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REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

FEBRUARY 1, 2012

Serial No. 112–110

Printed for the use of the Committee on Energy and Commerce

energycommerce.house.gov

U.S. GOVERNMENT PRINTING OFFICE

76–491 PDF WASHINGTON : 2012

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
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[1] Mr. Coukell did not answer submitted questions for the record.

REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS

WEDNESDAY, FEBRUARY 1, 2012

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:02 a.m., in room 2123 of the Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Rogers, Myrick, Murphy, Gingrey, Latta, Lance, Cassidy, Guthrie, Bilbray, Griffith, Pallone, Dingell, Towns, Capps, Schakowsky, Gonzalez, Ross, Matheson, Markey, Eshoo, Christensen, and Waxman (ex officio).

Staff present: Clay Alspach, Counsel, Health; Michael Beckerman, Deputy Staff Director; Mike Bloomquist, General Counsel; Anita Bradley, Senior Policy Advisor to Chairman Emeritus; Andy Duberstein, Deputy Press Secretary; Paul Edattel, Professional Staff Member, Health; Debbee Keller, Press Secretary; Ryan Long, Chief Counsel, Health; Carly McWilliams, Legislative Clerk; John O'Shea, Professional Staff Member, Health; Heidi Stirrup, Health Policy Coordinator; Alli Corr, Democratic Policy Analyst; Eric Flamm, FDA Detailee; Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor; Karen Nelson, Democratic Deputy Committee Staff Director for Health; and Rachel Sher, Democratic Senior Counsel.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The chair recognizes himself for 5 minutes for an opening statement.

Today, we will discuss reauthorizations of the Prescription Drug User Fee Act, PDUFA, the Best Pharmaceuticals for Children Act, BPCA, and the Pediatric Research Equity Act, PREA, all of which expire September 30 of this year. We will also discuss pharmaceutical supply chain issues.

PDUFA was first authorized by Congress in 1992 with the goal of expediting human drug applications through the FDA approval process. Under the act and its subsequent reauthorizations, the drug industry pays user fees to FDA, and FDA commits to meet

certain performance goals. I am pleased that the industry and FDA have reached an agreement for PDUFA V, and I look forward to hearing more of the details from our witnesses. Under the agreement, industry would pay over $700 million in fiscal year 2013, and higher amounts in the remaining 4 years.

The PDUFA V agreement is designed to speed new drugs to patients awaiting treatments and cures, while ensuring the highest safety standards. It is also designed to make the approval process more timely, predictable, and certain for drug sponsors and the venture capitalists who fund new drug research.

Among the highlights, the agreement increases the communication between FDA and drug sponsors, specifically building contacts and meetings into the regulatory review process. To increase the efficiency and predictability of the review process, a new 60-day validation period will be used for FDA and drug sponsors to communicate, interact and plan before the clock officially starts.

We are also here to discuss the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. BPCA gives FDA the authority to extend a 6-month period of market exclusivity to a manufacturer in return for specific studies on pediatric use. Under PREA, a manufacturer of a new drug or biologic is required to submit studies of a drug's safety and effectiveness when used by children.

Most prescription drugs have never been the subject of studies specifically designed to test their effects on children. Yet, when no pediatric-approved drugs exist for an illness, doctors often prescribe these medications to children, relying on the safety and effectiveness demonstrated with adults, in the absence of clinical data on how the drug may work in a child. As a father and grandfather, I view reauthorizing BPCA and PREA as a step toward obtaining that data and ensuring that our children and grandchildren receive the correct medications and correct dosages when they are ill.

We should not forget that Americans are the most innovative people on earth, and the United States leads the world in new drug development. Some 4 million jobs in the United States are directly or indirectly supported by the drug industry.

If the goals of the PDUFA V agreement are realized, we will continue to be the world leader in new, safe and effective life-saving and life-enhancing drugs; American patients will have timely access to treatments and cures for everyday maladies, chronic illnesses, and terminal diseases; and we will keep good, well-paying jobs here in the United States.

[The prepared statement of Mr. Pitts follows:]

Opening Statement of the Honorable Joseph R. Pitts
Subcommittee on Health
Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients
February 1, 2012

Today, we will discuss reauthorizations of the Prescription Drug User Fee Act (PDUFA), the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA), all of which expire September 30th of this year.

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Most prescription drugs have never been the subject of studies specifically designed to test their effects on children.

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As a father and grandfather, I view reauthorizing BPCA and PREA as a step toward obtaining that data and ensuring that our children and grandchildren receive the correct medications and correct dosages when they are ill.

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- We will continue to be the world leader in new, safe, and effective life-saving and life-enhancing drugs;
- American patients will have timely access to treatments and cures for everyday maladies, chronic illnesses, and terminal diseases;
- and we will keep good, well-paying jobs here in the U.S.

Mr. PITTS. I would like to thank all of our witnesses for coming today and now yield to the vice chairman, Dr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman and Madam Commissioner. Thank you very much for being here. Thank you for the hospitality you have shown to me and my staff on the two times we ventured out to the FDA during your tenure. I certainly appreciate the time you spent with us.

We are here to talk about the User Fee Act reauthorizations, but we are also here to ask some questions about how the FDA as a whole is successfully accomplishing its mission. If we don't understand where we are, it is hard to know where we are trying to go, and this committee has already laid an aggressive schedule and foundation for the user fee reauthorizations. Certainly, today's hearing is going to be a big part of that because it is an issue of patient safety, and we are all for patient safety. That is not a partisan issue. We are also all for creation of American jobs. That is not a partisan issue, or should not be a partisan issue either.

And the big question I have is the lack of predictability driving American drug manufacturers out of the country. We are trying to encourage job growth and innovation in this country. Does the FDA's slow approval process send venture capitalists elsewhere where they can find more stability? Is there a way to continue to streamline the approval process of single-molecule drugs where you have the most regulatory experience?

The FDA must have the infrastructure and programs in place in order that innovations are dealt with in a fashion that assures safety for the patient and a straightforward and streamlined approved process.

Mr. Chairman, I thank you for the recognition. I will yield back the balance of my time.

[The prepared statement of Mr. Burgess follows:]

Congressman Michael C. Burgess, M.D.
Opening Statement
Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients
Energy & Commerce Committee: Health Subcommittee
February 1, 2012

Thank you Mr. Chairman,

As the time approaches for the reauthorization of PDUFA it is essential we look not only if the FDA is meeting the goals outlined in statute, but if the agency as a whole is successfully accomplishing its mission. Where we are is just as important as where we want to go.

This Committee has already laid an aggressive foundation for the User Fee Reauthorizations. Today we have Commissioner Hamburg and I look forward to further advancing many of the issues that will impact all the agreements, and certainly PDUFA – the subject of today's hearing is no exception.

These Agreements present us with tremendous opportunity as we all want a strong and efficient FDA that provides both clarity for companies on approval and a watchdog for American patients – and thus need not fall subject to unnecessary partisanship.

Lack of predictability is driving American drug manufactures out of the country. When we are trying to desperately encourage job growth and innovation in this country, slow FDA approval process sends venture capitalists elsewhere where they can find more stability.

FDA can continue to streamline the approval process of single molecule drugs– which they have the most regulatory experience.

FDA must have the infrastructure and programs in place to ensure all innovations are dealt with in a fashion that ensures safety for the patient as well as a straightforward and streamlined approval process.

But if we can't handle the fundamentals, then we have a big problem.

I look forward to working with this subcommittee throughout the reauthorization process and having a constructive dialogue with FDA to make sure we get on the right path.

Thank you and I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman, and thank you, Mr. Pallone, for allowing me to give my statement at this point.

Today, we begin, once again, the process of reauthorizing the UFAs and our pediatric drug testing laws. I have been a part of this process since the inception of each of these programs, starting first with the Prescription Drug User Fee Act in 1992. In every reauthorization, we have worked together on a bipartisan basis. Of course, that is how it should be, given the role these laws play in helping FDA fulfill its vital public health mission.

The drug and device user fee programs ensure that FDA gets critical dollars to allow the agency to complete its premarket review in a timely manner so that patients have access to therapies at the earliest possible time. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act give FDA the authority to obtain information about the use of drugs in children. And this year, for the first time, we will be establishing two new programs to help speed FDA's review of low-cost generics and biosimilars.

As we begin this process, these are the primary goals we need to keep in mind. We must reauthorize and establish these essential programs in a timely way so that FDA can do its job protecting the health and safety of American patients. It would be irresponsible to allow this legislation to become a vehicle for the wish lists of members seeking to move their own controversial bills. I hope we should continue the long tradition of UFA bipartisanship and work together to ensure this does not happen.

I am concerned, however, about some of the bills our counterparts across the aisle have suggested will be under consideration. Some of these bills would prevent FDA from insisting on adequate data from clinical trials and forcing it to approve drugs and devices on an incomplete record. These proposals would prove disastrous for the safety and efficacy of our drugs and devices. Another would enrich the pharmaceutical industry by gutting the time-tested system of incentives provided under Hatch-Waxman. The cost of this windfall would fall on the backs of American patients who under that proposal would be forced to pay monopoly drug prices for 15 years.

Another controversial proposal the majority intends to consider would fundamentally reform FDA's mission by adding things like "economic growth, innovation, competitiveness, and job creation" to the agency's priorities. The title of this hearing suggested our colleagues across the aisle also believe that creating jobs should be one of FDA's many responsibilities. I hope we would all agree that FDA should not take jobs into consideration when it is reviewing the safety and effectiveness of a new medicine. We want FDA to ensure that our drugs and devices are safe and effective. Whether jobs will be created is simply not a part of that scientific public health equation. As a matter of fact, some of the new drugs, if they

are higher priced and don't do any more than the older drugs, may be a financial burden and one could then evaluate that at FDA, which is also not FDA's appropriate role.

It appears that many of these proposals are driven by rhetoric insisting that FDA has become too demanding of companies seeking to market their drugs and devices. As a result, innovation and jobs are being driven abroad. When we examine claims as serious as these, we must insist on data and on facts. Biased anecdotes from individual constituent companies do not qualify as fact. I am aware of no reliable data showing that these claims are true. To the contrary, I am aware of some studies showing, for example, that FDA actually approves drugs faster than our counterparts in Europe. I am also aware of a study showing that FDA is quite flexible in its requirements in reviewing orphan drug applications. NORD is here today and will testify on this study.

We should all be united in the goal of ensuring that we have a strong, well-resourced FDA that is armed with a full complement of authorities to protect us from unsafe drugs and to assure that those drugs work. That is FDA's fundamental mission, and it is in no one's interest to have a weak FDA. American consumers depend on FDA. If Americans lose confidence in the FDA, they will lose confidence in the pharmaceutical and medical device industries as well.

One final point. I appreciate that we are looking at the increasing globalization of our drug supply as a feature of our hearing. It is critically important issue. FDA has indicated that it needs an updated set of tools to deal with this dramatically different marketplace, and I look forward to hearing more on this issue from our witnesses today.

Mr. Dingell, Mr. Pallone, Ms. DeGette and I have proposed legislation, the Drug Safety Enhancement Act, that will go a long way toward providing FDA with these much-needed resources and authorities.

Thank you, Mr. Chairman. I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from New Jersey, Mr. Lance, for 5 minutes.

OPENING STATEMENT OF HON. LEONARD LANCE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. LANCE. Thank you, Mr. Chairman.

Congress first authorized PDUFA in response to lagging approval times for prescription drugs at the FDA. Under the agreement, the FDA collects funds from drug sponsors to help expedite the human drug approval process. Not only has PDUFA improved the approval times of drugs, but the past authorizations have led to improved safety policies, better communication and improved regulatory processes at the FDA.

The current reauthorization, PDUFA V, includes provisions to provide the FDA with tools to make safe and effective new medicines available to patients in a more efficient, consistent and timely manner while maintaining the high review standards for safety and efficacy. Additionally, the agreement contains new provisions to address problems that have arisen since PDUFA IV. This in-

cludes the implementation of a new benefit risk framework, patient-focused drug development, standardization of the risk evaluation and mitigation strategies, and a new implementation plan for the rare-disease program, something that is close to my heart.

I look forward to hearing from the panels on their views on the agreement and working with my colleagues on both sides of the aisle on the committee to reauthorize this vitally important legislation.

Thank you, Mr. Chairman, and I yield the balance of my time to Dr. Murphy.

[The prepared statement of Mr. Lance follows:]

Opening Statement of the Honorable Leonard Lance
Subcommittee on Health
Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients
February 1, 2012

Thank you Mr. Chairman.

Congress first authorized the Prescription Drug User Fee Act (PDUFA) in response to lagging approval times for prescription drugs at the US Food and Drug Administration (FDA.) Under the agreement, the FDA collects funds from drug sponsors to help expedite the human drug approval process.

Not only has the PDUFA legislation improved the approval times of drugs, but the past three authorizations have led to improved safety policies, better communication and improved regulatory processes at the FDA.

The current reauthorization, PDUFA V, includes provisions to provide the FDA with tools to make safe and effective new medicines available to patients in a more efficient, consistent and timely manner while maintaining the high review standards for safety and efficacy.

Additionally, the agreement contains new provisions to address problems that have arisen since PDUFA IV. This includes the implementation of a new benefit-risk framework, patient-focused drug development, standardization of the Risk Evaluation and Mitigation Strategies and a new implementation plan for the Rare Disease Program, an area I am particularly interested in.

I look forward to hearing from the panels on their views on the agreement and working with my colleagues on the committee to reauthorize this vitally important legislation.

Thank you, I yield back my time.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. I thank the gentleman for yielding.

As this committee begins the processing of reauthorizing the Prescription Drug User Fee Act, it is important to look back at where we were when this was first enacted.

Prior to the first PDUFA agreement in 1992, it took almost 2 years for the FDA to review new drug applications and roughly 70 percent of all new drugs were entering the market overseas before they became available to U.S. patients. By 2007, review time for new drugs had been reduced to just over 1 year. The backlog of applications that had been built up prior to PDUFA had been cleared, and today, 50 percent of new drugs are now marketed in the United States first, making us the world leader in bringing new treatments to market.

The certainty and transparency provided to drug manufacturers as a result of PDUFA have been key drivers of economic development in the biopharmaceutical sector. In 2009, the industry was directly supporting almost 650,000 jobs and as many as 4 million jobs indirectly while boasting a total economic impact of $918 billion annually.

Now industry and the FDA have come together and negotiated an agreement that seeks to expand transparency and consistency in the drug approval process while continuing to ensure patient safety. As this committee reviews this agreement, we must have three priority goals: one, ensuring the safety of patients; two, facilitating access to new treatments for patients as soon and as safely as possible; and three, establishing a review process that continues to allow U.S. pharmaceutical jobs to flourish. Let us gather the facts on these three essential goals and work together towards a bill that saves lives and saves jobs.

With that, Mr. Chairman, I will yield to Dr. Gingrey of Georgia.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, I thank the gentleman from Pennsylvania for yielding to me.

The reauthorization of the FDA user fee program presents Congress with the opportunity to improve upon the current U.S. drug and device approval pathway. These hearings also present us with an opportunity to work together for patients and businesses back home in our districts who tell us that reform is long overdue. I look forward to working with my colleagues on both sides of the aisle to accomplish this worthy goal.

To Dr. Hamburg, a special welcome. It is good to see you before this subcommittee again, Dr. Hamburg. You and I have spent time talking over the past year and a half about the potential that regulatory science holds as well as the need to spur antibiotic drug development, and I want to commend you for your leadership in these fields and personally thank you for your support of our efforts on Generating Antibiotic Incentives Now, the GAIN Act, H.R. 2182. My GAIN Act original cosponsors, Gene Green, Ed Whitfield, Diana DeGette, John Shimkus, Anna Eshoo, Mike Rogers, and the latest

edition, and not the least, Ed Markey, thank you for your efforts and that of your staff on the GAIN Act. This is truly a bipartisan piece of legislation. We created it together. We have advocated for it together, and it is because of our combined efforts that it has a real chance of becoming law.

Finally, thank you to the long list of GAIN Act supporters, and specifically, the Pew Charitable Trust, which I see will be testifying on the second panel.

With that, Mr. Chairman, I thank you for the time and I yield back.

[The prepared statement of Mr. Gingrey follows:]

Opening Statement of the Honorable Phil Gingrey
Committee on Energy and Commerce
Subcommittee on Health
February 1, 2012
Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients

The reauthorization of the FDA user fee programs presents Congress with the opportunity to improve upon the current U.S. drug & device approval pathway. These hearings also present us with an opportunity to work together for patients and businesses back home in our districts who tell us that reform is long overdue. I look forward to working with my colleagues on both sides of the aisle to accomplish this worthy goal.

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To my GAIN Act co-authors Gene Green, Ed Whitfield, Diana DeGette, John Shimkus, Anna Eshoo, & Mike Rogers - thank you for the efforts of you and your staff on the GAIN Act. This is truly a bipartisan piece of legislation. We created it together, we have advocated for it together, and it is because of our combined efforts that it has a real chance of becoming law. Finally, thank you to the long list of GAIN Act supporters and specifically the PEW Charitable Trust – which I see will be testifying on the second panel.

Mr. PITTS. The chair thanks the gentleman and yields to the ranking member of the subcommittee, Mr. Pallone, for 5 minutes.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts, and I welcome today's hearing and I am very much looking forward to working together on the critical business of this subcommittee.

This is the beginning of a multi-month process in this subcommittee that will involve many hearings, lengthy deliberations, negotiations amongst members and staff, and final legislation on critical FDA policy.

The User Fee Acts, which has become known as the UFAs, will include reauthorizations of some successful and some not as successful FDA programs. This will be our subcommittee's opportunity of working alongside the FDA, industry and other stakeholders to build upon and improve these critical programs. It will also include some new programs such as a generic drug user fee program that I am optimistic will help to advance generic drug utilization in this country.

But today's hearing will focus on the reauthorization of the Prescription Drug User Fee Act, otherwise known as PDUFA. Originally authorized in 1992, PDUFA has provided FDA with the additional resources it needs to efficiently review an application for a new drug or biologic to enter the marketplace.

I would like to first applaud the FDA and the brand drug industry for coming together on this thorough and responsible agreement. PDUFA has been a remarkable success, giving patients access to safe, effective and breakthrough medical treatments while supporting the advancement of science and promoting a thriving pharmaceutical industry in the United States, and I know that we all agree that failure to reauthorize PDUFA in a timely manner would be extraordinarily disruptive and a misstep for all parties involved, so I look forward to hearing from our witnesses about the important compromises made in this agreement and how it will help to strengthen the PDUFA program overall.

That said, I would like to note that as we set out to reauthorize this program for a fourth time, an important issue remains unresolved, and that is the growing globalization of the drug marketplace. I believe that Americans deserve the confidence that the drugs they rely on will help them get better and not make them more sick. That is why along with Mr. Dingell, Mr. Waxman and Ms. DeGette, I will be advocating for critical provisions of the Drug Safety Enhancement Act to be included in these reauthorizations. The bill would equip the FDA with the increased authorities and resources it needs to keep pace with an increasingly international marketplace of products. It is imperative that the FDA play a role in improving quality and safety standards of manufacturing facilities abroad. This legislation process presents a unique opportunity for this subcommittee to make extraordinary changes to enhance our drug safety laws, and it is my hope that my colleagues on both sides of the aisle, consumer advocates and the regulated industry,

can all come together to ensure we address the safety of the Nation's drug supply in a meaningful way.

Also under discussion today is the reauthorization of two pediatric programs, the Best Pharmaceuticals for Children Act, BPCA, and the Pediatric Research Equity Act, PREA, which are designed to provide necessary research on the appropriate use of prescription drugs in pediatric populations. These programs have been crucial in the successful cultivation of important research used by doctors and parents to better determine what kind of drug therapy is safest and most appropriate for a child. Above all else, we must ensure that the prescriptions our children use are tested appropriately and deemed safe. I believe that we can all agree that we have an enormous responsibility to our children to make certain that they have access to the best possible medical treatment. BPCA and PREA are two different but complementary approaches towards accomplishing that goal.

Now, the regulatory authority granted to FDA under PREA is linked to the expiration of BPCA and thus will also expire at the end of this fiscal year. I understand there are proposals being offered by some members on the subcommittee that would sunset the expirations on both programs, and I have some concerns with that approach, so I am eager to hear from our witnesses about their views on the linkage and expiration of these programs.

Now it is time for us to get to work on these critical issues. It is my hope that our subcommittee can work in a bipartisan manner and produce strong consensus legislation, and again, I want to thank all our witnesses for being here today, including Dr. Hamburg, who I have to say with regard to Dr. Hamburg, she has been incredibly cooperative, come to my district and I know other districts to talk about the FDA, and I do believe we have made substantial progress under your leadership, so I want to commend you for that. Thanks.

I yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

We have two panels today. Our first panel will have just one witness, Dr. Margaret Hamburg, the Commissioner of FDA, and we are happy to have you with us today.

Dr. Hamburg, you are recognized for 5 minutes for your opening statement.

STATEMENT OF MARGARET A. HAMBURG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION

Ms. HAMBURG. Good morning, Mr. Chairman and members of the subcommittee. I am Dr. Margaret Hamburg, Commissioner of Food and Drugs, and I really do appreciate this opportunity to discuss the reauthorization of both the Prescription Drug User Fee Act and legislation to promote pediatric drug testing, laws that will expire if not reauthorized this year. I will also talk about FDA's efforts to promote science and innovation as well as the continuing challenges of ensuring the safety of medical products in a global marketplace.

