Marginally positive result for reinfarction; not enough to market the drug for ACS indication.
IMPACT 2	401	Positive	Integrilin	
ESPRIT	JAMA 2001;285(19):2468-73.	Positive	Integrilin	I was not acknowledged as an author but in credits for being on executive committee
AMISTAD	398, 443	Positive	Adenosine	Reduction in infarct size, but subsequent Phase 3 trial was negative for improvement in clinical outcomes
PURSUIT	416	Positive	Integrilin	Positive phase 3 trial and contributed to long and successful product life cycle; validated by other trials
GUSTO 3	439	Non-inferior	Reteplase	Provided less expensive alternative to t-PA, and easier to administer
GUSTO 4	425	Negative	Abciximab	No benefit in acute coronary syndromes; this was adverse for the sponsor and surprising since abciximab was beneficial in the setting of percutaneous coronary intervention
SPICE	475	Non-inferior	Candesartan	This trial was investigating whether people intolerant to ACE-inhibitors (lifesaving drugs for heart failure) could tolerate candesartan (an angiotensin receptor blocker). It led to a positive Phase 3 trial and offered treatment for people otherwise intolerant
ASSENT-2	433	Non-inferior	TNK	Offered an easier to deliver

Trial	Publication #	Result	Product	Comment
				thrombolytic treatment
CARS	562	Negative	Warfarin	Very adverse to sponsor as it was hoped that low dose warfarin plus aspirin was a highly effective treatment with less bleeding but it didn't work out
OPTIME	584	Negative	Milrinone	Adverse to sponsor as milrinone had no benefit and some clear risks in this indication
GUSTO 2b	471	Negative	Contrast	
GUSTO 2b	NEJM 1997:336:1621-1628	Positive	Angioplasty	
ESCAPE	538	Negative	Swan Ganz Catheter	No benefit was found for this expensive invasive catheter and procedure
CAFFS	572	Positive	Intranasal steroids for chronic and recurrent rhinosinusitis	Positive for the sponsor
SYMPHONY	593	Negative	Sibrafiban	Negative for sponsor as oral GPIIb/IIIa inhibitors failed to improve outcomes in coronary disease
2nd Symphony	593	Negative	Sibrafiban	Stopped early; also negative
SADHEART	611	Positive	Sertraline in heart disease with depression (safety trial)	Treatment of depression in patients with severe coronary disease was safe and marginally effective
OVERTURE	614	Negative	Omapatrilat	This drug for heart failure failed the primary endpoint, and ultimately was not developed
BRAVO	667	Negative	Lotrifiban	Another failed oral GPIIb/IIIa inhibitor
VALIANT	683	Non-inferior	Valsartan	Major improvement in post-MI heart failure care for patients intolerant to ACE inhibitors

Trial	Publication #	Result	Product	Comment
A to Z	720, 731	Mixed	Simvastatin	This trial showed that higher does simvastatin trended towards more benefit than lower dose
Synergy	721	Non-inferior	Enoxaparin	This trial showed that enoxaparin was not inferior to heparin offering the advantage of subcutaneous administration rather than continuous infusion
HERS	Not listed as author, but was lead enroller	Negative	Hormone replacement therapy	This large trial preceded the Women's Health Initiative and showed an adverse effect of hormone replacement therapy on major clinical outcomes in post-menopausal women
CLIMB	775	Negative	Intradyalitic blood volume device	This device had an adverse effect on major clinical outcomes
PREVENT IV	791	Negative	Edifoligide	This trial stopped development
CHOIR	925	Negative	Erythropoieten	This was one of the first trials to demonstrate the serious adverse outcomes with high dose erythropoieten
EARLY ACS	952	Negative	Eptifibatide	This trial showed no significant advantage of early administration of epti. In acute coronary syndromes
NAVIGATOR	994; 995	Mixed	Nateglinide; valsartan	The goal was to prevent diabetes; valsartan had a modest benefit and nateglinide had no effect
ASCEND	1034	Negative	Neseritide	There was a tiny statistical benefit but not enough to recommend clinical use
Rocket-AF	1039	Non-inferior	Rivaroxaban	The treatment was non-inferior for death and stroke, and lowered intracranial hemorrhage and fatal bleeding
COAG	1139	Negative	Genetic tests for warfarin metabolism	Despite the known effects on measured anticoagulation status, there was no clinical benefit

Trial	Publication #	Result	Product	Comment
IMPROVE-IT	1207	Positive	Ezetimibe	Ezetimibe had a small benefit that was almost precisely what was predicted from the pre-trial data
ALEPREVENT	1208	Negative	Aleglitazar	Despite raising HDL, lowering LDL, lowering blood pressure and lowering weight, there was no reduction in cardiovascular events. Development was stopped.
Hypericum Depression Trial	JAMA 2002;287: 1807-1814	Negative	St John's Wort	Hypericum (St John's Wort) was no better than placebo for depression; sertraline only trended towards benefit
Scd-HEFT	NEJM 2005; 352: 225-237	Positive	Implanted cardiac defibrillator	Implanted cardiac defibrillators reduced mortality in high risk patients
PLATO	NEJM 2009; 361:1045-1057	Positive	Ticagrelor	Mortality benefit vs clopidogrel
APEX-AMI	JAMA 2007; 297:43-51	Negative	Pexulizumab	Adverse to sponsor; no benefit in large phase 3 trial
Gentamicin-Collagen Sponges	NEJM 2010; 363:1038-1049	Negative	Surgical sponges	The sponges, already on the market, increased infections in colorectal surgery rather than decreasing them



[Whereupon, at 12 p.m., the hearing was adjourned.]

○