I am joined today by Dr. Theresa Mullin, who is the Director of the Office of Planning and Informatics in the Center for Drug Evaluation and Research, and Deborah Autor, Deputy Commissioner for

Global Regulatory Operations and Policy. Dr. Mullin actually served as FDA's lead negotiator during the recent PDUFA reauthorization discussions and leads our long-range planning efforts within the Center for Drug Evaluation and Research. I have also charged Ms. Autor, Deb Autor, in a new role recently to really help the agency to adapt to the challenges of globalization and import safety as the Deputy Commissioner of a newly organized entity to really focus on these important challenges. Both are very distinguished and they are available to help answer some of the questions that you may have based on their ample experience and knowledge.

I am pleased to report that we have transmitted our recommendations for three user fee programs to help fund our prescription drug, generic drug and biosimilar review programs to Congress ahead of schedule. I am also very placed to announce this morning that FDA and industry have also agreed in principle to a user fee program for medical devices.

Congress first enacted the Prescription Drug User Fee Act, also known as PDUFA, back in 1992, as was noted. Before PDUFA, FDA's review process was understaffed, unpredictable and slow. Patients in the United States often had to wait for new products that were already available in foreign countries. PDUFA revolutionized the drug approval process by providing the funding necessary for us to conduct faster, more predictable reviews.

In the nearly 20 years since PDUFA was first enacted, FDA has approved over 1,500 new drugs and biologics. In the last fiscal year, FDA approved 35 new groundbreaking medicines, actually the largest number second to only one other year in the last couple of decades. We were able to approve two new treatments for hepatitis C, groundbreaking medicines using more advanced science, targeting molecular targets linking diagnostics and therapeutics. We approved the first drug for Hodgkin's lymphoma in 30 years and the first drug for lupus in 50 years, and just this week we approved innovative new drugs to treat cystic fibrosis and skin cancer, and we did it ahead of our PDUFA performance goals. The United States now in fact leads the world in the introduction of novel drugs.

We look forward to working with the subcommittee on the fifth authorization of PDUFA. In keeping with the requirements Congress put into place, we negotiated this new PDUFA agreement with industry while regularly consulting consumer, patient and health care professional organizations. The agreement contains several enhancements that address the concerns raised by industry and public stakeholders as well as the agency's priorities. These enhancements include initiatives to improve communication between FDA and industry to speed up drug development, advance the science behind drug regulation, particularly around rare diseases, enhance the way FDA evaluates the risks and benefits of therapies, modernize FDA's drug safety system, and require electronic submission and standardize the format of the data that we receive. Together, these improvements, along with additional funding industry will be providing under the agreement, will allow us to maintain our Nation's leadership in drug development while preserving our high standards for safety and efficacy.

On the same timetable for reauthorization as PDUFA are two laws designed to ensure that drugs are appropriately tested for their use in children, entitled the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, also known as BPCA and PREA. These two laws have dramatically improved our understanding of the safety and efficacy of drugs prescribed for our children, and I want to thank Representatives Mike Rogers and Anna Eshoo, who are leading the reauthorization efforts on these important laws.

Before enactment of BPCA in 1997, all too often, health care professionals were forced to rely on imprecise and ineffective methods to provide medications for children such as adjusting dosing based on weight or crushing pills and mixing them in food. But today, as a result of BPCA and PREA, approximately 400 drugs have been studied and labeled specifically for pediatric use. We welcome the opportunity to work with Congress to reauthorize these successful programs.

Lastly, I will turn to the challenges posed by globalization and FDA's efforts to meet these challenges. Today, approximately 40 percent of the drugs Americans take are manufactured outside our borders and up to 80 percent of the active pharmaceutical ingredients in those drugs come from foreign sources. Over the next decade, FDA will transform itself from a domestic agency operating in a globalized world to a truly global agency fully prepared for a regulatory environment in which product safety and quality knows no borders.

To achieve this transformation, the agency is developing a new, more international operating model that relies on strengthening collaboration, improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources. We are eager to work with Congress to ensure that our regulatory authorities keep pace with an increasingly globalized world.

So I thank you for the opportunity to testify today and I am happy to address any questions that you may have.

[The prepared statement of Ms. Hamburg follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

MARGARET A. HAMBURG, M.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS"

February 1, 2012

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Margaret Hamburg, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the fifth authorization of the Prescription Drug User Fee Act (PDUFA), also referred to as "PDUFA V," and the renewal of legislation to promote pediatric drug testing. I will also talk about FDA's efforts to promote the science and innovation necessary to ensure that we are fully equipped to address the public health issues of the 21st century and the continuing challenges of a global marketplace.

Background on PDUFA

FDA considers the timely review of the safety and effectiveness of New Drug Applications (NDA) and Biologics License Applications (BLA) to be central to the Agency's mission to protect and promote the public health. Prior to enactment of PDUFA in 1992, FDA's review process was understaffed, unpredictable, and slow. FDA lacked sufficient staff to perform timely reviews, or develop procedures and standards to make the process more rigorous, consistent, and predictable. Access to new medicines for U.S. patients lagged behind other countries. As a result of concerns expressed by both industry and patients, Congress enacted PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. At the same time, FDA committed to complete reviews in a predictable time frame.

These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval.

Three fees are collected under PDUFA: application fees, establishment fees, and product fees. An application fee must be submitted when certain NDAs or BLAs are submitted. Product and establishment fees are due annually. The total revenue amounts derived from each of the categories—application fees, establishment fees, and product fees—are set by the statute for each fiscal year (FY). PDUFA permits waivers under certain circumstances, including a waiver of the application fee for small businesses and orphan drugs.

Of the total $931,845,581 obligated in support of the process for the review of human drug applications in FY 2010, PDUFA fees funded 62 percent, with the remainder funded through appropriations.

PDUFA Achievements

PDUFA has produced significant benefits for public health, providing patients faster access to over 1,500 new drugs and biologics, since enactment in 1992, including treatments for cancer, infectious diseases, neurological and psychiatric disorders, and cardiovascular diseases. In FY 2011, FDA approved 35 new, groundbreaking medicines, including two treatments for hepatitis C, a drug for late-stage prostate cancer, the first drug for Hodgkin's

lymphoma in 30 years, and the first drug for lupus in 50 years. Of the 35 innovative drugs approved in FY 2011, 34 met their PDUFA target dates for review.

Substantially Reduced Review Times

PDUFA provides FDA with a source of stable, consistent funding that has made possible our efforts to focus on promoting innovative therapies and help bring to market critical products for patients.

According to researchers at the Tufts Center for the Study of Drug Development, the time required for the FDA approval phase of new drug development (i.e., time from submission until approval) has been cut since the enactment of PDUFA,[1] from an average of 2.0 years for the approval phase at the start of PDUFA to an average of 1.1 years more recently.

FDA aims to review priority drugs more quickly, in six months vs. 10 months for standard drugs. Priority drugs are generally targeted at severe illnesses with few or no available therapeutic options. FDA reviewers give these drugs priority attention throughout development, working with sponsors to determine the most efficient way to collect the data needed to provide evidence of safety and effectiveness.

Reversal of the "Drug Lag"

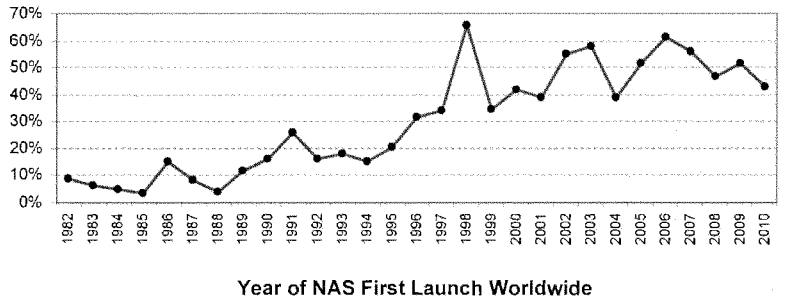
Importantly, PDUFA has led to the reversal of the drug lag that prompted its creation. Since the enactment of PDUFA, FDA has steadily increased the speed of Americans' access to important new drugs compared to the European Union (EU) and the world as a whole. Of

[1] Milne, Christopher-Paul (2010). *PDUFA and the Mission to Both Protect and Promote Public Health* [PowerPoint slides]. Presentation at the FDA PDUFA Public Meeting, Rockville, MD.

the 35 innovative drugs approved in FY 2011, 24 (almost 70 percent) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency. Of 57 novel drugs approved by both FDA and the EU between 2006 and 2010, 43 (75 percent) were approved first in the United States.

Figure 1 below shows that since the late 1990s, the United States has regularly led the world in the first introduction of new active drug substances.[2] Preliminary data show that in 2011, over half of all new active drug substances were first launched in the United States.

Figure 1. U.S. Share of New Active Substances (NAS) First Launched on the World Market



In recent years, FDA's drug review times also have been, on average, significantly faster than those in the EU. It is difficult to compare length of approvals for FY 2011 because many of the drugs approved in the United States have not yet been approved in the EU. A comparison of drugs approved in the United States and the EU between 2006 and 2010 is illustrative, however. For priority drugs approved between 2006 and 2010, FDA's median

[2] Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005), PharmaProjects R&D Annual Review (2006-2010). New active substances include novel chemical or biological substances not previously approved to treat any disease. There is a close, but not complete overlap, between new active substances and new molecular entities: new active substances exclude radiopharmaceuticals.

time to approval was six months (183 days), more than twice as fast as the EU, which took a median time of 13.2 months (403 days). For standard drug reviews, FDA's median time to approval was 13 months (396 days), 53 days faster than the EU time of 14.7 months (449 days).

A recent article in the journal *Health Affairs* also compared cancer drugs approved in the United States and EU from 2003 through 2010. Thirty-five cancer drugs were approved by the United States or the EU from October 2003 through December 2010. Of those, FDA approved 32—in an average time of 8.6 months (261 days). The EU approved only 26 of these products, and its average time was 12.2 months (373 days). This difference in approval times is not due to safety issues with these products. All 23 cancer drugs approved by both agencies during this period were approved first in the United States.[3]

Providing Guidance to Industry

Increased resources provided by user fees have enabled FDA to provide a large body of technical guidance to industry that clarified the drug development pathway for many diseases and to meet with companies during drug development to provide critical advice on specific development programs. In the past five years alone, FDA has held over 7,000 meetings within a short time after a sponsor's request. Innovations in drug development are being advanced by many new companies as well as more established ones, and new sponsors may need, and often seek, more regulatory guidance during development. In FY 2009, more than half of the meetings FDA held with companies at the early investigational stage and

[3] "Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe," *Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal, Health Affairs, June 2011.*

midway through the clinical trial process were with companies that had no approved product on the U.S. market.

Weighing Benefit and Risk

It should be noted that FDA assesses the benefit-risk of new drugs on a case-by-case basis, considering the degree of unmet medical need and the severity and morbidity of the condition the drug is intended to treat. This approach has been critical to increasing patient access to new drugs for cancer and rare and other serious diseases, where existing therapies have been few and limited in their effectiveness. Some of these products have serious side effects but they were approved because the benefit outweighed the risk. For example, in March of last year, FDA approved Yervoy (ipilimumab) for the treatment of unresectable or metastatic melanoma. Yervoy also poses a risk of serious side effects in 12.9 percent of patients treated with Yervoy, including severe to fatal autoimmune reactions. However, FDA decided that the benefits of Yervoy outweighed its risks, especially considering that no other melanoma treatment has been shown to prolong a patient's life.

As discussed in more detail below, PDUFA V will enable FDA to develop an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making.

Speeding Access

PDUFA funds help support the use of existing programs to expedite the approval of certain promising investigational drugs, and also to make them available to the very ill as

early in the development process as possible, without unduly jeopardizing patient safety. We are committed to using these programs to speed therapies to patients while upholding our high standards of safety and efficacy. Balancing these two objectives requires that we continue to evaluate our use of the tools available to us and consider whether additional tools would be helpful.

The most important of these programs are Priority Review (discussed earlier), Accelerated Approval, and Fast Track. In 1992, FDA instituted the Accelerated Approval process, which allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need based on a surrogate endpoint that is reasonably likely to predict clinical benefit, but is not fully validated to do so, or, in some cases, an effect on a clinical endpoint other than survival or irreversible morbidity. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement for a clinically meaningful outcome, such as survival or symptom improvement. For example, viral load is a surrogate endpoint for approval of drugs for the treatment of HIV/AIDS. The use of a surrogate endpoint can considerably shorten the time to approval, allowing more rapid patient access to promising new treatments for serious or life-threatening diseases. Accelerated Approval is given on the condition that post-marketing clinical trials verify the anticipated clinical benefit. Over 80 new critical products have been approved under Accelerated Approval since the program was established, including nearly 30 drugs to treat cancer. Three of the 30 new molecular entities (NMEs) approved in 2011 were approved under Accelerated Approval. NMEs represent the truly innovative new medicines.

Once a drug receives Fast Track designation, early and frequent communications between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communications ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

FDA also recognizes circumstances in which there is public health value in making products available prior to marketing approval. A promising but not yet fully evaluated treatment may sometimes represent the best choice for individuals with serious or life-threatening diseases, who lack a satisfactory therapy.

FDA allows for access to investigational products through multiple mechanisms. Clinical trials are the best mechanism for a patient to receive an investigational drug, because they provide a range of patient protections and benefits and they maximize the gathering of useful information about the product, which benefits the entire patient population. However, there are times when an individual cannot enroll in a clinical trial. In some cases, the patient may gain access to an investigational therapy through one of the alternative mechanisms, and FDA's Office of Special Health Issues assists patients and their doctors in this endeavor.

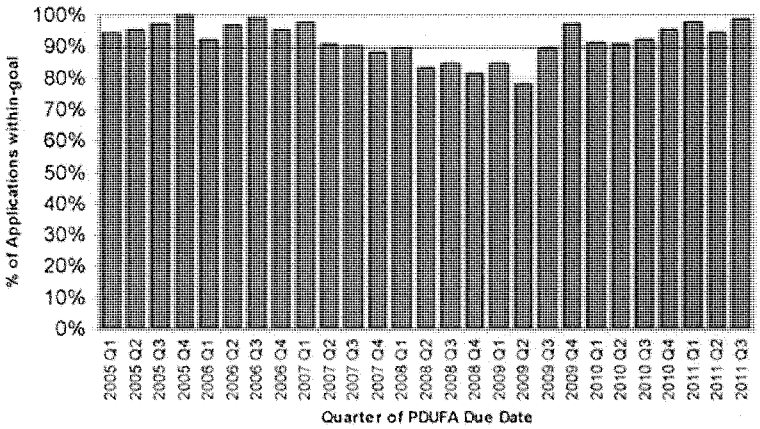
Challenges for the Current Drug Program

Although we can report many important successes with the current program, new challenges have also emerged that offer an opportunity for further enhancement. While new authorities from the Food and Drug Administration Amendments Act of 2007 (FDAAA) have strengthened drug safety, they have put strains on FDA's ability to meet premarket review performance goals and address post-market review activities. In addition, there has been a significant increase in the number of foreign sites included in clinical trials to test drug safety

and effectiveness, and an increase in the number of foreign facilities used in manufacturing new drugs for the U.S. market. While foreign sites can play an important role in enabling access to new drugs, the need to travel much farther to conduct pre-approval inspections for clinical trials and manufacturing sites overseas has created additional challenges for completion of FDA's review within the existing PDUFA review performance goals, while at the same time trying to communicate with sponsors to see if identified issues can be resolved before the review performance goal date.

Despite these challenges, FDA has maintained strong performance in meeting the PDUFA application review goals, with the exception of a dip in FY 2008-09, when staff resources were shifted within the discretion afforded FDA to ensure timely implementation of all of the new FDAAA provisions that affected activities in the new drug review process. Recent performance data show that FDA has returned to meeting or exceeding goals for review of marketing applications under PDUFA. This is shown in Figure 3.

CDER PDUFA Application Review Performance (NDAs, BLAs, Efficacy Supplements) 2005 - 2011



CDER data as of 11/30/2011. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

However, FDA wants to meet not only the letter, but also the spirit of the PDUFA program. That is, we want to speed patient access to drugs shown to be safe and effective for the indicated uses while also meeting our PDUFA goals.

The NDA/BLA approval phase of drug development is reported to have the highest success rate of any phase of drug development. That is, the percentage of drugs that fail after the sponsor submits an NDA/BLA to FDA is less than the percentages that fail in preclinical development, and each phase of clinical development. At the same time, it is critical to our public health mission that we work with industry and other stakeholders to take steps to reduce uncertainty and increase the success of all phases of drug development. We must leverage advances in science and technology to make sure that we have the knowledge and tools we need to rapidly and meaningfully evaluate medical products. The science of

developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products—known as regulatory science—is about more than just speeding drug development prior to the point at which FDA receives an application for review and approval. It also gives us the scientific tools to modernize and streamline our regulatory process. With so much at stake for public health, FDA has made advances in regulatory science a top priority. The Agency is both supporting mission-critical science at FDA and exploring a range of new partnerships with the National Institutes of Health (NIH) and academic institutions to develop the science needed to maximize advances in biomedical research and bring the development and assessment of promising new therapies and devices into the 21st century. With this effort, FDA is poised to support a wave of innovation to transform medicine and save lives.

For example, FDA is working to improve the science behind certain clinical trial designs. Recent advances in two clinical trial designs—called non-inferiority and adaptive designs—have required FDA to conduct more complex reviews of clinical trial protocols and new marketing applications. Improving the scientific bases of these trial designs should add efficiency to the drug review process, encourage the development of novel products, and speed new therapies to patients.

FDA has also taken steps to help facilitate the development and approval of safe and effective drugs for Americans with rare diseases. Therapies for rare diseases—those affecting fewer than 200,000 people in the United States—represent the most rapidly expanding area of drug development. Although each disease affects a relatively small population, collectively, rare diseases affect about 25 million Americans. Approximately one-third of the NMEs and new biological products approved in the last five years have been drugs for rare diseases.

Because of the small numbers of patients who suffer from each disease, FDA often allows non-traditional approaches to establishing safety and effectiveness. For example, FDA approved Voraxaze (glucarpidase) in January 2012 to treat patients with toxic methotrexate levels in their blood due to kidney failure, which affects a small population of patients each year. Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. Patients receiving high doses of methotrexate may develop kidney failure. Voraxaze was approved based on data in 22 patients from a single clinical trial, which showed decreased levels of methotrexate in the blood. Prior to the approval of Voraxaze, there were no effective therapies for the treatment of toxic methotrexate levels in patients with renal failure.

Just yesterday, January 31, 2012, FDA approved Kalydeco (ivacaftor) to treat patients age 6 or older with Cystic Fibrosis (CF) and who have a specific genetic defect (G551D mutation). CF occurs in approximately 30,000 children and adults in the United States. The G551D mutation occurs in approximately 4 percent of patients with CF, totaling approximately 1,200 patients in the United States. CF is a serious inherited disease that affects the lungs and other organs in the body, leading to breathing and digestive problems, trouble gaining weight, and other problems. There is no cure for CF, and despite progress in the treatment of the disease, most patients with CF have shortened life spans and do not live beyond their mid-30's. Ivacaftor was given a Priority Review by FDA. Due to the results of these studies showing a significant benefit to patients with CF with the *G551D* mutation, ivacaftor was reviewed and approved by FDA in approximately half of the six-month Priority Review period. Ivacaftor will be the first medicine that targets the underlying cause of CF; currently, therapy is aimed at treating symptoms or complications of the disease.

PDUFA Reauthorization

In PDUFA IV, Congress directed FDA to take additional steps to ensure that public stakeholders, including consumer, patient, and health care professional organizations, would have adequate opportunity to provide input to the reauthorization and any program enhancements for PDUFA V. Congress directed the Agency to hold an initial public meeting and then to meet with public stakeholders periodically, while conducting negotiations with industry to hear their views on the reauthorization and their suggestions for changes to the PDUFA performance goals. PDUFA IV also required that minutes from negotiation sessions held with industry be made public.

Based on a public meeting held in April 2010, input from a public docket, and the Agency's own internal analyses of program challenge areas, FDA developed a set of potential proposed enhancements for PDUFA V and in July 2010, began negotiations with industry and parallel discussions with public stakeholders. These discussions concluded in May 2011 and we held a public meeting on October 24, 2011, where we solicited comments on the proposed recommendations. We also opened a public docket for comments. We considered these comments, and on January 13, 2012, we transmitted the final recommendations to Congress.

We are very pleased to report that the enhancements for PDUFA V address many of the top priorities identified by public stakeholders, the top concerns identified by industry, and the most important challenges identified within FDA. I will briefly summarize these enhancements.

A. *Review Program for New Drug Applications, New Molecular Entities, and Original Biologics License Applications*

FDA's existing review performance goals for priority and standard applications—six and 10 months respectively—were established in 1997. Since that time, additional requirements in the drug review process have made those goals increasingly challenging to meet, particularly for more complex applications like new molecular entity (NME) NDAs and original BLAs. FDA also recognizes that increasing communication between the Agency and sponsors during the application review has the potential to increase efficiency in the review process.

To address the desire for increased communication and greater efficiency in the review process, we agreed to an enhancement to FDA's review program for NME NDAs and original BLAs in PDUFA V. This program includes pre-submission meetings, mid-cycle communications, and late-cycle meetings between FDA and sponsors for these applications. To accommodate this increased interaction during regulatory review, as agreed to with industry, FDA's review clock would begin after the 60-day administrative filing review period for this subset of applications. The impact of these modifications on the efficiency of drug review for this subset of applications will be assessed during PDUFA V.

B. *Enhancing Regulatory Science and Expediting Drug Development*

The following five enhancements focus on regulatory science and expediting drug development.

1. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

FDA recognizes that timely interactive communication with sponsors can help foster efficient and effective drug development. In some cases, a sponsor's questions may be complex enough to require a formal meeting with FDA, but in other instances, a question may be relatively straightforward such that a response can be provided more quickly. However, our review staff's workload and other competing public health priorities can make it challenging to develop an Agency response to matters outside of the formal meeting process.

This enhancement involves a dedicated drug development communication and training staff, focused on improving communication between FDA and sponsors during development. This staff will be responsible for identifying best practices for communication between the Agency and sponsors, training review staff, and disseminating best practices through published guidance.

2. Methods for Meta-analysis

A meta-analysis typically attempts to combine the data or findings from multiple completed studies to explore drug benefits and risks and, in some cases, uncover what might be a potential safety signal in a premarket or post-market context. However, there is no consensus on best practices in conducting a meta-analysis. With the growing availability of clinical trial data, an increasing number of meta-analyses are being conducted based on varying sets of data and assumptions. If such studies conducted outside FDA find a potential safety signal, FDA will work to try to confirm—or correct—the information about a potential harm. To do this, FDA must work quickly to conduct its own meta-analyses to include publicly available data and the raw clinical trial data submitted by drug sponsors that would

typically not be available to outside researchers. This is resource-intensive work and often exceeds the Agency's on-board scientific and computational capacity, causing delays in FDA findings that prolong public uncertainty.

PDUFA V enhancements include the development of a dedicated staff to evaluate best practices and limitations in meta-analysis methods. Through a rigorous public comment process, FDA would develop guidance on best practices and the Agency's approach to meta-analysis in regulatory review and decision-making.

3. Biomarkers and Pharmacogenomics

Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time by helping to demonstrate benefits, establish unmet medical needs, and identify patients who are predisposed to adverse events. FDA provides regulatory advice on the use of biomarkers to facilitate the assessment of human safety in early phase clinical studies, to support claims of efficacy, and to establish the optimal dose selection for pivotal efficacy studies. This is an area of new science where the Agency has seen a marked increase in sponsor submissions to FDA. In the 2008-2010 period, the Agency experienced a nearly four-fold increase in this type of review work.

PDUFA V enhancements include augmenting the Agency's clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmaeogenomic markers. The Agency would also hold a public meeting to discuss potential strategies to facilitate scientific exchanges on biomarker issues between FDA and drug manufacturers.

4. Use of Patient-reported Outcomes

Assessments of study endpoints known as patient-reported outcomes (PROs) are increasingly an important part of successful drug development. PROs measure treatment benefit or risk in medical product clinical trials from the patients' point of view. They are critical in understanding drug benefits and harm from the patients' perspective. However, PROs require rigorous evaluation and statistical design and analysis to ensure reliability to support claims of clinical benefit. Early consultation between FDA and drug sponsors can ensure that endpoints are well-defined and reliable. However, the Agency does not have the capacity to meet the current demand from industry.

PDUFA V enhancements include an initiative to improve FDA's clinical and statistical capacity to address submissions involving PROs and other endpoint assessment tools, including providing consultation during the early stages of drug development. In addition, FDA will convene a public meeting to discuss standards for PRO qualification, new theories in endpoint measurement, and the implications for multi-national trials.

5. Development of Drugs for Rare Diseases

FDA's oversight of rare disease drug development is complex and resource intensive. Rare diseases are a highly diverse collection of disorders, their natural histories are often not well-described, only small population sizes are often available for study, and they do not usually have well-defined outcome measures. This makes the design, execution, and interpretation of clinical trials for rare diseases difficult and time consuming, requiring frequent interaction between FDA and drug sponsors. If recent trends in orphan designations

are any indication, FDA can expect an increase in investigational activity and marketing applications for orphan products in the future.

Another PDUFA V enhancement includes FDA facilitation of rare disease drug development by issuing relevant guidance, increasing the Agency's outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug development for sponsors and FDA staff.

C. *Enhancing Benefit-Risk Assessment*

FDA has been developing an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making. Part of FDA's decision-making lies in thinking about the context of the decision—an understanding of the condition treated and the unmet medical need. Patients who live with a disease have a direct stake in the outcome of drug review. The FDA drug review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and the potential gaps or limitations in available treatments in a therapeutic area.

PDUFA V enhancements include expanded implementation of FDA's benefit-risk framework in the drug review process, including holding public workshops to discuss the application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting. FDA would also conduct a series of public meetings between its review divisions and the relevant patient advocacy communities to review the medical products available for specific indications or disease states that will be chosen through a public process.

D. *Enhancement and Modernization of the FDA Drug Safety System*

The enhancements for PDUFA V include two post-market, safety-focused initiatives.

1. Standardizing Risk Evaluation and Mitigation Strategies

FDAAA gave FDA authority to require a Risk Evaluation and Mitigation Strategy (REMS) when FDA finds that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. Some REMS are more restrictive types of risk management programs that include elements to assure safe use (ETASU). These programs can require such tools as prescriber training or certification, pharmacy training or certification, dispensing in certain health care settings, documentation of safe use conditions, required patient monitoring, or patient registries. ETASU REMS can be challenging to implement and evaluate, involving cooperation of all segments of the health care system. Our experience with REMS to date suggests that the development of multiple individual programs has the potential to create burdens on the health care system and, in some cases, could limit appropriate patient access to important therapies.

PDUFA V enhancements initiate a public process to explore strategies and initiate projects to standardize REMS with the goal of reducing burden on practitioners, patients, and others in the health care setting. Additionally, FDA will conduct public workshops and develop guidance on methods for assessing the effectiveness of REMS and the impact on patient access and burden on the health care system.

2. Using the Sentinel Initiative to Evaluate Drug Safety Issues

FDA's Sentinel Initiative is a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved medical products. FDAAA required FDA to collaborate with federal, academic, and private entities to develop methods to obtain access to disparate data sources and validated means to link and analyze safety data to monitor the safety of drugs after they reach the market, an activity also known as "active post-market drug safety surveillance." FDA will use user fee funds to conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, post-marketing requirements, or post-marketing commitments. This may shorten the time it takes to better understand new or emerging drug safety issues. PDUFA V enhancements will enable FDA to initiate a series of projects to establish the use of active post-market drug safety surveillance in evaluating post-market safety signals in population-based databases. By leveraging public and private health care data sources to quickly evaluate drug safety issues, this work may reduce the Agency's reliance on required post-marketing studies and clinical trials.

E. *Required Electronic Submissions and Standardization of Electronic Application Data*

The predictability of the FDA review process relies heavily on the quality of sponsor submissions. The Agency currently receives submissions of original applications and supplements in formats ranging from paper-only to electronic-only, as well as hybrids of the two media. The variability and unpredictability of submitted formats and clinical data layout present major obstacles to conducting a timely, efficient, and rigorous review within current

PDUFA goal time frames. A lack of standardized data also limits FDA's ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to REMS and other post-marketing requirements. PDUFA V enhancements include a phased-in requirement for standardized, fully electronic submissions during PDUFA V for all marketing and investigational applications. Through partnership with open standards development organizations, the Agency would also conduct a public process to develop standardized terminology for clinical and non-clinical data submitted in marketing and investigational applications.

F. *User Fee Increase for PDUFA V*

The cost of the agreed upon PDUFA V enhancements translates to an overall increase in fees of approximately six percent.

G. *PDUFA V Enhancements for a Modified Inflation Adjuster and Additional Evaluations of the Workload Adjuster*

In calculating user fees for each new fiscal year, FDA adjusts the base revenue amount by inflation and workload as specified in the statute. PDUFA V enhancements include a modification to the inflation adjuster to accurately account for changes in its costs related to payroll compensation and benefits as well as changes in non-payroll costs. In addition, FDA will continue evaluating the workload adjuster that was developed during the PDUFA IV negotiations to ensure that it continues to adequately capture changes in FDA's workload.

Best Pharmaceuticals for Children Act /Pediatric Research Equity Act

Background

The Best Pharmaceuticals for Children Act (BPCA), enacted in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA) and reauthorized in 2002 and 2007, provides incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides six months of additional exclusivity for a drug (active moiety), in return for conducting pediatric studies in response to a written request (WR) issued by FDA. To qualify for pediatric exclusivity, the pediatric studies must "fairly respond" to a WR issued by FDA that describes the needed pediatric studies (including, for example, indications to be studied or number of patients). The Patient Protection and Affordable Care Act (Affordable Care Act) extended availability of pediatric exclusivity to biological products but, due to the recent nature of this change, no biological product has received pediatric exclusivity to date.

The Pediatric Research Equity Act (PREA), enacted in 2003, works in concert with BPCA. PREA provides FDA the authority to require pediatric studies under certain conditions. PREA requires pediatric assessments of drugs and biological products for the same indications previously approved or pending approval, when the sponsor submits an application or supplemental application to FDA for a new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration.

Both BPCA and PREA expire September 30, 2012, if not reauthorized.

Need for Pediatric Information

Before enactment of BPCA in 1997, approximately 80 percent of medication labels in the Physician's Desk Reference did not have pediatric-use information—data to establish the correct dose for pediatric patients or confirm safety or efficacy in the pediatric population. All too often health care professionals were forced to rely on imprecise and ineffective methods to provide medications for children, such as adjusting dosing based on weight or crushing pills and mixing them in food. Pediatric patients are subject to many of the same diseases as adults and are, by necessity, often treated with the same drugs and biological products as adults. Inadequate dosing information may expose pediatric patients to overdosing or underdosing. Overdosing may increase the risk of adverse reactions that could be avoided with an appropriate pediatric dose; underdosing may lead to ineffective treatment. The lack of pediatric-specific safety information in product labeling also means caretakers and health care professionals are unable to monitor for and manage pediatric-specific adverse events. In situations where younger pediatric populations cannot take the adult formulation of a product, the failure to develop a pediatric formulation that can be used by young children (e.g., a liquid or chewable tablet) also can deny children access to important medications.

Success of BPCA and PREA

Together, BPCA and PREA have generated pediatric studies on many drugs and helped to provide important new safety, effectiveness, and dosing information for drugs used in children. Both statutes continue to foster an environment that promotes pediatric studies and to build an infrastructure for pediatric trials that was previously non-existent.

Over the past 15 years, approximately 400 drugs have been studied and labeled for pediatric use under these two laws. Since 1997, BPCA, the exclusivity incentive program, has generated labeling changes for 250 products. The labeling for 120 products has been updated to include new information, expanding use of the product to a broader pediatric population; the labeling of 29 products had specific dosing adjustments; the labeling of 69 products was changed to show that the products were found not to be safe and effective for children; and 55 products had new or enhanced pediatric safety information added to the labeling.[4]

Since PREA was enacted, FDA has approved approximately 1,450 NDAs and supplemental NDAs that fell within the scope of PREA (i.e., applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens). These approvals have resulted in approximately 231 labeling changes involving pediatric studies linked to PREA assessments. In addition, FDA has approved approximately 105 BLAs and supplemental BLAs that fell within the scope of PREA.

Examples of New Pediatric Information Generated by BPCA and PREA

- Migraine headaches – Axert (almotriptan) was studied and labeled for age 12 years and older. Before enactment of BPCA and PREA, no medications were studied and labeled for migraines in children.
- Diabetes – Apidra (insulin gluilsine recombinant) has been studied and labeled down to age 4 for Type 1 diabetes.

[4] These numbers add up to a number greater than 205 because some products had more than one change to the labeling.

- Arthritis – Actemra (tocilizumab) has been studied and labeled down to age 2 for Active Systemic Juvenile Idiopathic Arthritis (SJIA).
- Pain – Ofirmev/acetaminophen injection has been studied and labeled down to age 2 for mild-to-moderate pain/moderate-to-severe pain with adjunctive opioid analgesics and reduction of fever.
- Brain Tumors – Afinitor (everolimus) has been studied and labeled down to age 3 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

BPCA and PREA require review of adverse event reports on a regular basis. To date, adverse event reviews have been presented to the Pediatric Advisory Committee (PAC) for 129 products. In addition, as directed by BPCA, FDA has worked with NIH and the Foundation for the National Institutes of Health (FNIH) to facilitate the study of off-patent drugs not eligible for exclusivity under BPCA.

Despite the successes of these two programs, there is more work to be done. There is still a large number of drug and biological products that are inadequately labeled for children. More broadly, long-term safety and effects on growth, learning, and behavior are critically important to the safe use of certain medications and continue to be understudied. Due to technical challenges and the need for sequential studies, slow but deliberate progress is being made studying the safety and efficacy of approved therapies used to treat neonates (age birth to one month). These issues are still of concern, as it is this youngest population that is undergoing marked physiologic and developmental changes, which are affected by drug therapies.

FDA welcomes the opportunity to work with Congress to ensure that the benefits of an incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs.

Challenges Posed by Globalization

In addition to reauthorizing PDUFA, FDA is also committed to meeting challenges posed by increased globalization. When President Franklin Delano Roosevelt established the modern FDA in 1938, the percentage of food and medical products imported into the United States was minimal. Today, approximately 40 percent of the drugs Americans take are manufactured outside our borders, and up to 80 percent of the active pharmaceutical ingredients in those drugs comes from foreign sources. In July 2011, FDA published a special report, "Pathway to Global Product Safety and Quality," our global strategy and action plan that will allow us to more effectively oversee the safety of all products that reach U.S. consumers in the future. As detailed in the plan, over the next decade, FDA will focus on strengthened collaboration, improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources through partnerships with counterpart regulatory agencies, other government entities, international organizations, and other key stakeholders, including industry.

Toward this goal, I created a directorate in July 2012, focused on grappling with the truly global nature of today's food and drug production and supply. I appointed a Deputy Commissioner for Global Regulatory Operations and Policy to provide broad direction and support to FDA's Office of Regulatory Affairs and Office of International Programs, with a mandate from me to make response to the challenges of globalization and import safety a top

priority in the years to come and to ensure that we fully integrate our domestic and international programs to best promote and protect the health of the public.

CONCLUSION

PDUFA IV expires on September 30, 2012, and FDA is ready to work with you to ensure timely reauthorization of this critical program. If we are to sustain and build on our record of accomplishments, it is critical that the reauthorization occur seamlessly without any gap between the expiration of the old law and the enactment of PDUFA V.

Thank you for your contributions to the continued success of PDUFA and to the mission of FDA. I am happy to answer questions you may have.

Mr. PITTS. The chair thanks the gentlelady and I will now begin the questioning and recognize myself for 5 minutes for that purpose.

Commissioner, I believe the PDUFA agreement contains helpful improvements to the drug review process, and I am particularly interested in the process improvements for the review of new molecular entities. Would you explain these improvements and how they will add to the predictability and transparency of the review process?

Ms. HAMBURG. Well, there are a number of important elements. One is, you know, to really focus on the transparency, consistency and predictability issues that are so important to industry that you mentioned through enhanced communication and sitting down early in the process and midway through the process to really make sure that we all understand where we are, where we are going, what are the expectations, and to be able to, you know, much more rapidly surface issues as they emerge and address them so that we can, you know, really streamline the process and avoid unnecessary delays or confusion.

Mr. PITTS. I understand that FDA and the industry have a tentative agreement on the medical device user fees. As you know, Chairman Upton and I have set a deadline of reauthorizing the user fees by the end of June. I think my colleagues on the other side of the aisle would agree that reauthorizing the user fees by the end of June is in the best interest of the FDA and the American people. We received the three other user fee proposals by January 15 but we did not receive the medical device user fee proposal as required under statute. Given the need to reauthorize the user fees as soon as possible, when will the FDA send us the legislative language and the proposed agreement for the Medical Device User Fee Act so this committee can begin its work? Could you give us a specific date? And how does the Administration plan to expedite the process so the committee can get the device information as soon as possible?

Ms. HAMBURG. Well, we are really delighted to be able to come before you this morning and say that we have an agreement in principle, and that was actually just announced within the last hours. There are still some i's to dot and t's to cross. We will move as swiftly as we can to be able to present it to all of you to begin to work on it. We do want to follow the process that Congress laid for us of course, though, which does require that the recommendations be presented at a public meeting and also that a docket be opened with at least 30 days of comment. As soon as we have finalized this agreement and we are very nearly there, we will begin that process, and while I can't specify an exact date, we are very mindful of the timeframe that you have set forward and are very appreciative of that timeframe that you have set forward, and we are very eager to move this as swiftly and as surely as possible. This is an important agreement and one that we are very, very pleased to be able soon to finalize and move to this next stage.

Mr. PITTS. Thank you. Companies that want to manufacture prescription drugs in the United States are at a competitive disadvantage because there are manufacturing plants in China with very little oversight. Now, there is a 2-year inspection requirement for

domestic manufacturers but no similar requirement for foreign manufacturers including those located in China. Shouldn't we ensure that our regulatory oversight system does not create an uneven playing field for American manufacturers? Wouldn't a risk-based inspections approach make more sense in ensuring resources are spent inspecting higher-risk facilities like those in China rather than setting arbitrary statutory requirements?

Ms. HAMBURG. Well, I think the issue of how we can really respond to the globalized world that we live in where there are manufacturing facilities around the world that are making products coming into the United States is one of the most important challenges before us and certainly one of the priorities that I have taken on during my tenure as Commissioner. We very much need to rethink many of the ways that we have traditionally done business. Many of our authorities were actually put in place in a world that looks very different back when President Roosevelt created the modern FDA in 1938. Most drugs were in fact produced in this country and that is certainly not the case anymore.

So we are both trying to expand our ability to do inspections internationally, which are more complex and a bit more costly. We certainly are trying to introduce risk-based approaches so that we use our limited resources as widely as possible. We are also trying to work more closely with regulatory counterparts who share this challenge of having to do inspections in many more places and many more countries so that we can actually share information and begin to in many instances, you know, rely on the work of others to leverage resources towards the goal of expanding our presence internationally and, as you say, leveling the playing field so that people who have manufacturing overseas don't have to wait longer than those that are producing domestically. We also think that by more coordination with regulatory authorities, we can reduce the burden on industry by having more harmonization of standards, approaches and expectations and perhaps reducing the overall number of inspections that they will be subject to.

Mr. PITTS. The chair thanks the gentlelady and yields to the ranking member, Mr. Pallone, for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Hamburg, in your testimony you mention the challenges posed by increasing the global marketplace. As you know, Mr. Dingell, Ms. DeGette, Mr. Waxman and I have introduced a bill, the Drug Safety Enhancement Act, that gives FDA some authorities and an infusion of resources to address these challenges. Could you comment on the bill and whether FDA supports the bill? Some have asserted that FDA already has the authority to do some of the things that are included in the bill and that FDA could just proceed with its current authority. Can you comment to what extent that is true and whether having explicit new authority would be helpful?

Ms. HAMBURG. You know, we really do feel, as I mentioned, that the ability to respond to the challenges of a globalized world is among the most important issues before us and that we really have increased vulnerabilities and increased demands that, you know, really threaten our ability to fulfill our critical mission to ensure the safety of products that the American people use and count on,

so we are very eager to work with the members of this committee and Members of Congress more broadly to identify authorities that will make a difference in our ability to better ensure the safety of the supply chain and these important products that are being manufactured and distributed on a global basis to enable us to do better screening of products coming into this country, to be able to act when we identify products that are coming in that may pose a risk in terms of safety and quality, so we are very, very interested in the work that you are doing, appreciate your leadership and stand ready to provide whatever information that we can.

Mr. PALLONE. Thank you. A topic that has garnered a lot of attention over the years is the issue surrounding conflicts of interest on FDA's advisory panels. Obviously, if the advisory committee is to be credible and useful, it has to have a limited number of members who have conflicts. In the 2007 legislation, we included a provision that prohibited FDA from seating more than a certain percentage of conflicted advisory committee members, but both before and since the 2007 law, FDA has encountered difficulty trying to fill advisory committees with qualified and unconflicted members, and many have asserted that the waiver caps are to blame, but my understanding is that FDA has not come close to hitting those caps. So I am concerned about reports of weakened advisory committees because I think they are very important.

I wanted to ask you, do you agree that FDA has indeed encountered problems in filling advisory committees in recent years, and what is the impact, if so, of these vacancies on the ability of FDA to obtain expertise? Have there been instances in which the advisory committee meetings were delayed because FDA could not identify a sufficient number of outside experts, and to what extent are the waiver caps the problem or, you know, related to this?

Ms. HAMBURG. Well, this is a very important issue and one, you know, that very much goes to our ability to bring the best possible science to bear on our decision making. We also must have a process that has integrity, and so we have been, you know, working on this issue, talking with stakeholders and reviewing our policies and experience. It is one of those issues unfortunately in a way that the more you get into it, the thornier and more complex it gets, and on the one hand, there are people who would like to see us step away and relax some of our conflict-of-interest policies so that we can bring those individuals who are most expert to the table to serve on our advisory committees, and there are others on the other end of the spectrum who are very, very concerned that we need to have individuals who do not have——

Mr. PALLONE. I am just trying to—because my time—specifically, have there been problems filling these advisory committees in recent years?

Ms. HAMBURG. At the present time, as you noted, we are not bumping up against our cap in terms of waivers, and we have actually been making an aggressive effort to fill empty slots on our advisory committees and have made progress. It is a challenge to get people on our advisory committees for many reasons, both that it is a huge time commitment and——

Mr. PALLONE. Do you have any ideas about what you could do to improve it——

Ms. HAMBURG. Well, I think——

Mr. PALLONE [continuing]. And whether we could help in some way with the legislation?

Ms. HAMBURG. You know, we have been looking at this pretty closely and we don't at the moment see major areas where a legislative fix is required but I think it is something that we want to continue to work on. The input and engagement with our various stakeholders is absolutely crucial, and, you know, the role of the advisory committees is, you know, very foundational to a lot of what we do and so we want to make sure that we have the right balance of expertise without conflict of interest that might compromise the value of the input of those individuals, and we do think that transparency is a very important aspect of moving forward on this, and that is a strategy that enables often individuals to be able to bring their expertise with fuller understanding also though of their engagement either with sponsors of a product or an industry or positions that they have taken in the past on related issues.

Mr. PALLONE. I thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from New Jersey, Mr. Lance, for 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman, and good morning to you, Dr. Hamburg. I have not had the privilege of meeting you previously, and it is my honor to do so.

On the front of advancing personalized medicine, what steps might the FDA be taking to modernize the current regulatory structure? I have a bill in the hopper, the Modern Cures Act, that I believe might be able to be helpful in this area.

Ms. HAMBURG. Well, it is such an important area and we certainly are on the cusp of dramatic advances in terms of opportunities for care and treatment, and we are already seeing breakthroughs including a new therapy that was announced yesterday for cystic fibrosis where we are able to really see a therapy targeted to individuals with a particular genetic marker and really treat the underlying pathway of a disease in a new way.

With respect to activities at the FDA to enable us to really realize the potential of personalized medicine, a major area of focus is the investments in advancing regulatory science that we have embarked on with our colleagues in industry and academia, and I am very happy that a focus on new investments in regulatory science is part of the PDUFA V agreement because I think that will enable us to further develop the tools that will matter to both drug development and regulatory review and enable us to really target therapies for the people who will respond or for the people who will have unacceptable adverse consequences of therapy. We can also stratify populations and learn who will benefit and who will perhaps have unacceptable risks.

Mr. LANCE. Thank you.

Ms. HAMBURG. There is one other thing. I have also reorganized the agency in order to try to bring new leadership in, and we have a Deputy Commissioner for Medical Products who has a background in personalized medicine, and he will be working across

drugs, biologics and devices to coordinate activities, which is very important to make personalized medicine real.

Mr. LANCE. Thank you.

Ms. HAMBURG. I am sorry.

Mr. LANCE. I look forward to working with you on that.

Section 9 of the goals letter, enhancing regulatory science and expediting drug development, includes a subsection on advancing development of drugs for rare diseases. Specifically, the proposal provides for by the end of fiscal year 2013 that the FDA will complete a staffing and implementation plan for the CDER rare disease program within the Office of New Drugs and a CBER rare disease liaison within the Office of Center Director, and the FDA will increase by five the staff of the CDER rare disease program and will establish and fill the CBER rare disease liaison position. Would you please indicate to the committee assurances that you can provide that these additional staff will lead to greater efficiency and not create an additional layer of delay with no or limited value?

Ms. HAMBURG. You know, I think that we are moving in a direction that is very positive and will help support and extend our efforts in the rare and neglected disease area. I think it is an area where we have made terrific progress in terms of being able to work with sponsors to identify new promising drug candidates and move them through the system where we have been able to apply new and better science and more flexible regulatory tools, innovative clinical trial designs being one important aspect of that, and I think you will have the opportunity to hear more about that.

But I think the new proposal in the PDUFA agreement will enable us to have some individuals who are really focused on some of the unique needs and concerns in the rare and neglected disease areas and to be able to work across many components of the agency to ensure that we are doing all that we can, bringing the best possible science to bear and never forgetting this important aspect of drug development and getting new products to the people who need them.

Mr. LANCE. Thank you, Commissioner. And finally, on biomarkers, innovative drug development is increasingly dependent on the use of new biomarkers of disease to target the right patients. What is the FDA doing to encourage the use of biomarkers in drug development?

Ms. HAMBURG. It is such a key aspect of how we can bring new and better science to bear on drug development and drug review. We already have been, you know, quite involved in biomarker development including through the biomarker consortium that brings industry and academia together with government, both FDA and NIH, to try to identify and validate biomarkers for regulatory use. Biomarkers have an essential role to play in identifying potential toxicities so that if a drug is going to fail, it can fail early and we can speed the process. Biomarkers have a critical role to play in terms of serving as surrogate end points for clinical trials so that we can get important information about whether a drug is working or not without having to have extended trials and follow the whole course of the disease to give us early indications, and in other ways, you know, really gives us tools to accelerate the drug development process and the review process. It is an area that industry

shares our excitement and enthusiasm about the opportunities in science, and I think its inclusion in the PDUFA V agreement reflects that we think that by focusing on this area, we can really make huge strides forward.

Mr. LANCE. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from California, Ms. Capps, for 5 minutes for questions.

Mrs. CAPPS. Thank you, Mr. Chairman.

Thank you so much for your testimony, Dr. Hamburg, and for being with us today. You and your team have done such terrific work coming together on the PDUFA V agreement, and I look forward to working with you to move this bill forward. I also wanted to acknowledge that while these user fee agreements are a critical piece to ensuring that the FDA has the resources to do its job and continue to be the gold standard in this work around the world, at the same time we here in Congress must not shirk our responsibility to adequately fund the agency so that you can do that work, and I hope that in our bipartisan agreement that we will also work across the aisle during the appropriations process to do just that.

I hope to get to two topics in this very fast-moving 5 minutes that I have. In your testimony, Dr. Hamburg, you mentioned the Sentinel system for postmarket surveillance. This program holds great promise for more efficient and effective postmarket surveillance to protect the public's health, save money on research and curb potential drug recalls. Your testimony says that PDUFA V will allow user fees, and this is a quote, "to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action." Would you explain just a little bit more, not too long, about what that means? How do the goals described in PDUFA V differ or expand upon the pilot projects that have already been completed in PDUFA IV?

Ms. HAMBURG. Well, of course, FDAAA began us on the path of really strengthening our postmarketing surveillance capabilities and focusing on safety in the postmarket setting, and what we hope to be able to accomplish now with PDUFA V is to really use the data available in the postmarket setting and the data management and analytic tools to be able to very quickly ask and get answers to questions of an emerging drug safety concern. If we hear that a particular drug might be associated with an elevated risk of another kind of problem, we can query the database, and we are now up to 100 million patient lives in the database, and can answer that will help us to determine the level of concern associated with an emerging safety issue and help us decide, do we really need to ask for additional clinical studies to further evaluate the safety risk or are we comfortable with a determination that it doesn't appear to be a true correlation.

Mrs. CAPPS. I understand. That is important. Do you have the authority—should you need to expand the scale of this program, do you have the authority on your own to evaluate and make decisions along the way?

Ms. HAMBURG. I believe that we have all the authorities that we need, and obviously PDUFA V will help to give us additional resources that we need, and part of what is exciting about what we are doing as well is that it is a real partnership working with the

private sector and the broader patient community in terms of being able to access important data, which of course is utilized in a patient-confidential manner but——

Mrs. CAPPS. Great.

Ms. HAMBURG [continuing]. We do now have these large information resources that enable us to do things that we couldn't do before.

Mrs. CAPPS. Great. Another topic, in your testimony you touched on the scale-up of electronic submissions to the agency, and in July I asked your colleague, Janet Woodcock, about reports that clinical trial data submitted to the FDA do not routinely reporting based on sex or other important demographics. As you may know, this issue is one we have long struggled with. It is a key component of a bill that I have, my Heart for Women Act. In her response, she noted that while she couldn't confirm these reports, the use of electronic submissions would make it easier for the FDA to identify if companies are indeed submitting the disaggregated data as required by law. Can you tell me where the agency is at this moment on moving toward an electronic-only submission system and what are the benchmarks put forward in PDUFA V for that kind of adoption?

Ms. HAMBURG. Yes. Well, we are very excited about this component of PDUFA V. It has many benefits, both streamlining and modernizing our systems to help speed review and reduce burdens ultimately on both industry and our staff, but it has the additional benefit that it will enable us to deal with data in much more targeted ways and to be able to ask and answer critical questions around such important matters as gender and race and age and other factors that we very much need to understand more deeply to be able to provide the best possible products and the best possible care to our citizens.

Mrs. CAPPS. Thank you very much. I yield back.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentleman, Dr. Burgess, for 5 minutes for questions.

Mr. BURGESS. Thank you, Commissioner, again for being here.

Commissioner, we need your help. Last year, February 2011, this committee sent a letter regarding documents from the Food and Drug Administration relating to the issue of contaminated heparin, and you recall that national tragedy was prior to your becoming Commissioner but at the same time we are having difficulty coming to a conclusion on that, and while I recognize that you talked about the issues of globalization, you are no longer going to be a domestic agency but a global agency, I mean, here is where you have to show value because you had a compound manufactured in communist China that was used to adulterate a biologically derived product, heparin, a blood thinner. This hypersulfated chondroitin sulfate that was used to contaminate the heparin was a molecule that was produced in a lab and patented in the People's Republic of China and found its way into our drug supply with loss of life in dialysis centers when people were administered a bolus of heparin.

Last year, February 23rd, the committee sent a letter. Your Office of Legislative Affairs has documents from at least four employees but we don't have them at the committee level. In November,

your agency committed to a timetable to complete the production of heparin documents by the end of January 2012. We are there but we don't have any documents. So what has been happening over at your Office of Legislative Affairs for over 6 months? This is a poor reflection on the agency and one where our committee and you all need to work together and it is not happening.

Ms. HAMBURG. Well, as you point out, heparin was a very serious event that we all take very seriously in terms of the initial response at the time but also making sure that we have the systems in place to prevent that particular problem from occurring again or other similar problems. I am surprised by what you say. I am eager to work directly with you to make sure you are getting what you need because my sense was that our staff was spending literally thousands of hours culling through documents for you, answering questions, briefing committee staff on these issues, that we had sent up some 50,000 pages of documents. But if you——

Mr. BURGESS. If I may interrupt, that may be the case but we don't have them, so over the next 2 weeks can we elicit your help in getting this committee and the Subcommittee on Oversight and Investigation the information that it needs?

Ms. HAMBURG. Absolutely. I commit to working very closely with you to make sure that you are getting the materials that you are requesting and need.

Mr. BURGESS. Well, we are grateful for the more sophisticated testing that would reveal this problem in the future for new heparin but if there is someone out there who seeks value in contaminating our drug supply chain, it may not be heparin next time, it may be something else, and I don't have a sense that we understand what happened when this adulteration occurred.

We are all concerned about drug shortages. You hear about it. It is in the newspapers. There is a particular chemotherapeutic agent named Doxil which you are probably familiar with that has the company apparently involved in the manufacture of Doxil has said they are not going to make any more, so now we are in a tough spot because other companies are willing to take up that slack but all remaining Doxil has to be used for treating patients. It can't be used for doing the clinical trials, randomized clinical trials that would be necessary. So what options do we have in this very rare situation to allow the patients who are depending upon that chemotherapeutic agent to continue to receive it and at the same time speed the approval of generic doses of Doxil?

Ms. HAMBURG. Well, I am not familiar with all the details of the particular case of Doxil that you raise. But it is speaks to a set of important issues around drug shortages in terms of, you know, really needing to work closely with companies to get early warning when decisions are made to discontinue manufacturing or if they believe that there is an emerging quality or manufacturing concern to help identify other sources of available product to treat the conditions that patients may have when there are potential shortages and to help work with sponsors to expedite the standing up of manufacturing capability.

Mr. BURGESS. Right. We appreciate this is a complex problem, a multifactorial problem, but in this specific instance what we're ask-

ing is, Can you use your flexibility on the issue of bioequivalents to help get these patients the drugs that they so desperately need?

Ms. HAMBURG. You know, as I said, I don't know enough about the specifics in terms of the option in that case so I would not want to comment in the setting. I will certainly go back and make sure that the people with the direct knowledge and expertise address that.

Mr. BURGESS. We will follow up with that. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from Illinois, Ms. Schakowsky, for 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman, and thank you, Dr. Hamburg, for being here. I have four questions and I am going to get right to them, but I do want to associate myself with Ms. Capps' complimentary remarks to you and also the need to make sure that we adequately fund the FDA.

My first question is this. There was a 2010 report from the HHS Office of Inspector General which found that "80 percent of approved marketing applications for drugs and biologics contain data from foreign clinical trials." So my question is, does the FDA have adequate resources to do clinical trial oversight in places like China and Peru?

Ms. HAMBURG. Well, this is part of the overall growing demands on FDA in terms of oversight of both foreign manufacturing facilities and research that is being done in other countries. It certainly is something that we are putting time and attention to. We are working both with the regulatory authorities in a wide range of countries——

Ms. SCHAKOWSKY. Do you have the resources to——

Ms. HAMBURG. We need additional resources in order to be really provide the level of oversight that we think is necessary and appropriate, and we need some new models for doing business as well in terms of coordination with regulatory authorities sharing information and also increasing regulatory oversight capacity in many countries to ensure good clinical practice.

Ms. SCHAKOWSKY. So it is authority and resources, right?

Ms. HAMBURG. Indeed.

Ms. SCHAKOWSKY. I have been very interested in the issue of cosmetic safety, and here is my question. It relates to authority. If the FDA had reason to believe a cosmetic product was harmful, could it issue a mandatory recall of that product?

Ms. HAMBURG. I believe that we could work with the company to encourage a voluntary recall, but in order to pursue a mandatory recall, we would have to engage with the court system and pursue it through that venue.

Ms. SCHAKOWSKY. There has been a lot of publicity around the product, the hair straightener product, Brazilian Blowout, and I know that the FDA wrote to the manufacturer to inform them they had determined their products to be both misbranded and adulterated, but apparently it is still being used in salons across the United States. So do you plan any further actions against the manufacturer of Brazilian Blowout?

Ms. HAMBURG. It is my understanding that we are involved in some continuing discussions with the manufacturers trying to bet-

ter understand the issues involved and working with them around our concerns. I also believe that OSHA is engaged on this issue in terms of some of the workplace health concerns around the people that are providing the services in those beauty salons.

Ms. SCHAKOWSKY. Right, the employees there, OSHA has moved in on their behalf.

Now, I want to ask you about the ubiquitous advertising, direct-to-consumer advertising that we see on television. Some of them, I have to tell you, seem like if you really listen to all the cautionary things, it is like "and death could result" it seems like always at the end. It is almost humorous to me while you see people skipping through the flower fields. Anyway, what I am asking is that do you actually have any resources for direct-to-consumer advertising monitoring to ensure that consumers do have a balanced understanding of the drugs and the risks advertised to them, the accuracy of those? Where are you with monitoring those direct-to-consumer ads?

Ms. HAMBURG. Well, we do have a group that is charged with working on the oversight of direct-to-consumer advertising and there is a process that involves the screening of the direct-to-consumer advertisements.

Ms. SCHAKOWSKY. But you didn't have fees for that, right?

Ms. HAMBURG. We don't have fees associated with that. I gather that in the last PDUFA negotiation, this has been identified as possible area of focus, but actually including it was moved away from for a number of reasons that I think may have included the willingness to match or include budget authority. I am not sure of all the details but it was considered in PDUFA IV but——

Ms. SCHAKOWSKY. Let me just say——

Ms. HAMBURG [continuing]. But it is not part of PDUFA V.

Ms. SCHAKOWSKY. Given the prevalence of those ads on television, it seems to me that that would be a major focus, and I hope we can work together to make that happen. Thank you.

Ms. HAMBURG. Thank you.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentleman from Kentucky, Mr. Guthrie, for 5 minutes for questions.

Mr. GUTHRIE. Thanks, Dr. Hamburg. Thanks for coming. It is nice to have you here today. I have a related question, I want to get to another question, and it is related because it is user fee related. On the Tobacco Control Act, I have a question on that. The concern is, there is a user fee by tobacco companies to fund the Center for Tobacco Products, and my understanding, there is not transparency in the use of that money in terms of performance reporting or financial reporting like it is in PDUFA, you have to account for where that money is being used. My understanding is, there is not a report, not required statutorily for you to issue a report. I wonder if you have any comment on the transparency or use of those funds.

Ms. HAMBURG. Well, the user fees that are involved in supporting the tobacco program and its activities are scrutinized, and we have developed, you know, very strict oversight mechanisms and firewalls in terms of their targeted use for tobacco program activities, but you are correct that the legislation did not require the

same kind of performance reporting as for other user fees, and, you know, I think that are obviously—I would certainly understand that Congress would like to know more about how those user fees are being utilized. I would say that, you know, we take, as I said, the oversight of those resources and their appropriate use very seriously and do have a stringent process that is involved with that.

Mr. GUTHRIE. Yes, I don't think anybody has commented that you all were using it improperly, just that they don't have the access to the information that you do. So if I implied that, I apologize. But just the idea that other user fee programs, and maybe we should have financial reporting. Of course, Congress didn't ask you to do that when we passed that bill before.

The one thing, and I have been kind of focused on a little bit is this use of guidance documents, so I know it is not right on PDUFA but while we are here talking about that, and just a couple of examples, and I'm not getting into the details of specifics, but just like draft guidance for industry and FDA staff commercially distributed in vitro diagnostic products. I know that is very detailed. But when that was issued and it went forward, there were citations about 2 weeks after guidance document. Well, first it was brought forth as nonbinding, not for implementation, but my understanding is that the FDA has to take an action citing that guidance document I guess 2 weeks after implementation. So the question is, and I want to leave you time to respond, essentially the Administrative Procedures Act has the rulemaking process and there is some concern that FDA is using the guidance documents in a way that should be through the whole rulemaking process and comments. A lot of stakeholders have brought that to our attention. Do you have any comment on the use of guidance documents as binding even though they say nonbinding?

Ms. HAMBURG. Well, you know, we have found a lot of interest from the industries that we regulate in the role of guidance. There may be some mixed views, but I will tell you that what I generally hear is that guidance is very useful in giving an indication of where the agency is, where we are going and thinking about a particular problem. While they are not binding in the same way that rulemaking is, they are much quicker to put forward and they are welcomed. In fact, one of the things that I think came up in the PDUFA negotiations was examining ways to actually support the guidance production system because there are a lot of areas, personalized medicine being one, where it would be helpful to sponsors of products to have more guidance in order to know what directions to pursue and get the insight into our thinking and approaches. So I think that it is overall my sense is very useful but I think it does sometimes create an uncomfortable situation where people don't know whether it is an enforcement document or whether it is simply guidance.

Mr. GUTHRIE. See, I don't disagree with anything you said there at all. I think that you are absolutely right. People want some direction because the rulemaking process does take time so where is the direction we need to go in the interim, but I guess the concern is when they become treated like rules, that they didn't actually go through the Procedures Act, and that is a just a concern that we have.

Thanks. I yield back.

Mr. PITTS. The chair thanks the gentleman and yields to the ranking member emeritus from Michigan, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you. I commend you for this hearing. It is very much needed, and significant reform of food and drug laws is very much needed.

I ask unanimous consent my opening statement be inserted into the record at this point.

Mr. PITTS. Without objection.

[The prepared statement of Mr. Dingell follows:]

Statement from Representative John D. Dingell
House Committee on Energy and Commerce
Subcommittee on Health
"Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients."
February 1, 2012

I want to thank the Chairman for holding today's hearing on the reauthorization of the Prescription Drug User Fee Act (PDUFA). Legislation updating FDA's authority to protect American people from unsafe pharmaceuticals is desperately needed as shown from a large number of scandals in recent years.

This hearing is a critical first step in crafting legislation that will affect millions of Americans who take prescription medication. FDA has the tremendous responsibility of ensuring these medications are safe and effective for use, and ensuring patients have access to innovative new treatments in a timely fashion.

The agreement proposed by FDA and the industry will help to achieve this goal by ensuring FDA has adequate funding: to hire review and inspection staff needed for drug approvals, to improve the communication between FDA and industry during the approval process to ensure a more predictable and efficient process, and to improve regulatory science at the FDA.

One way that we can strengthen this proposed agreement is by focusing on the safety of our drug supply chain. What many Americans don't realize is the staggering fact that the number of drug products being manufactured outside of the United States doubled between 2001 and 2008. A globalized drug supply demands a globalized FDA that can enforce and oversee the quality of drugs entering our market from both domestic and foreign drug manufacturers.

This Committee has heard previously from Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, that FDA does not have the authorities it needs to oversee our drug supply. Currently FDA does not have the authority to require a manufacturer to notify FDA if they know that a drug has been adulterated, to recall drugs that the FDA believes are causing harm to the public's health, to refuse or seize imported drugs that are unsafe or counterfeited at the border, or to require a drug manufacturer to know their suppliers.

Further, we must ensure FDA has the resources needed to conduct comparable inspections of domestic and foreign drug manufacturers. FDA is now required to inspect domestic drug facilities once every two years, but does not have a similar requirement in the law for foreign drug facilities. I would hope my colleagues would agree that we must hold foreign drug manufacturers to the same high standards we hold domestic drug manufacturers.

H.R. 1483, the Drug Safety Enhancement Act, builds on the success of the food safety reform law – H.R. 2751, the FDA Food Safety Modernization Act – enacted by Congress last year and we have the opportunity to do the same thing for pharmaceuticals that we did for food. FDA must have updated authorities and needed resources to properly oversee a globalized drug supply.

With the PDUFA expiring at the end of this fiscal year, this Committee must work quickly and efficiently to ensure that we pass legislation that will reauthorize this program in order to avoid any personnel disruptions at the FDA. The hardworking employees of the FDA are looking for Congress to do our job, so that they can continue to do theirs.

I look forward to working with the Chairman and my colleagues on the other side of the aisle on reauthorization. Thank you.

Mr. DINGELL. I would like to begin by making a couple of observations. We have renewed PDUFA on a number of occasions and have expanded to a number of other activities by Food and Drug for a fee is now paid willingly by the industry. Each time this legislation has been extended, it has been extended with the active support of the industry. I authored PDUFA for some very interesting reasons. This committee conducted an extensive investigation of Food and Drug involving some serious misbehavior, accepting of gratuities and things of that kind, because of the fact that the agency did not have the resources to properly handle the issuance of permits for new pharmaceuticals, and the end result was, there were huge numbers of complaints from industry and some very unfortunate corruption existed in the agency.

One of the interesting things, and I hope my colleagues will listen to this, about PDUFA and one of the reasons that it and its half sisters and brothers have been supported by the industry is that a good pharmaceutical brings into the manufacturer, or did at the time it was first put in place, about $250 million a year, and if each time that a company found that it is delayed in putting a pharmaceutical to work and getting approved, that company finds that it has massive losses, massive losses stemming from the fact that it cannot market while its patent, which exists for 17 years, is running. Food and Drug does not have the resources to do this.

Now, Food and Drug is also moving forward to see to it that they have legislation which would enable them to begin to collect fees for certain changes in the law with regard to other pharmaceutical regulatory activities by that agency. These would impose the same burden on foreign manufacturers, who are now bringing in huge amounts of counterfeits and other unfortunate things into this country, to the great detriment and the hurt not only of our law but also of American manufacturers and Americans who are being poisoned. I would observe that we had a rather hideous example of this when a lot of Americans were killed or seriously hurt by heparin which came in.

So these questions first of all to Commissioner Hamburg. Has the law kept up with the changing environment? Yes or no.

Ms. HAMBURG. No.

Mr. DINGELL. It is badly in need of change, is it not?

Ms. HAMBURG. Yes.

Mr. DINGELL. And you have a number of changes which you will suggest for the record on this matter. Is that not so?

Ms. HAMBURG. We would love to work with you on this.

Mr. DINGELL. But the answer is yes?

Ms. HAMBURG. Yes.

Mr. DINGELL. It is also so that these will enable you to address not only changes in domestic production and the law as regards to domestic production but also with regard to the foreigners who are now sending in huge amounts of unsafe pharmaceuticals that you simply do not have the resources to address. Is that not so?

Ms. HAMBURG. It is correct.

Mr. DINGELL. Unfortunately, yes. Now, does Food and Drug have the authorities, the resources to adequately oversee such a heavily outsourced drug industry?

Ms. HAMBURG. We don't currently have the resources——

Mr. DINGELL. You don't have the resources, do you?

Ms. HAMBURG [continuing]. To fulfill as we would like our mission.

Mr. DINGELL. Good. I am giving you easy questions. These are all yeses or nos.

Ms. HAMBURG. It is hard to answer just yes or no.

Mr. DINGELL. Unless I indicate otherwise.

Now, will you submit for the record the key authorities that FDA needs to oversee the drug supply chain?

Ms. HAMBURG. With pleasure.

Mr. DINGELL. Now, one of the additional problems that you have is that the components are now coming in from overseas. In the case of heparin, it was the components which caused the damage to the health of the American people, was it not?

Ms. HAMBURG. We believe that the contaminant was introduced into the crude heparin preparation, yes.

Mr. DINGELL. Thank you.

Now, I have, Mr. Chairman, an analysis of H.R. 1483, the Drug Safety Enhancement Act of 2011, and I would ask unanimous consent that it be inserted into the record at this point.

Mr. PITTS. Without objection.

[The information follows:]

H.R. 1483, the Drug Safety Enhancement Act of 2011

Forty percent of pharmaceuticals and 80 percent of active pharmaceutical ingredients for the US market are now produced in foreign countries, often China and India. Such facilities often operate under lower standards than US manufacturers, creating safety risks and an uneven playing field.

The Drug Safety and Enhancement Act seeks to hold manufacturers responsible for the safety of pharmaceuticals manufactured in foreign countries for the US market and ensuring that the FDA provides oversight of foreign manufacturers equivalent to that exercised on domestic companies.

This bill will:

- **Require manufacturers to implement improved quality and safety standards, including stronger supply chain management**
- **Require manufacturers to notify FDA of counterfeits or safety concerns and to list country of origin of drugs and drug components**
- **Strengthen oversight of importers and customs brokers**
- **Give FDA needed authorities including mandatory recall authority, subpoena power, and clear extraterritorial jurisdiction.**
- **Strengthen criminal and civil penalties to better deter crime**
- **Increase FDA inspections of foreign manufacturing to put it on par with domestic facilities**
- **Create new funding mechanisms for FDA inspectional activities , so globalization doesn't create burden on US taxpayers**

Require all manufacturers to implement basic quality and safety standards, including stronger supply chain management

- Companies selling drugs in the US market must implement quality system to ensure the safety and integrity of their products, including drug ingredients manufactured by a contractor or supplier. Quality systems should include management responsibilities, quality responsibilities, risk management, and supply chain management.
- Companies must be able to document their supply chains, and demonstrate quality control
- Companies must perform on-site audits of suppliers before beginning to purchase product from that supplier, and must implement quality agreements with suppliers

Require manufacturers to notify FDA of concerns about counterfeits or manufacturing defects that put Americans at risk, and to list country of origin of drugs and drug components

- Companies must notify the FDA when use of or exposure to drug may result in illness or injury to humans or animals; significant loss or theft; reasonable probability that a drug has been or is being counterfeited; repeated failures by a component manufacturer to ensure compliance with quality systems; any incident causing a drug to be mistaken for, or its labeling applied to, another drug; and any contamination or significant chemical or physical change or deterioration after distribution, or any failure of a distributed lot to meet established specifications.

- Require manufacturers of finished drug products to list on their websites the countries of origin for their finished drugs as and the active ingredients in those drugs.

Strengthen oversight of importers and customs brokers

- Require importers and customs brokers to register with the FDA, and permit FDA to require additional documentation at importation. Create an importer registration fee to support oversight activities
- Require the Secretary to create good importer practice regulations

Give FDA needed authorities including mandatory recall authority, subpoena power, and clear extraterritorial jurisdiction.

- Give FDA the power to order a drug recall, allowing for an industry appeals process (as exists for food and medical devices)
- Give FDA power of subpoena for documents and witnesses, as with other regulatory agencies
- Allow FDA to destroy imported drugs at the border valued less than $2,000 that pose a health threat (so they don't get turned away, only to come back in through another port)

Create protections to allow FDA to exchange information with other regulators and receive information from whistleblowers

- Allow the FDA to exchange confidential information in a protected manner with other agencies and foreign governments, and to the public where warranted.
- Create protections for industry whistleblowers that wish to alert FDA to violations of the FFDCA and the Public Health Service Act.

Strengthen penalties to better deter crime and noncompliance

- Increase criminal penalties for knowing violations of the Federal Food, Drug, and Cosmetic Act to up to 10 years in prison and fines in accordance with title 18 of US Code. Knowing violations should include adulteration, misbranding, refusal of inspection, and counterfeiting
- Create civil penalties of $500,000 per violation per day for drug-related violations of the FFDCA. Cap penalties at $10,000,000 for a single proceeding that covers a number of violations
- Add asset forfeiture as a punitive measure for drug-related violations of the FFDCA

Increase FDA inspections of foreign manufacturing sites and improve oversight systems

- Require that all plants making finished drugs or active ingredients be inspected once every two years (or every four years if appropriate) – a standard more like that used inside the US
- Make delay or refusal of an inspection a prohibited act
- To facilitate tracking and oversight, require submission of unique ID numbers by manufacturing establishments, importers, and customs brokers.
- Create a dedicated foreign inspectorate within FDA

Create new industry registration fees to support FDA inspectional activities

- Fees will be set at the amount necessary to support increased drug safety activities and ensure that the added costs of manufacturing moving to low-cost countries does not create extra burden for taxpayers.

Mr. DINGELL. Madam Commissioner, one last question. You are familiar with the provisions of 1483. They are significantly similar to the additional powers and resources that Food and Drug received in the last couple Congresses ago to address the question of food safety, and you are finding that those new authorities are working very well there, are you not?

Ms. HAMBURG. Those new authorities are very, very important. We of course are struggling to fully implement the demands of the Food Safety Modernization Act but we are moving forward, and the additional authorities really are able to put us in a position to do things that are very, very important to prevent problems and address them swiftly.

Mr. DINGELL. And they particularly allow you to control imports and to address the question of possible seizure of unsafe pharmaceuticals which you had previously no capacity to address. Is that not so?

Ms. HAMBURG. That is correct.

Mr. DINGELL. Mr. Chairman, I have used more time than I am entitled to. Thank you for your courtesy.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Georgia, Dr. Gingrey, for 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you.

Dr. Hamburg, I love you just as much as the chairman emeritus does. He said he had some easy questions for you. In that spirit, I definitely have one that I think is easy but another one that may not be quite so easy. First, for the easier of the two, I am holding in my hand a news report that ran yesterday from U.S. News and World Report, and it reads, "Antibiotic-resistant bacteria found in 37 United States states." Can you tell me your thoughts on the magnitude of the threat that antibiotic-resistant bacteria pose to the United States patients?

Ms. HAMBURG. Antibiotic resistance, as you well know, is a huge and growing problem and one that we must take very seriously. We are seeing across various, you know, classes of antibiotics more and more resistance. That is greatly worrisome in terms of, you know, rendering important tools for controlling disease and preventing spread. We are seeing them, you know, rendered useless, increasing the burden of disease and the costs of care and potentially putting us in a position in some instances where we don't have the kinds of therapeutic interventions that we have come to expect, so it is something we need to address and we need to address it together, and FDA has a critical role to play.

Mr. GINGREY. And I really appreciate that. I will put in more plug for the GAIN Act. So much for the easier of the two.

Now, this next question is not meant to be unfriendly at all but I think it is very important. Ranking Member of the Health Subcommittee, Mr. Pallone, sort of addressed this earlier. I want to follow up on what he said, though.

A number of constituencies, both patients' groups and industry, recognize there are great advancements in our understanding of the human genome and science behind biologics. These same constituencies, however, have shared with me their concerns regarding current conflict-of-interest rules governing the FDA. Their contention is this: If the rules are not changed to take into these emerg-

ing sciences nor the limited number of individuals who understand these emerging sciences, these sciences may progress beyond the FDA's ability to understand how to properly assess the science. And I understand that currently the cap on the waivers for these conflict-of-interest rules has not been reached but I also understand that there are maybe a number of obesity drugs, as an example, within the FDA review process that have been stalled because of a preconceived lack of understanding of the science behind the drugs. I will cut right to the chase. Simply put, I do not believe the FDA cap is the issue here. I just want to understand this. Is it the FDA's contention that changes to the current conflict-of-interest rules governing the FDA advisory panels would not benefit the FDA, patient groups or businesses when considering whether to invest in new drug development?

Ms. HAMBURG. Well, I think your question raises a number of really important points and of course goes beyond simply the conflict-of-interest rules and the advisory committees but how do we bring in the best possible expertise as we pursue our regulatory oversight of critical products to address critical medical and public health needs, and advisory committees are one important element of that but there are other ways that we do it as well.

You know, for example, you mentioned obesity drugs. Well, we have a working relationship now spearheaded out of George Washington University where we are trying to bring together critical partners to help us think through how we can really improve our regulatory pathways for obesity reduction drugs including, you know, health care providers, scientific experts and patients. So I think there are different ways to bring in expertise, and part of what is exciting in PDUFA V, I think, is the focus on investments in regulatory science, which is an important venue for bringing the right expertise together, framing the right questions and making sure that we bring the best minds to bear in getting the critical answers.

Mr. GINGREY. Well, let me interrupt you because I am just about out of time, and I am encouraged to hear that and I thank you for that response, but that is why I am supportive, quite honestly, of my colleague from Texas, Dr. Burgess's bill in regard to lifting these caps on waiver so that we have that expertise and maybe we approach it from two aspects, but thank you very much, Dr. Hamburg, and Mr. Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Arkansas, Mr. Ross, for 5 minutes for questions.

Mr. ROSS. Thank you, Mr. Chairman, and Commissioner Hamburg, thank you for joining us today.

I believe that keeping a safe, affordable emergency inhaler available without a prescription, specifically Primatene Mist, is critical for asthmatics. Therefore, I am a little confused as to why the FDA took Primatene Mist off the market after December 31st of last year. Primatene has been available for over 40 years, and now, because of an environmental issue, not a health issue but an EPA environmental issue, the FDA has pulled Primatene from retail shelves and will not allow the existing supply chain to be sold. Here is why this concerns me. If the FDA allowed the existing supply to be sold, asthmatics could have access to an over-the-counter

emergency inhaler for at least the next few months until another affordable over-the-counter emergency inhaler without harmful environmental impacts, as alleged by the EPA, is approved. Not only did the FDA deny access to the Primatene Mist in our supply chain but you have now stopped the phase III studies for development of an over-the-counter replacement for Primatene, and now Americans are without an OTC emergency inhaler and probably will be for the rest of the year when there are at least a million units of this inhaler sitting in a warehouse in California.

So Americans now have to go see a doctor. If they get a prescription, then they have got to get it filled if they can afford it as a substitute for this over-the-counter product, and here is where it really hits home for me. I represent a very large, a very rural, a very poor district, and Primatene Mist can be purchased over the counter for asthmatic patients for 20 bucks and prescription albuterol is costing those same patients 50 to 65 bucks, and the cost is not only to consumers but also to the government. It is estimated it is costing our government, the federal government, between $300 million and $1.1 billion due to asthmatics' increased hospitalizations, ER visits and an increased cost of going from the over-the-counter inhaler to one that requires a prescription, and of course, much of this cost of the $300 million to $1.1 billion obviously is coming from Medicare and Medicaid because there is not another OTC emergency inhaler.

So these figures are taken from the FDA's final rule ordering the removal of Primatene Mist based on not 2012 but 2008 cost estimates. So when we say it is costing the government $300 million to $1.1 billion, those are probably low numbers, and I believe that the denial letter from the EPA states it deferred to the FDA in denying the sale of the last remaining units. In other words, the EPA left it up to FDA. FDA chose not to. A lot of folks where I come from, they can't afford a $50 substitute for a $20 product that they have been taking for way too many years because of their asthmatic condition.

And so I would ask or suggest that you look into resolving this issue by considering releasing the remaining units of Primatene Mist and expedite the development of an emergency over-the-counter inhaler for asthma that is affordable and back on the U.S. market as soon as possible, and I would love to get your comments and thoughts on that.

Ms. HAMBURG. Well, it is obviously a complicated issue, but I think it is important to understand the broader context and the medical issues here. As part of the Montreal convention, there was a move—there was an environmental issue, as you point out, to remove chlorofluorocarbons from various products including asthma inhalers. It has been a very long transition period and we have been working with the various manufacturers of asthma inhalers to transition towards other delivery vehicles that don't have the CFCs. Of course, the manufacturer of Primatene Mist has been part of these discussions and they were given an extended period, some additional time for transition and we had indicated that we would welcome an application for another product.

But in terms of the concerns you raise about the public health of individuals, I want to make it clear that there really is—we en-

gaged in a very broad process of consensus development about the medical necessity of this product, talking with health care providers, scientific experts, public health professionals and patients and patient groups, and there is great concern about Primatene Mist or over-the-counter epinephrine-based—solely epinephrine asthma inhaler being used without the oversight and management of a medical provider and is really in the best interest of patients that have asthma, which can be a very serious and life-threatening condition, to have a medical provider. There are better treatments for the management of asthma overall. The epinephrine inhaler is a transient effect that briefly improves moderate symptoms but doesn't address the underlying cause of the asthma, and so we really think that in the best interest of individuals having access to a medical provider, going to a community health center where you pay on the basis of your ability to pay, local free clinic or public hospital or there are also sponsored programs to make medicines available at cheaper rates by various companies is important to the overall health and wellbeing of individuals suffering from asthma.

I recognize the inconvenience of not being able to get an over-the-counter product for immediate relief if you don't have your prescription inhaler with you, etc. We really tried to make it a smooth phase-out process with ample warning and information, both to enable patients to find alternative products and health care providers and to ensure that the health of individuals would be protected. But I understand the issues that you are raising and the concerns that you have.

Mr. ROSS. Well, it is not about convenience, it is not about trying to sell these million units that are in a warehouse in California. It is about having a product that people can afford. Too many of my folks can't afford to go to a doctor. They can't afford a $50 inhaler. They are having a tough time affording a $20 inhaler. I am just saying we ought to continue—whatever CFCs are out there, they have been out there and people have been on this stuff forever in order to be able to breathe, and we ought to find a way to be able to let them continue to get it until another over-the-counter product that is EPA approved can be developed. Otherwise they can't afford it. They are going without it. They are showing up in the emergency room and it is costing our government well over a billion dollars as we make this transition.

Mr. PITTS. The gentleman's time is expired. The chairman thanks the gentleman and recognizes the gentleman from Ohio, Mr. Latta, for 5 minutes for questions.

Mr. LATTA. Well, thank you, Mr. Chairman, and Commissioner, thanks very much for being with us today. I really appreciate it, and very interesting testimony today.

I would like to just kind of switch a little bit over on the pediatric side, and I see in your testimony you state, you know, that both these statutes, the BPCA and the PREA, continue to foster an environment that promotes pediatric studies and builds an infrastructure for pediatric trials that previously were nonexistence. If I could, I would just like of like to—from experience I have had, I have talked to a lot of pediatric docs, researchers, hospitals and parents of children that have severe illnesses, and I guess I would like to ask you, first of all, what they see is that the adult side

sometimes is getting more of the dollars that are going in for the research, and on the second question, when these drugs are coming through, are they getting equal treatment as the adult medicines that are going—when the FDA is making its determination decisions?

Ms. HAMBURG. Well, I think that the BPCA and PREA legislation have been enormously helpful in creating a framework to really focus attention on the importance of doing pediatric studies on drugs that had previously really been only studied in adult populations and providing some incentives to move in that direction. We still have a considerable ways to go. There are, I think, reasons why pediatric trials often are not as likely to be done as adult trials that include both the recruitment issues of getting kids into trials, both logistics and ethics issues, and——

Mr. LATTA. Can I interrupt you right there? To solve that then, when you are talking about getting the kids into the trials and also the ethics issue, how should we go about trying to get that changed or promote to get more children into them so that these drugs can be——

Ms. HAMBURG. Well, I think that this path is a good one and we need to continue these programs and strengthen them as it becomes more routine for drug sponsors to be expected to also examine the drugs in pediatric populations, you know, both creates a very different climate where there is now an expectation and a commitment and accountability for doing so, and it also, I think, helps to expand the opportunities and the expertise for doing pediatric clinical trials. But I think it is an area—obviously it is not exclusively within the realm of FDA but where we need to as a nation be continuing to put more attention and resources to create pediatric clinical trial networks, to train the clinical researchers to do that work, and to encourage both on the medical product and the medical device side more innovation and attention to the needs of pediatric populations.

Mr. LATTA. Let me ask then, in your testimony you say there is slow but deliberate process that is being made in setting the safety and the efficiency of the approved therapies for certain ages. Would you say that would be the same thing, it is trying to get these—getting the children into these tests, or how would you address that statement in your testimony?

Ms. HAMBURG. You know, to be honest, I am not quite sure the question you are asking, but——

Mr. LATTA. You state that slow but deliberate progress is being made in these studies and again, is that going back to the whole issue of trying to get the children and maybe infants into some of these studies and the ethics side?

Ms. HAMBURG. I see. There definitely are some additional barriers I think to recruiting pediatric patients into clinical trials, and we need to work on those, and it is—I think it is, as I said, a broader issue of really having the support for the clinical trial networks, the training of the pediatric researchers, the education of both families and pediatric community providers about the importance of pediatric clinical trials and the opportunities that they can represent for both individual patients and for extending knowledge

about appropriate pediatric care, so I think it is something that we really do need to work on and we need to work on it together.

Mr. LATTA. Thank you.

Mr. Chairman, my time is expired and I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from New York, Mr. Towns, for 5 minutes for questions.

Mr. TOWNS. Thank you very much, Mr. Chairman, and also the ranking member for holding this hearing today. Also, thank you very much, Commissioner, for being here.

PDUFA has been an effective and essential tool in assuring that safe, effective drugs are brought to the market in a timely fashion. However, we must be certain that we are striking the proper balance between the benefits of speedy approval of new treatments and the risk that different patient populations are willing to accept in order to gain access to them.

Let us also keep in mind that different patient groups may be willing to tolerate different degrees of risk. This is why it is crucial for FDA to communicate with the affected patient population when reviewing new treatments.

In your written testimony, Commissioner, you indicated that the FDA takes into consideration the benefits and risks of new drugs on a case-by-case basis. Considering the degree of unmet medical needs and the severe or morbidity of the conditions the drugs intended to treat when conducting this assessment, do you see the input of the patient population affected by the condition?

Ms. HAMBURG. Well, we do, and one of the exciting things about the PDUFA V framework also is a real focus on developing better strategies to formalize and systematize how we think about benefit-risk and importantly the engagement of patients and their perspectives, and part of what we hope to accomplish over the next 5 years, if this PDUFA agreement is reauthorized, is to in a formal way through a series of public meetings, four a year over the 5-year period to really target different disease conditions and engage with the patient community about their perspectives of the available drugs, their experience of benefits and risks, what kind of risks they are willing to tolerate, etc., and that will be, I think, very, very useful, in addition, you know, really building on work that we do every day as we look at important products in terms of thinking about what are the other options available to patients and how serious, life-threatening, life-disrupting is the condition, and we do weigh risks and balance them with benefits, and in our approvals we are often willing to accept a considerably high level of risk in some cases when there is true benefit to the patient.

Mr. TOWNS. Thank you very much, and let me say to my colleagues, I hope we recognize the importance of making certain that we fund you adequately as we make some demands as we move forward.

I applaud the agency for instituting the accelerated approval process in 1992. Do you feel that the program has been successful, particularly in the rare disease space?

Ms. HAMBURG. You know, it has been a very valuable program and we have seen, you know, a high number of drugs move forward through the accelerated approval process. We also—and many of them, a large percentage have been in the rare and neglected dis-

ease space. We also often give a full approval straightaway to rare and neglected diseases when we have, you know, good science, a good product and an impact on the underlying condition that is meaningful. So I think we have made enormous progress in the last couple of decades moving forward in orphan drugs, rare and neglected diseases and have been able to apply a lot of regulatory flexibility in how we approve those drugs, and I think you may be able to hear more about that in the second panel from the NORD representative.

Mr. TOWNS. Let me ask you, what challenges do you face with orphan drugs? What challenges do you actually face? Very quickly.

Ms. HAMBURG. Well, very often, the challenge is how to do the science that enables us to get the answers that we need. If you are talking about small numbers of patients, how can you tailor the clinical studies so that you can get robust, meaningful answers with only a small number of patients. I think historically also there were concerns about incentivizing industry to want to work on some of these disease areas where there would be limited patient numbers, and I think that the orphan drug program and the incentive structure there has helped to shift that dynamic, and I think that as we really begin to draw on the advances in science and technology today, there are very special opportunities in the rare and neglected disease areas to produce the kinds of product like the way we were able to approve yesterday for cystic fibrosis. We were able to really see a targeted therapy for a particular underlying genetic marker and really provide a breakthrough treatment, even though the number of patients with that particular condition is quite limited. In this case, we are estimating about 1,200 cystic fibrosis patients.

It is a very exciting time and it is an area where I think there is a lot of opportunity, and PDUFA obviously has identified that as an area where we can make some real progress.

Mr. TOWNS. Thank you, Mr. Chairman. I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from North Carolina, Ms. Myrick, for 5 minutes for questions.

Mrs. MYRICK. Thank you, Mr. Chairman.

I appreciate you being here today, and that is kind of along the same lines of what I wanted to talk about and that, is, the guidelines for approval of certain drugs. While the FDA is tasked with protecting public health, I don't think it should be in a position of withholding or removing approval of drugs that treat fatal illnesses. When a patient is expected to die imminently from a disease, the FDA's decision of whether or not to approve that drug should be made on a different metric than the approval of a drug that is intended to treat a less serious condition.

Your agency does claim to factor this in, and I know you see it as part of your mission to move treatment forward for patients, but it doesn't seem to me that you give enough weight to the fact that dying patients will tolerate a riskier drug. Sometimes they won't respond and will succumb to the disease but sometimes they respond well, and aggregate clinical data doesn't always reflect that properly. So can you just tell me why the FDA shouldn't have a

separate metric for determining approvals for diseases like metastatic or otherwise fatal cancers, ALS and other deadly illnesses?

Ms. HAMBURG. Well, we do, as we were discussing earlier, you know, really take very seriously the importance of balancing risk and benefit and recognizing when you have a serious life-threatening illness with no or limited other treatment options. The proposed drug must be viewed in a very different context than if it is one of six potential drugs for a disease, you know, that has only a very minor impact on the tasks of daily living. So we do take that very, very seriously, and if you look at our approvals, it is clear that as I said, in some instances, there is significant risk associated with a drug that we will approve, but we do at the end of the day have to ask the question of, is there an overall benefit to the patient, and that can be very difficult and challenging. But that is, you know, an important part of what we are charged with.

I think, again, you mentioned the sort of stratified populations, that there may be some who respond and some who don't, and that is why the deepening of the scientific understanding is so important and to continue to work as PDUFA V, you know, has indicated in the area of regulatory science and really identifying how we identify—we need to really define who are the subpopulations of responders so that we can target the benefits to the people.

Mrs. MYRICK. No, I understand. We have talked about that before. That is one that I refer to simply because of people that I know who are very successfully being treated with that for other than the uses that you had approved.

Also, with the compassionate use process for terminally ill patients who have very few other clinical options, it doesn't always work very well. Companies understandably worry that patients who don't fit the trial guidelines who have completed the trial for their drug will negatively alter their clinical data if they are allowed to take an experimental treatment under a compassionate use exception. Yesterday, a 41-year-old ALS patient was in our office, and he saw significant symptom improvement while involved in a clinical trial, but his participation in the trial ended and then he was denied access to the drug under compassionate use because of these concerns.

So in your opinion, what else can FDA or Congress, for that matter, do to improve the likelihood that patients with no other clinical option can access treatment through compassionate use? I mean, this is an ongoing problem. I understand where you come from but it is also pretty hard to look somebody in the face and say I am sorry, I can't help.

Ms. HAMBURG. Well, it is, you know, a huge issue and one that certainly without knowing the specifics of that instance, you know, we do try to work with patients' families and providers under those kinds of circumstances to see if we can help facilitate access to a product.

Mrs. MYRICK. Can we refer him to you?

Ms. HAMBURG. Pardon me?

Mrs. MYRICK. Can we refer him to you?

Ms. HAMBURG. You know, I think you could. You know, I can't make any promises but——

Mrs. MYRICK. No, I understand.

Ms. HAMBURG [continuing]. Absolutely and we can——

Mrs. MYRICK. He is so young, you know.

Ms. HAMBURG. Yes, no, and, you know, it is an area that we need as a society to continue to work on.

Mrs. MYRICK. Well, my time is almost up so I will yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentlelady and yields to the gentleman from Utah, Mr. Matheson, 5 minutes for questioning.

Mr. MATHESON. Thank you, Mr. Chairman, and Dr. Hamburg, welcome. Thank you for coming today.

I would like to focus my questions on a national track and trace program or a drug pedigree issue, which I know Mr. Dingell talked about and some others as well. You probably know, I have worked with my colleague, Mr. Bilbray, and a lot of stakeholders on crafting legislation to implement a single national pedigree standard. Last year, February 2011, the FDA held a 2-day track and trace public workshop. One of the reoccurring concerns from stakeholders at the workshop was the need for timely guidance on a single national pedigree standard prior to States going off and implementing their own systems. Implementation of a national standard could take years to implement. Could you speak to the timeframe necessary for Congress, the FDA and industry to act on this? And in speaking on that also, if PDUFA passes without a national pedigree solution included, what are the implications for where we are going to be in terms of our domestic pharmaceutical supply chain over the next 5 or 10 years?

Ms. HAMBURG. Well, it is a very important question, and since I happen to be sitting next to an expert on this topic and you have been hearing me talk an awful lot, I think I may actually let my colleague, Deputy Commissioner Deb Autor, respond to that because she really has been working on those important issue for a very long time.

Mr. MATHESON. Great.

Ms. AUTOR. Thank you. Congressman, as you mentioned, we did hold a public workshop on track and trace and we have had over 120 participants in that workshop and a lot of comments that have been submitted to the docket on a track and trace system. We are working hard on working on those standards, and I would be happy to talk to you more about how we can work together towards a national uniform pedigree system. We are concerned that if a national system doesn't go into place, we run the risk of having a patchwork of State laws including California's law that is scheduled to go into effect in 2015. We believe track and trace provides very important assurances to the integrity of the drug supply by giving us and industry and pharmacies and consumers the information they need to know to be assured that their drugs are safe and effective.

Mr. MATHESON. Do you think the FDA needs further authority from Congress in order to implement a national standard?

Ms. AUTOR. Yes. We have authority now to implement standards but it is not clear in the law that those standards will be binding on everybody in the industry, and it is not clear that they would effectively preempt State law, so in fact, I think national legislation on this would be useful.

Mr. MATHESON. That is good to know.

Now, the safety of our pharmaceutical supply chain has an important overlap with the drug shortage issue that we have been talking about. I saw a survey by the American Hospital Association that showed 42 percent of those hospitals facing shortages purchased a more expensive product from a new distributor. However, in this instance, there is no meaningful way for that hospital to be sure the drug they are buying has traveled a safe and secure path. Do you think a single national pedigree standard would help hospitals ensure the integrity of products bought outside their normal source of supply?

Ms. HAMBURG. I think, you know, that the issue of supply chain and shortages are linked but they also have many distinct characteristics, and I think that as we are grappling with the drug shortage problem, which is, as you know, a very real problem and growing, you know, we are trying to look at all the critical factors that are involved and, you know, they range from issues of limited numbers of manufacturers of a given product to aging production facilities, to cost reimbursement issues, and some of the issues around consolidation of providers and manufacturers.

The issue of the security of the supply chain and quality being built into both manufacturing and assurances of quality throughout the supply chain obviously play a role in shortages to some degree, and also understanding the supply chain is important in understanding what kinds of products and quality products people might be accessing in relation to a shortage. So it is a complicated issue.

Mr. MATHESON. And I know there are a lot of separate issues in the two. It just seems to me that in a shortage situation, that——

Ms. HAMBURG. In a shortage situation, it is absolutely critical that whatever you are using as an alternative product, we can know is safe and high quality.

Mr. MATHESON. Yes, shortages create stress on the system, and stress creates opportunity for bad things to happen.

Mr. Chairman, my time is up. I will yield back. Thanks.

Mr. PITTS. The chair thanks the gentleman and yields to the gentleman from Louisiana, Dr. Cassidy, for 5 minutes for questions.

Mr. CASSIDY. Dr. Hamburg, thank you for being here.

Now, I have learned to say in this job, I know what I have been told, not what I know, so let me just preface this by this. I am told that there is a difference between calendar days and FDA days, so on page 4 of your testimony where you mention that the FDA approval phase of new drug development has shrunk. I heard previously people come and say you have got to be kidding, they kick it back to us, they don't include this, and actually the time has grown. I have learned to say what I have been told, not what I know, so I come to the font, if you will, to say is that true? Is calendar days actually longer even though FDA days are theoretically shorter?

Ms. HAMBURG. Well, in terms of the way the performance goals have historically been structured, you know, in fact, one is looking at the FDA time and the clock can be stopped for different kinds of activities and ultimately what matters to patients and, you know, truly what matters to all of us involved in the process is how long does it take for a product to actually get to the person who needs it. But I think one of the things that has been very, very en-

couraging as we have watched the PDUFA process really take hold in terms of the resources capacities and focus of our review activities is that we have seen the number of drugs approved in the first cycle increase and it is over 60 percent now, I think, which means that we are getting drugs to people in the first review process, which is really critical because——

Mr. CASSIDY. Now, your answer suggests to me that indeed calendar days may have increased for any given drug but it doesn't go through two cycles so maybe net it is less.

Ms. HAMBURG. On the drug side, I don't believe that that is the case. The device side, it is a little bit of a different scenario, and that is why I was sort of avoiding speaking to specific details, but on the drug side, we are seeing changes in the absolute time that it takes to get a product to market in really across-the-board way, particularly for priority review.

Mr. CASSIDY. Let me go to my next question. I thank you. We will later hear testimony from the Pew Health Group, which kind of relates to something which we previously spoke about, that if you are a domestic pharmaceutical, you are getting reviewed every 2 years, and if you are overseas, it may be every decade. And I understand here we are now creating resources but in a previous conversation, you mentioned that union contracts limit the ability of FDA to assign people to go overseas to inspect. Now, does this address that issue as well?

Ms. HAMBURG. You know, I think that the union issue is really not central to the discussion. The issue about the increased cost complexity demands on the system of increasing the numbers of international inspections is, and we are really embarked on a series of activities to be able to strengthen our capacity to have a global presence and either directly inspect or get inspectional information.

Mr. CASSIDY. So you imply that, if you will, as a workaround so even through the contract may inhibit it, you have a workaround in which you could third party it?

Ms. HAMBURG. You know, I think that the union issue is really a non-issue here. We work closely with the union around the activities of union employees.

Mr. CASSIDY. Now, that is a little bit different than what we heard last time in which we were told that people had to volunteer, they could not be assigned, and that sort of thing.

Ms. HAMBURG. Well, we definitely seek volunteers for our foreign inspectional activities. We are addressing it in a number of ways. We do have a dedicated foreign inspectional cadre that really like to travel and have specifically volunteered.

Mr. CASSIDY. So just a pointed question, knowing that right now it is every 10 years or so overseas, if you had tomorrow to say listen, we haven't inspected them for 5 years, you two are going and we expect an inspection report from you in however long it takes to do an inspection report, would you be able to do that?

Ms. HAMBURG. Well, we are dramatically ramping up our foreign inspections and we are doing it through both using domestically based inspectors who travel overseas. We are doing it through having foreign offices and inspectors who are based in country. We are doing it sharing inspectional information with our regulatory counterparts in other countries.

Mr. CASSIDY. Now, if I may interrupt, because I am almost out of time. I don't mean to be rude. But nonetheless, we are only doing it every 10 years. What do you project if we have this hearing 3 years from now that the frequency of inspection of an overseas plant will be by whatever mechanism we assign staff to do so?

Ms. HAMBURG. We are looking ultimately for parity between our domestic inspectional schedule and our foreign inspectional schedule. We want a level playing field, and it is interesting, we are not talking today so much about the generic user fee agreement but the foreign inspection are a particular issue around generic drugs and their manufacture and actually through leadership from the generic industry, you know, we have a first-time-ever user fee agreement that very much focuses on how can we strengthen the resources and programs to meet those demands of foreign inspections.

Mr. CASSIDY. Mr. Chairman, you have been very generous. Thank you. I yield back.

Mr. PITTS. The chair thanks the gentleman. That concludes the questions from the members of the subcommittee. We will go to the rest of the members of the committee, and the chair recognizes Dr. Christensen from Virgin Islands for 5 minutes for questions.

Mrs. CHRISTENSEN. Thank you for the opportunity to sit in on this important hearing and to be able to ask questions.

Most of the questions that I had around risk and benefit balancing and how it affects the time I think have already been asked several times and answered, so I am not going to ask that one. But I have a specific question on supply chain that relates to the territories, and I don't really expect you to answer it right this minute but maybe giving me an opportunity to work with your staff on it. The medicines that come to the U.S. Virgin Islands are sometimes held by Food and Drug through Customs in Puerto Rico and almost always confiscated when they are being sent back to their supplier. We are outside of the Customs zone. That is part of the problem. But we are part of the United States. Our pharmacists are licensed, trained and licensed in the United States, and we are purchasing from U.S. companies. So what we would like to pursue is having a waiver or some special procedure to avoid this problem because it is a great burden to my hospitals and my pharmacies and of course, it had a deleterious impact on patients' access to clinically important drugs, and I am hoping that as you look through a new international regulatory system that we can find a way to fix that within that. So again, if you want to comment on it, fine, but I think it is——

Ms. HAMBURG. Well, only to say thank you for bringing this to our attention, and I think that we would like to work with you to better understand the nature of what is happening and why and what can be done to address it.

Mrs. CHRISTENSEN. Right. And we have talked in the previous administration about it, so some of your staff may know about it, but I know it is a fresh one for you.

Could you tell me how the FDA's new Office of Minority Health works, for example, with the Office of Pediatric Therapeutics to ensure that racial and ethnic minority children are appropriately,

ethically and adequately included in drug research on children and pediatric populations?

Ms. HAMBURG. Well, we are just standing up this new Office of Minority Health. It was actually something—the opportunity to put it in place was part of the health care reform act, and it is intended to sort of cut across the full range of activities within FDA but with a special focus on a set of important scientific, medical and public health issues including how can we assure the appropriate representation of racial and ethnic minorities in clinical studies and I think there are huge opportunities both to work with our Office of Women's Health and our pediatric offices but to work across, you know, all of the medical product areas so that we can really address these critical concerns.

Mrs. CHRISTENSEN. On BPCA and PREA, often in children, the side effects of medicine or anything might not be seen for many years. Is there a requirement for the pharmaceutical industry to follow children for a certain period of time after they have been involved in clinical trials?

Ms. HAMBURG. You know, I am not sure that I can give you the complete response. We obviously have ongoing efforts to monitor adverse events, whether they are near term or long term, and our ability to do that in a meaningful way is enhanced by what we have been able to do in terms of strengthening our postmarket surveillance activities. In certain disease areas, there might be a particular concern anticipating possible longer-term risks or specific side effects in children and it might be part of the structuring of the clinical trial at the time of its initiation through PREA to put in place certain requirements and expectations about ongoing monitoring. But there may be some additional activities as well that I am not fully aware of.

Mrs. CHRISTENSEN. Maybe we can follow up on some discussions with your office around that and see if there is something that needs to be done in terms of children and long-term impacts.

Thank you, Mr. Chairman, I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentleman from Virginia, Mr. Griffith, for 5 minutes for questions.

Mr. GRIFFITH. Thank you, Mr. Chairman, and I know we have plowed through some of this territory but I think it is interesting. As a member of the committee but not of this subcommittee, it has been very educational and I do appreciate you being here, Mr. Chairman, and I appreciate you letting me participate.

But you have heard from both sides of the aisle what I am about to say, and that is, we have all been contacted by constituents. That is why I am here today. I was contacted by a constituent who feels that the strong risk aversion at the FDA is creating at least the perception that it is slowing down or stopping the approval of new, innovative treatments for cancer and other life-threatening terminal diseases. And I like some of the others who have spoken here today, and I am not going to make you go through all the things you have already testified, are very concerned that if you are facing a certain death, you are willing to take more risk, and you are wondering why the government is getting in the way. So I would ask you first, you have already been over a number of things that the FDA is doing to try to make that process better,

but have you given consideration to creating a waiver process where a consumer who is facing one of these diseases can waive liability and any concerns about a particular drug or biologic treatment or whatever in order to get that treatment when they are facing the consequences? Obviously, there has to be a disclaimer of all the either known or unknown risks involved, but have you all given consideration to doing something like that? Because thank God, I have never had to face that and hope I never do, but there are a lot of folks out there like the 41-year-old we heard about, and you have heard from both sides of the aisle, folks are willing to take those risks, particularly when they are younger and particularly if they have young children, as I do. You know, I would take those risks in a heartbeat if it was going to give me extra time with my kids.

So I am just wondering, have you thought about creating some kind of a waiver—ok, this hasn't been approved but I am willing to take that risk? And if you haven't thought of that, would you? And then let me follow up with, and what other things is the FDA is doing that you have not already testified to, because I don't want you to have to be like a broken record and go over the things that you have already mentioned.

Ms. HAMBURG. Well, you know, obviously this is such an important point and it is something that goes to the very heart of what we do because, you know, our mission really is to try to get the best possible treatments to people who need them, and, you know, as we have already talked about, we are putting an increasing focus on how we think about benefits and risks and weigh them. We already do accept, you know—have a much higher tolerance for risk when you are talking about a disease that is serious, life threatening, has no other treatment. I don't believe that we have really explored the exact proposal that you put forward, and I think it would certainly require broader discussions than just within the FDA. And we do have some other programs. Compassionate use was mentioned for trying to get drugs to people that are in desperate, life-threatening situations but perhaps, you know, in the interest of time and completeness, you know, we could provide you with some additional information about the programs that we are undertaking, and we certainly can continue to think about other strategies including the one that you mentioned.

Mr. GRIFFITH. Well, and if you would, and, you know, this is one of those things where sometimes folks just sitting around the table brainstorming might come up with one of those eureka moments and have an epiphany.

Let me shift a little bit to another question that has come up in my district. I represent a rural district. There are many recognized off-label uses for approved drugs but—I will pick up Dr. Cassidy's point. But I am told that the FDA severely restricts communications to doctors and patients about these uses. Representing a rural district, I have heard about doctors who find it difficult to get the information about off-label uses that could benefit many of their patients. So what can we do to better, both as the FDA and what can we do as Congress to help you better inform doctors, especially in rural communities so they know about potential effective off-label uses of approved treatments?

Ms. HAMBURG. Well, off-label use, as you know, you know, is an important part of many medical practices and FDA doesn't regulate the practice of medicine and off-label use is something that we recognize is happening and frequently I have talked with people within FDA about how can we really collect better information to understand off-label use so that it could inform the broader issues around the approved indications for the use of a drug, but I think that the big concern is when drug companies are actively marketing an unapproved drug for an off-label use and that is where the controversies have been really focused on.

Mr. GRIFFITH. Yes, ma'am. Thank you for your time. I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from California, Ms. Eshoo, for 5 minutes for questions.

Ms. ESHOO. Thank you, Mr. Chairman, for holding this hearing and also for extending both you and the ranking member a legislative courtesy to me to join this hearing today. It has always been a great source of pride to me to have served on this subcommittee for some 15 years, most of the years that I have been in the Congress, and I miss being here but I look forward to coming back and I am glad I am here today.

I would like to ask unanimous consent that the lovely statement that I have be added to the record.

Mr. PITTS. Without objection.

[The prepared statement of Ms. Eshoo follows:]

Statement of the Honorable Anna G. Eshoo
House Committee on Energy and Commerce, Subcommittee on Health
Hearing on the Prescription Drug User Fee Act, the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act
February 1, 2012

Mr. Chairman, thank you for holding this hearing today on the reauthorization of the Prescription Drug User Fee Amendments, the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act. These critically important laws have improved patient access to important therapies and our nation's regulatory system.

The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 when drug review times were lagging and FDA simply couldn't keep up with the flood of new drug applications. Through user fees paid by applicants, PDUFA gave FDA the resources it needed to hire and support more staff. The program has been successful at reducing review-time backlogs and expediting safe and effective therapies to patients.

Along with faster drug approvals, Congress also recognized the need to study drugs in children. Children are not just small adults—drugs react differently in their bodies and must be studied accordingly. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are the result of this need. BPCA and PREA have vastly changed the medical landscape for those treating children and have resulted in new dosing information, new indications of use, new safety information, and new data on effectiveness. The drugs studied under these programs treat a range of diseases in children, including cancer, HIV/AIDS, diabetes, allergy, and asthma.

As the original author of BPCA and PREA, I'm proud to report that 426 drug labels have been created specifically for children since the passage of these laws. Before BPCA and PREA,

the vast majority of drugs (more than 80 percent) used in children were used off-label, without data for their safety and efficacy. Today that number has been reduced to 50 percent. While we still have a long way to go, we've made remarkable progress in the last decade.

Congress has the responsibility to periodically review the program to ensure that pediatric needs are being met and the program runs efficiently. Through its design, BPCA was intended for reauthorization every 5 years— and has been since I introduced it in 2002. The program's reward of six-months of market exclusivity for doing additional studies in children is a substantial one and should not be taken lightly. Providing 6 months of market exclusivity for performing pediatric research is a major incentive, and we owe it to the beneficiaries of this program—children—to devote our ongoing timely attention to the issue.

In this year's reauthorization, it's important for us to look at areas in need of improvement. FDA must have the tools it needs to ensure companies are thinking about pediatric populations as early as possible in the drug development process, and that they're able to enforce timelines that are routinely missed. We should encourage further study into untested age groups, like neonates, and we should close loopholes which may allow companies to access the market exclusivity incentive without completing additional studies.

I'm proud of how far these programs have come in improving medical care for children and I look forward to working with my colleagues to improve both programs even further.

Ms. ESHOO. Commissioner Hamburg, it is wonderful to see you. I think that you know that I was the original author of both PREA and the BPCA, so I come here today with a great sense of pride and I welcome the comments and the questions that members have asked about both pieces of legislation that the Congress is preparing to reauthorize.

As you know, PREA was created to ensure that drug companies were doing important clinical trials in children, an area which had been most frankly woefully underserved before the passage of the legislation. And without adequate pediatric labeling, doctors were left to guess what the appropriate dosages for children would be. I think there was maybe this assumption that was being made that children are little adults, and they are not; they are children. So I think that this has—we took a very important step with the passage of that legislation, and I think it is why it is crucial for companies to develop their pediatric plans as early in the drug development process as possible.

Now, I understand that the FDA has draft guidance asking companies to submit their pediatric plans at the end of phase II but the PREA statute requires submission at the time of the new drug application. I think the sooner that companies focus on pediatric populations, the sooner kids will receive the drugs that they need in some cases to survive. So can you say with confidence that pediatric study discussions always start as early as the FDA recommends?

Ms. HAMBURG. Well, first, let me say thank you for your leadership, and before you walked into the room, I had actually made note of it in my opening remarks. But BPCA and PREA have been very important pieces of legislation and have enabled enormous progress in the pediatric therapeutics area. The question you raise, you know, is an important one. I know it has been under discussion within the agency and beyond, and I think it is sort of an ongoing discussion in terms of what is the most appropriate timing, and frankly, there probably is no one cookie cutter approach. It probably really does depend on the particular product in question and the types of trials required. But I think in general, my sense is that early engagement is always helpful and the ability——

Ms. ESHOO. I ask because of how the statute reads. Do you have any idea what the percentage of pediatric plans are actually completed at the end of phase II? I mean, if you don't know, maybe you can get that to us.

Ms. HAMBURG. We can get that to you.

Ms. ESHOO. Now, if a company does not submit its pediatric plan by the end of phase II, as the draft guidance recommends, does FDA have any enforcement mechanisms to address it?

Ms. HAMBURG. Now, you know, I want to make sure that I answer your question properly.

Ms. ESHOO. I ask this because I think it would be helpful to have legislation to ensure that companies submit their pediatric plans at the end of phase II. In fact, Congressman Markey and I are working on this, and maybe I should just turn the question around. Would it be helpful to you to have legislation that addresses what I just stated?

Ms. HAMBURG. Well, we do feel that at least as I understand it currently, you know, we have the tool of misbranding as a way of trying to respond to when the commitment is not met by the company with respect to completion of the pediatric studies, and that does seem like a bit—not quite the right regulatory or——

Ms. ESHOO. I can sense it in your voice that there is——

Ms. HAMBURG. Yes, it creates a situation——

Ms. ESHOO. So you think legislation would be helpful?

Ms. HAMBURG. I think that looking at that and if there is an approach that could be more targeted and flexible, that that would be very useful in terms of pushing companies to complete this important work and doing it in a constructive way that ultimately benefits the patients.

Ms. ESHOO. Thank you very much, and thank you for your work, Mr. Chairman, and our ranking member, thank you again for your legislative hospitality.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentleman from California, Mr. Bilbray, for 5 minutes for questions.

Mr. BILBRAY. Thank you very much for your courtesy, Mr. Chairman, and I just realized that at least on the other side of the aisle, there is a few that may remember the time I served on the committee for 6 years. A whole lot of new faces on this side.

Doctor, we talk a lot about safety and regulation to protect it. We have an over-the-counter consumer product that is connected to over 500 deaths a year, and we continue to allow that to be sold over the counter. Do you want to explain to this committee why aspirin in its existing form is not more regulated or more restricted from consumer use even though there is what some people would call a very high death rate related to its use?

Ms. HAMBURG. Well, you know, aspirin obviously is a widely available product that we know has associated risks but also benefits. I don't think that I am prepared in this setting to discuss the whole context of the oversight and regulation of aspirin but I think it is an important reminder that even drugs that the average American would probably consider sort of safe and routine do have consequent risks and they need to be addressed in an ongoing way and that the FDA does in fact have a responsibility for the lifecycle of products, not just for approval but for monitoring safety, efficacy and benefit, overall benefit to patients over the whole course of the product's use.

Mr. BILBRAY. Now, would it be fair to say, or if you can refer to your experts around you or whatever, would it be fair to say on the flip side of that issue that aspirin probably can be documented as being one of the most lifesaving drugs that have been readily available to the public in the last 30, 40, 50, 60 years?

Ms. HAMBURG. Aspirin has many benefits on different levels. That would be fair to say.

Mr. BILBRAY. Do you have any idea if there was any other drug out there that we could point to that probably has saved as many lives as aspirin has?

Ms. HAMBURG. You know, I am not really prepared to make those comparisons or have that——

Mr. BILBRAY. I would be very interested if you would take a look at the reality we have with aspirin, and I ask you to consider, and let us be very frank about it. If this product with its fatality problems came before the FDA today, could our existing system actually process it and get it out onto the market, or is it just one of those products that became so institutionalized before our regulatory oversight got where it is today? And my question is, do you think aspirin could get through the system today?

Ms. HAMBURG. Well, I wondered if that might be the ultimate question that you would be asking, and I guess that my answer in the form of a true bureaucrat is that I wouldn't be prepared to speculate without having really reviewed the information and the data, but I understand the issue that you are raising.

Mr. BILBRAY. I mean, my issue is the fact that if you only look at the negatives and if you focus, even if you look at the positives but if you focus on the negatives, in today's life, which usually happens, there are huge opportunities that may be denied, and my biggest concern is that I am looking at this and I don't see any way aspirin would be approved in our system, and how many people would die every year in this country and around the world if it wasn't available to the consumer? And I have to ask myself, do we know how many other drugs or treatments may be out there that have come later that cannot be accessible? So my big question is, has anybody ever challenged themselves to say do we have any idea how many deaths may be caused because we don't allow products like aspirin on the market today?

Ms. HAMBURG. Well, you know, as I was saying earlier in discussions, you know, we look in a very clear-eyed way at risks and benefits of the products that come before us, and I think we are striving now to deepen our strategies for addressing that and, you know, we do take a lot of risks. There is a sense that we are very risk-adverse.

Mr. BILBRAY. Doctor, I appreciate that and I am not blaming you. I am blaming the fact that the political side, we would raise holy hell, you would seeing us standing on the House Floor giving big speeches damning you for allowing this on the market, and I just want to sensitive that.

Let me just say one thing. One of the great breakthroughs we did with AIDS in the 1990s when I was here was that we changed a lot of regulations, and multi-triaging was one of those things that we really moved the protocol for AIDS that hadn't been done for other research in other treatments. When it comes to cancer, it really appears that multi-triaging and a combination of drugs and uses may be one of those things we have learned from the AIDS success. Where we going now with FDA improving the ability for researchers and for pharmaceuticals to look at multiple drug use in the treatment of diseases such as AIDS and do we have an expedited process to try to move that process along?

Ms. HAMBURG. Well, I began my career in public service working on HIV/AIDS drug development and know exactly what you mean in terms of the importance of the breakthroughs, and it was really a combination of bringing the science together with the resources and commitment of industry, academia and the patient groups, and we were able to move very forward very swiftly and we were able

to introduce, you know, some new regulatory approaches, etc. in the cancer arena and in other areas as well, other infectious diseases and other disease domains, we have a real opportunity as our science has deepened to do some of the kinds of things that you were just mentioning, and we actually just recently put out guidance to help industry think in some new ways about testing drugs in combination rather than doing one after another after another.

Mr. BILBRAY. And taking 20 years to do it.

Ms. HAMBURG. Yes.

Mr. BILBRAY. Mr. Chairman, I know my time is expired. To my colleagues, just to follow up on that, one of those other great successes that my colleagues will remember is that in the AIDS crisis, we could do blood tests and monitor virus levels to be able to see what cocktails were working rather than what we have now in cancer where you basically have to wait for the cancer to show up again. You have clinical trials in process right now on the East Coast for a blood test for lung and for breast cancer that is being looked at. Has anybody in your agency taken a look at the fact that this is not just a product that may be able to detect cancer for treatment but maybe one of those huge breakthroughs that cancer researchers are looking at to be able to more efficient in their research, much like they do with AIDS? Is anybody considering the connection between this blood test may not only be a good treatment but may be an essential part of research to address this issue?

Ms. HAMBURG. Yes, and let me just clarify that actually partly stemming from the work in HIV/AIDS, we do use surrogate markers including the kind of markers identified through blood tests in our approval process. That is really what accelerated approval is all about, is identifying what can serve as surrogate endpoints for an early approval followed by additional clinical studies to confirm or not confirm the initial promise as indicated in those studies. So we take that very seriously. We use it in our decision making, and certainly what you were describing would fit within that framework of regulatory——

Mr. BILBRAY. Thank you for your courtesy, Mr. Chairman.

Mr. PITTS. I thank the gentleman and recognize the gentleman from Massachusetts, Mr. Markey, for 5 minutes for questioning.

Mr. MARKEY. Thank you, Mr. Chairman.

The Web site clinicaltrials.gov was transformed into a mandatory registry that I created along with Representative Waxman in the 2007 FDA amendments. This Web site publishes information about the results of clinical trials designed to evaluate medical treatments but several problematic loopholes exist. For example, a drug company finds out from a clinical trial that a diabetes drug is not only ineffective but also causes severe side effects. As a result, the company abandons the drug's development, never seeks approval with the FDA and never publishes the results because there is no incentive to do so. Commissioner Hamburg, will the results of this trial ever have to be posted on the clinical trials database?

Ms. HAMBURG. As I understand it, currently, no. That is an important issue that you raise. I think it could be addressed but it is not included in——

Mr. MARKEY. So if another researcher decided to pursue clinical trials of this same drug, they would have no idea about the dangers identified from the previous trial and would put more people at risk of the same adverse health effects that had already been identified so generally do you agree that it would be a good public health measure to ensure that results of all registered trials, regardless if the drug is approved or not, are posted on the database?

Ms. HAMBURG. I believe that NIH through its rulemaking process is currently looking at this question in terms of whether trials for drugs that aren't actually approved could be posted. I think you also raise a broader issue that certainly we are talking about with industry and others in terms of more transparency and the benefits, the common good of making more information about, you know, not just what works but what doesn't as well.

Mr. MARKEY. Thank you. Now, some clinical trials that occur entirely overseas can be used to support a drug application with the FDA even though they are not subject to the disclosure requirements of the clinical trials database. Do you agree that any clinical trial regardless of where it takes place should be subject to the same transparency requirements if the trial is used as part of the company's approval application to the FDA?

Ms. HAMBURG. You know, yes, you know, in general we certainly agree that more transparency, more information is beneficial and we think that this is a bit of a disconnect and, you know, we would be interested in working with you further.

Mr. MARKEY. So this is something that Ms. Eshoo and I are working on, this next subject, which is that the FDA data shows that since 2007, 78 percent of PREA's pediatric study requirements were not completed by their due dates, if at all. These are products that could benefit children but the studies needed to provide that information are not always being completed. Pediatric studies are especially challenging and companies may have a perfectly acceptable reason for asking FDA to extend their deadlines, but if the company does not meet its pediatric requirements and fails to provide a reasonable justification, what enforcement options does the FDA have?

Ms. HAMBURG. Well, we do, as I was discussing with Congresswoman Eshoo earlier, have, you know, a limited arsenal of tools and it really is an area where it is important, number one, to understand the reasons for the delays, and as you note, there are some reasons that are understandable, but these are studies that are important to get done. We need to support companies in getting them done and there should be expectations and accountability on the completion of those studies.

Mr. MARKEY. Yes, it is my understanding that the FDA's only option for enforcement is misbranding the product if there is an enforcement action that you can take but that is an option very rarely, if ever, taken by the FDA. If the FDA were to deem a lifesaving treatment misbranded because the company failed to complete its pediatric requirements, children who were being prescribed the drug off-label would lose access to it. Adults would also lose access. Is that correct?

Ms. HAMBURG. That is correct, and that is why in some ways—I have heard it internally referred to as the nuclear option.

Mr. MARKEY. So either FDA triggers the nuclear option of misbranding, costing everyone access to that drug, or they can do nothing, and that is very different from the way many other violations of the Food, Drug, and Cosmetic Act are handled, which can incur civil monetary penalties. Have civil monetary penalties been effective in other areas to ensure compliance?

Ms. HAMBURG. I think that they have been and they do give more flexibility and the ability to target the action to what needs to be done in a more effective way.

Mr. MARKEY. And I see no reason, Ms. Eshoo and I agree on this, that companies failing to meet their obligations to children should enjoy those special protections. So we would like to work with you in giving you the flexibility to impose those penalties.

And just finally, Ms. Schakowsky and Ms. Baldwin and I introduced a cosmetics bill last Congress. We reintroduced the same cosmetics bill in this Congress, and as you know, most people believe that the government makes sure that personal care products like shampoo and cosmetics are safe before they are sold. Does the FDA have statutory authority to require safety testing of cosmetic ingredients before they go on the market?

Ms. HAMBURG. We do not do premarket approval for cosmetics except in a very limited domain of color additives.

Mr. MARKEY. And can you require a recall of any product in cosmetics?

Ms. HAMBURG. If there were serious safety issues raised with public health consequences, we would work with the company to get them to voluntarily——

Mr. MARKEY. But it is voluntary. You don't have a mandatory power.

So Ms. Schakowsky and Ms. Baldwin and I are very interested again in pursuing that legislation and working with Mr. Pallone and working with the chairman towards the goal of finding a way of giving you the authority that you need to work on these issues. So if you would be willing to work with us, we are willing to work with you and with Mr. Pallone and others to see if we can do something legislatively in this area.

Thank you, Mr. Chairman.

Ms. HAMBURG. Terrific. Thank you.

Mr. PITTS. The chair thanks the gentleman. That concludes round one, and we will go to one follow-up on each side for round two. The chair recognizes Dr. Burgess for a follow-up question.

Mr. BURGESS. Dr. Hamburg, thank you for spending so much time with us here this morning. I just wanted to follow up on something that Mr. Ross from Arkansas brought up about the over-the-counter asthma inhalers, and while I recognize the problem actually originated in the EPA, not at the FDA, on the removal of CFCs as a propellant, you know, the fact of the matter remains, I spent New Year's Eve driving from pharmacy to pharmacy to make sure I had an adequate supply of Primatene because as he correctly points out, it is two vials for $32, so it is a fairly reasonable price compared to the expensive price of the albuterol, which is a prescription device.

My understanding is that the over-the-counter iteration that is non-CFC is currently in process with the HFA as a propellant and

that FDA is evaluating that. I would just encourage you to do so with all great dispatch. These are things that have been around for a long time, and most people with asthma, as I do, experience times when the disease is much worse and times when it is not so bad, and those times when it is not so bad, I may get quite far away from having anything around the house that would be available to help me, and it was always comforting to know at 2 o'clock in the morning I could drive to a 24-hour pharmacy and purchase a Primatene inhaler. Now the only option is—and I am a doctor, I can write my own prescription, but for the vast majority of people, you have to go to the emergency room, likely going to get a breathing treatment and a pulse oximeter, maybe a blood gas, and you are going to spend $1,500, $2,500 for what could have been fixed, as Mr. Ross correctly points out, for a $20 charge at an all-night pharmacy.

So it is important to get the over-the-counter option back out there. Many people use these rescue inhalers not frequently but from time to time, and that is the part of the population that really would benefit from having these back and available again. Can we look to you to help us get those?

Ms. HAMBURG. We have indicated that, you know, we would welcome an application and we will work to expedite the review.

Mr. BURGESS. Because the active ingredient is not any different than what it has been for the last 100 years, right? And the difference is the propellant, and if it used in the albuterol inhalers, it can't possibly be harmful. I think it is as good as CFC. CFC gets you a much better dispersion. The HFA always ends up in the oropharynx and you have to relearn how to use it.

But this is important to people, and every member of this committee, in fact, every Member of Congress is going to be hearing about this at some time during the year when their constituents run out of their existing supply of CFC inhalers and find that they cannot replace them.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman, and Mr. Pallone is recognized for 5 minutes for one follow-up.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Hamburg, some have suggested that FDA is insisting on too much clinical trial prior to approval and that it is resulting in an export of innovation and jobs abroad, and to help address this situation, some of the members have suggested that FDA's mission statement should be changed to include things like job creation and innovation. In fact, there is a bill, the Food and Drug Administration Mission Reform Act, that would accomplish this.

Now, even assuming there is some truth to these reports, and I think that there is important evidence to suggest that there is not, revising FDA's mission statement seems like a drastic measure to me, and I just wanted you to comment on the implication of revising FDA's mission statement to include things like job creation. How would FDA even begin to assess whether certain agency actions would create jobs?

Ms. HAMBURG. Well, I think that it is very, very important that FDA as a science-based regulatory agency with a public health mission really focus our efforts on determining the safety, efficacy and

quality of the products that come before us and that we do our work in the context that clearly understands that we need to make sure that we are bringing products to people in a timely way that they need and count on and that we do need to do everything we can to make sure we have the most modern and streamlined approaches and that we work closely with product sponsors in a way that is transparent, consistent and predictable to achieve our common goal of making important products available to people.

I think that our safety and efficacy standards are very important to the success of industry as well as to improving and protecting the health of the public.

Mr. PALLONE. But what I am trying to find out is whether you would want to revise the FDA's mission statement to include things like job creation.

Ms. HAMBURG. Well, I was going to get to that and I think it would be very hard for us to factor in to this science-based decision making the question of how would approving or not approving this product impacts jobs and how would approving or not approving a product impact jobs of a competitor, and it would get very, very complicated, and frankly, I think it would be quite inappropriate and would ultimately not serve the American people well or serve industry well, and I think it is something that would be extremely hard to quantify, and I think that, you know, what is really important is that we make sure that operating within the ecosystem of biomedical innovation and product development that we ensure that we are doing our job as well as we can, which is to apply science-based, data-driven processes to our decision making, do it in as modern and streamlined a way as possible, and work as effectively with industry and other stakeholders to deliver the products that people need.

Mr. PALLONE. Thank you.

Mr. PITTS. The chair thanks the gentleman. That concludes our questions for panel one. The chair thanks the panel, specifically Dr. Hamburg, for your excellent testimony. It is very important information you have shared with the committee.

We will now excuse panel one and call panel two to the witness table, and while we change panels, we will take a 5-minute recess and reconvene at 12:45.

[Recess.]

Mr. PITTS. We will ask all of guests and witnesses to please take their seats, and would like to ask at this time unanimous consent to enter into the record a statement by NCPA, that is community pharmacists, and NACDS, National Association of Chain Drug Stores, into the record. It has been shared with the other side, so without objection, so ordered.

[The information follows:]

WWW.NCPANET.ORG

Statement of the National Community Pharmacists Association to the United States House of Representatives Committee on Energy and Commerce Subcommittee on Health Hearing on "Reauthorization of PDUFA: What it Means for Jobs, Innovation and Patients"

February 1, 2012

Dear Subcommittee Chair Pitts, Ranking Member Pallone and Members of the Subcommittee:

NCPA welcomes this opportunity to provide input and suggestions to the Subcommittee as it addresses the reauthorization of PDUFA and related issues. The National Community Pharmacists Association (NCPA) represents America's community pharmacists, including the owners of more than 23,000 community pharmacies, pharmacy franchises and chains. Together, these small business entities employ over 300,000 full-time employees and dispense nearly half of the nation's retail prescription medicines.

Specifically, NCPA would like to provide the following comments and suggestions regarding a number of issues that may be considered in tandem with PDUFA including: potential proposals to "track and trace" prescription drugs as they move through the supply chain; the lack of standardization for Risk Evaluation and Mitigation Strategies (REMS) and Medication Guides; drug shortages; the creation of a "transition" class of drugs; and the regulation of internet pharmacies.

Potential Proposals to Enhance Supply Chain Security

NCPA believes that the current pharmaceutical supply chain is safe and secure and accordingly independent community pharmacies have trust and confidence in their pharmaceutical wholesale suppliers. However, NCPA does feel that there are a number of different approaches or tactics that could be employed to provide further confirmation of integrity such as the development of federal licensure standards for wholesalers that would be administered by the states, and the imposition of greater penalties for cargo theft.

With respect to a potential inclusion of a "track and trace" system for prescription drugs, NCPA is working with a diverse group of stakeholders on a consensus approach that could add an additional layer of security to the current pharmaceutical supply chain. Our view on such a system is that it should be: 1) used sparingly – for example, only in cases of recalls; 2) allow for human readable identifiers on the saleable unit; 3) not be used by manufacturers as a prerequisite for the ability of pharmacists to purchase their products, or return recalled or outdated products; and 4) and not impose significant burdens and hardships on certain sectors of the supply chain or serve as an unfunded mandate at a time when small businesses, such as independent pharmacies, are already struggling under a crushing burden of federal and state regulations.

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Lack of Standardization for REMS and Medication Guides

NCPA continues to have concerns with the lack of standardization for Risk Evaluation and Mitigation Strategies (REMS), particularly medication guides. The FDA currently requires pharmacists to distribute an increasing number of highly variable paper medication guides for hundreds of drugs. These typically long, written documents may be of little value to patients, but add significant costs and burdens to the health care system. Instead, NCPA urges the FDA to transition to a simple, succinct document that would be produced by manufacturers and provided by pharmacies to patients. Pharmacies could provide this document to patients, either in print or electronic form, following face-to-face counseling. Such a simplified document could be an effective tool to reinforce proper medication use and improve overall health outcomes. In addition, NCPA urges the FDA to standardize the REMS procedures within the prescription filling process.

Drug Shortages Impact on Independent Community Pharmacies

NCPA's community pharmacist members and their patients are greatly affected by drug shortage issues. For example, there is currently a serious shortage of some ADHD medications which may be due in part to DEA manufacturer allocation issues.

Nevertheless, community pharmacies often have little notice of shortages from manufacturers and NCPA believes that a better process needs to be established to avert shortages. In addition, federal reimbursement policies should require that Medicaid and Medicare Part D programs suspend the Federal Upper Limits (FULs) or Maximum Allowable Cost (MAC) pricing on these drugs, as pharmacy benefit managers (PBMs) are often slow to provide higher reimbursement for these drugs to pharmacies after a shortage hits the market, and the price to the pharmacist spikes. Pharmacies should also be relied upon to compound medications that may be in short supply, as was the case during last year's Tamiflu shortage during which the FDA called on pharmacists to compound medications to compensate for the shortage.

NCPA Support for a "Transition" Class of Medications

NCPA supports the creation of a "transition" class of medications, which would be dispensed by a pharmacist after consultation with the patient. These medications would initially be prescription medications that would most likely be transitioned to full OTC status after a period of monitoring by a pharmacist. The creation of such a medication class would provide assurances to the manufacturer, the FDA, and consumers that the product could be used safely and effectively before a complete switch to OTC status is made. A transition class would also reduce consumer health care costs, increase convenience, and provide a vehicle for post-market supervision, while providing a guarantee of consumer protection. Pharmacists should be fairly compensated for their role in providing medications through such a "transition" class.

NCPA Supports Efforts to Eradicate Rogue Internet Pharmacies but Cautions Against Overly Broad Definition of "Internet Pharmacy"

NCPA supports public policy efforts to eradicate rogue internet websites that illegally sell prescription drugs, especially controlled substances. However, we oppose broad sweeping attempts to classify every brick and mortar pharmacy that maintains an internet site as an internet pharmacy. Such approaches are unnecessary because traditional pharmacies are already heavily regulated by both federal and state authorities.

We appreciate the opportunity to submit these comments for the record, and look forward to participating in the development of patient-centered PDUFA legislation.

Statement

Of

The National Association of Chain Drug Stores

For

U.S. House of Representatives
Energy and Commerce Committee
Subcommittee on Health

Hearing on:

Reauthorization of PDUFA:
What It Means for Jobs, Innovation, and
Patients

February 1, 2012
10:00 a.m.
2123 Rayburn House Office Building

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The National Association of Chain Drug Stores (NACDS) thanks the Members of the Subcommittee on Health for consideration of our statement for the hearing on "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients." NACDS and the chain pharmacy industry are committed to partnering with policymakers and others to work on viable strategies to address drug safety and the appropriate use of prescription medications in order to help promote optimal drug therapy treatment and patient health outcomes.

NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies – from regional chains with four stores to national companies. Chains operate more than 40,000 pharmacies and employ more than 3.5 million employees, including 130,000 pharmacists. They fill over 2.6 billion prescriptions annually, which is more than 72 percent of annual prescriptions in the United States. The total economic impact of all retail stores with pharmacies transcends their $900 billion in annual sales. Every $1 spent in these stores creates a ripple effect of $1.81 in other industries, for a total economic impact of $1.76 trillion, equal to 12 percent of GDP. For more information about NACDS, visit www.NACDS.org.

While we believe that the U.S. supply chain is the safest in the world, we are working with supply chain stakeholder coalitions to help enhance safety through additional achievable and feasible means for the security and integrity of the U.S. drug distribution supply chain. We also champion efforts to prevent illegitimate Internet drug sellers from targeting U.S. consumers with unsafe medications. To that end, we have endorsed federal legislation (S.2002) that will work toward providing consumers with a safe and secure means to identify legitimate online pharmacies. We also support providing patients with a useful and understandable drug information document (the "one document solution"), and providing patients with a safe and legal means for disposal of their unused medications. We believe that these are important issues surrounding the use of prescription drugs.

In addition, we are devoted to important initiatives to improve patients' adherence to their prescribed medications. Chain pharmacies and their pharmacists work with their patients daily to provide them

with information and counseling on the proper use of their prescription medications and the importance of adhering to their prescription drug treatment.

NACDS and the chain pharmacy industry look forward to working with Members of Congress on issues related to prescription drug use.

NACDS SUPPORTS FDA'S PDUFA GOALS

We are pleased that FDA has proposed to apply user fees toward efforts to enhance and modernize the U.S. drug safety system. To enhance patient safety, FDA plans to devote user fees toward reviewing drug applications for look-alike and sound-alike proprietary names and related factors that could contribute toward medication errors such as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design. We wholeheartedly support this proposal that would reduce the potential for medication errors throughout the healthcare delivery system.

We are also supportive of FDA's plans to utilize user fees to develop techniques to standardize prescription drug Risk Evaluation and Mitigation Strategies (REMS) and better integrate them into the existing and evolving healthcare system. The success of any REMS is highly dependent on the ability of all relevant stakeholders to provide ample input during the design phase of the program, well before implementation. The concerns of pharmacies and other healthcare providers must be considered in order for REMS to be successful. Since REMS could impact pharmacy operations and workflow and even a pharmacy's ability to provide the affected medication to a patient, we welcome more opportunities to work with FDA to standardize REMS.

In addition, we strongly encourage FDA's proposal to develop methodologies for assessing whether REMS are achieving their goals of mitigating risks and assessing the effectiveness and impacts of REMS on patient access and on the healthcare system. We believe that REMS should be subject to review by pharmacies and other relevant healthcare providers, such as by a representative panel of expert reviewers to include pharmacists who practice in pharmacy settings affected by the REMS.

Although pharmacies are not directly responsible to FDA for the design, implementation, and success of REMS, pharmacies are subject to the elements of REMS in order to meet the needs of their patients.

THE ROLE OF MEDICATION THERAPY MANAGEMENT (MTM)

Services provided by community pharmacists improve drug safety. Pharmacists are uniquely qualified to provide Medication Therapy Management (MTM) services to patients, which help ensure that patients are prescribed the correct medications and that they are taking them properly. Unfortunately however, MTM services are infrequently compensated, which limits pharmacists' ability to provide these services to patients.

When patients are prescribed the correct medications, they are less likely to experience adverse effects, such as allergies and drug interactions. Thus, they are more likely to take their medications as directed, that is, to adhere to their therapy. Patient adherence to their medication therapy leaves fewer unused medications in medicine cabinets that can be diverted and abused by others. Properly reimbursing pharmacists for providing MTM services is a greatly underutilized tool for addressing the problems of prescription drug diversion.

Pharmacist MTM services and the improved medication adherence that can result also provide the dual benefits of improving patient health outcomes and reducing the use of other more costly healthcare services. Research has shown that an estimated one-third to one-half of all patients in the United States do not take their medication as prescribed. They may fail to take their prescription medications, take their medication incorrectly, or stop taking their medication altogether. These circumstances seriously undermine quality of life and quality of care, patient outcomes and the value of healthcare dollars spent. Poor medication adherence costs the U.S. approximately $290 billion annually – 13% of total healthcare expenditures. Community pharmacies and their pharmacists are uniquely situated to assist patients in complying with their prescribed medication treatment and explaining the benefits of adherence. Programs such as CheckMeds in North Carolina, a program where community pharmacists provided MTM services involving nearly 27,000 seniors in 2008 and

2009, showed the benefits and savings by avoiding more costly healthcare services such as emergency rooms and hospitalizations and prescription drug savings. For every dollar spent in this program for pharmacist medication therapy management services, the benefit was $13.55 in savings.

TARGET ILLEGITIMATE INTERNET DRUG SELLERS WITH THE "CHOKEPOINT" APPROACH

NACDS also believes that addressing the problem of illegitimate Internet drug sellers is an important component of drug safety. These illicit online drug sellers have websites that target U.S. consumers with ads to sell drugs often without any prescription required. They are almost without exception located outside of the U.S. yet have websites camouflaged to look like legitimate pharmacy websites. They operate in clear violation of U.S. state and federal laws and regulations that protect public health and safety. They sell drugs to consumers without the safety precautions of a legitimate prescriber-patient relationship, a valid prescription, and a licensed U.S. pharmacy.

These illegal Internet sites that profit from these illegitimate activities are often mistakenly referred to as Internet "pharmacies." They are not pharmacies; they are *illegitimate Internet drug sellers*. They are not licensed as pharmacies by any U.S. jurisdiction, nor do they comply with any of the rigorous state and federal laws governing pharmacy licensure and the practice of pharmacy by pharmacists. Instead, these illegitimate Internet drug sellers are shipping unapproved, counterfeit, mislabeled, or adulterated products within or into the country.

We support targeting illegal Internet drug sellers through the *chokepoint approach*, rather than placing unwarranted burdens on legitimate, state licensed pharmacies that have associated branded Internet websites. Under the chokepoint approach, entities such as domain name registrars that issue websites, financial entities that handle payment transactions, Internet Service Providers that show the illegitimate websites on the Internet, and common carriers that provide the mailing services would have authority to stop illicit transactions at their point of interaction with these bad actors.

CHAIN PHARMACY ROLE IN SECURING U.S. DRUG SUPPLY CHAIN

We are proud of the systems and initiatives that our members have developed with other industry stakeholders to improve U.S. drug supply chain security.

Chain pharmacy has taken a leadership role to further ensure the integrity of the products they dispense. For example, many pharmacies have made changes in their purchasing practices, such as requiring their wholesale distributors to purchase prescription drug products directly from manufacturers. Chain pharmacy has been engaged with supply chain stakeholder coalitions working to enhance security for many years, and is currently involved with a coalition that includes manufacturers and wholesalers seeking feasible and achievable means to enhance supply chain security.

Our industry has also been engaged at the state level to enhance supply chain integrity. We supported state-level legislation requiring enhanced wholesale distributor licensure requirements and chain of custody "pedigrees" for drug distributions outside the recognized and safe "normal distribution channel." More than 60% of the states have enacted laws and regulations to strengthen the security of the drug distribution supply chain. We have also supported increased fines and penalties for violations of these state laws. Our members have seen marked improvements in the security of the drug distribution supply chain since the adoption of these initiatives and state laws. While there were several incidents of drug counterfeiting in the early 2000's, we are not aware of notices from the FDA of drug counterfeiting in the U.S. normal distribution supply chain since that time. It appears that these initiatives and stricter requirements have removed the bad actors from operating within the legitimate drug supply chain.

Chain pharmacy remains committed to working with Congress on the security of the U.S. drug distribution supply chain. However, we remain concerned with mandates to track and trace prescription drugs due to disruptions, complexities, and the substantial resources that would be required. These would occur at a time when the healthcare system is seeking to reduce costs. Moreover, with drug manufacturers almost universally applying "line of sight" "two-dimensional bar codes" on their products, these concerns would become quite real. Nevertheless, we remain

committed to working with Congress and the supply chain stakeholders to maintain and enhance supply chain security through viable means.

IMPROVED PATIENT MEDICATION INFORMATION "ONE DOCUMENT SOLUTION"

As FDA has recognized, patients typically receive several different types of medication information, developed by different sources that may be duplicative, incomplete, or difficult to read and understand. We agree with FDA that the current patient medication information (PMI) is not adequate to ensure that patients receive essential information in a clear and easily understandable format. We are very pleased that FDA is holding public hearings to gather information to assist the agency with the adoption of a single PMI document that is standardized with respect to format and content, the "one-document solution." For each medication, patients want a single, useful document, designed and written for them, that recognizes their information needs, that focuses concisely on critical information, and that provides them with clear instructions on where to go for further advice and instruction.

Existing requirements for multiple medication information documents, containing redundant or even conflicting information, creates logistical and financial burdens for pharmacies that compromise effective patient counseling. It would be far more convenient, efficient, and ultimately more effective for pharmacists to counsel patients by providing a single PMI document that could easily be understood and facilitate a discussion concerning proper use of medication.

We believe the best approach to the development of PMI is manufacturer development with FDA approval. Only this approach could absolutely ensure that all PMI meet FDA standards of accuracy and comprehensibility, and that the information is properly balanced to communicate risks and benefits. In our view, each FDA-approved drug would eventually have a single, standardized, manufacturer-developed, FDA-approved PMI document.

CONCLUSION

NACDS thanks the Subcommittee for consideration of our comments. We look forward to working with policy makers and stakeholders on these important issues.

Mr. PITTS. I would like to now welcome panel two and thank all of you for agreeing to testify before the subcommittee today, and I would like to quickly introduce our expert panel.

Mr. Geno Germano, President and General Manager of Specialty Care and Oncology at Pfizer, is our first guest. Dr. David Gollaher, President and CEO of California Healthcare Institute. Mr. Richard Pops, Chairman and CEO of Alkermes. Mr. Pops is testifying on behalf of the Biotechnology Industry Organization. Mr. Allan Coukell, Director of Medical Programs for the Pew Health Group; Ms. Diane Dorman, Vice President of Public Policy at the National Organization of Rare Disorders; Dr. David Wheadon, the Senior Vice President for Scientific and Regulatory Affairs at PhRMA; and Dr. Daniel Frattarelli, Chair of the American Academy of Pediatrics' Committee on Drugs.

So we will go in that order. Again, thank you all for coming. We have your prepared statements, and we will ask each of you to summarize in 5 minutes your opening statements.

Mr. Germano, we will begin with you. You are recognized for 5 minutes.

STATEMENTS OF GENO GERMANO, PRESIDENT AND GENERAL MANAGER, SPECIALTY CARE AND ONCOLOGY, PFIZER, INC.; DAVID L. GOLLAHER, PRESIDENT AND CHIEF EXECUTIVE OFFICER, CALIFORNIA HEALTHCARE INSTITUTE; RICHARD F. POPS, CHAIRMAN AND CHIEF EXECUTIVE OFFICER, ALKERMES, ON BEHALF OF BIOTECHNOLOGY INDUSTRY ORGANIZATION; DAVID E. WHEADON, SENIOR VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; ALLAN COUKELL, DIRECTOR OF MEDICAL PROGRAMS, PEW HEALTH GROUP, THE PEW CHARITABLE TRUSTS; DIANE EDQUIST DORMAN, VICE PRESIDENT, PUBLIC POLICY, NATIONAL ORGANIZATION FOR RARE DISORDERS; AND DANIEL A.C. FRATTARELLI, CHAIR OF PEDIATRICS, OAKWOOD HOSPITAL AND MEDICAL CENTER, ON BEHALF OF THE AMERICAN ACADEMY OF PEDIATRICS' COMMITTEE ON DRUGS

STATEMENT OF GENO GERMANO

Mr. GERMANO. Thank you, Chairman Pitts and members of the subcommittee. My name is Geno Germano. I am President and General Manager of Specialty Care and Oncology at Pfizer. Founded in 1849 in New York City, we have grown to become the world's largest biopharmaceutical company, providing treatments for a myriad of diseases that afflict people around the world. I appreciate this opportunity to testify on behalf of Pfizer and our 40,000 U.S. colleagues to unequivocally support the reauthorization of the Prescription Drug User Fee Act.

Behind the acronym PDUFA is another acronym: R&D, research and development. Research and development is the lifeblood of Pfizer. It is the lifeblood of our industry and it is the lifeblood of great American innovation. Today it takes on average more than a billion dollars and 12 to 15 years to research and develop a new medicine. Approximately one in 10,000 compounds that enter the drug discovery phrase is every approved by the Food and Drug Administration and made available to patients. Our R&D is ulti-

mately codified in our patents. Patents represent our license to move forward and are a fundamental legal basis for our existence.

It is important to remember, we file our patents on compounds in the very early stages of development, often a decade or more before the review process begins at the FDA. Therefore, by the time we had submitted an application to FDA, the patent life is already eroded to a meaningful extent, making an effective and efficient process with FDA imperative for our firm.

Biopharmaceutical companies like Pfizer typically have at most between 10 and 14 years to recoup our investment before generic competition enters the market. However, the public value, the public health value of our investment continues for generations to come.

It is through this foundational work in R&D and manufacturing that the biopharmaceutical industry supports more than 3 million U.S. jobs and nearly $300 billion in total output to GDP. PDUFA will help keep R&D and new medicine introductions in the United States.

The financial commitment and significant time and resources required to develop a drug reflect the uncertainties inherent in our business. The scientific uncertainties are ultimately reduced to the core question: does the benefit of the drug outweigh the risk? And this is a question we and FDA seek to answer, and it will vary depending upon the treatment and the intended patient population. Regulatory uncertainties can complicate this dynamic if the review process at FDA is ambiguous and inefficient. This is why a strong partnership and communication with the FDA are essential.

As the head of the specialty care business, I am intimately engaged in the development of our medicines. My business focus is on developing therapies for complex and rare diseases, many forms of cancer, and vaccines for the prevention of life-threatening infections.

Prevnar 13, a vaccine for the prevention of pneumococcal disease, is a great example of an important medical advancement. In December of last year, Prevnar 13 received approval from FDA for adults 50 years of age and older under the accelerated review process, a pathway specifically intended to speed new medicines to market for significant unmet health needs. Then last Friday, FDA approved our new cancer medicine, Enlighta, that we developed for patients with advanced renal cell cancer whose disease continues to progress after first-lien therapy fails. The development pathway for critical medicines and vaccines like these are not cookie cutter in nature, and it is essential to have a strong, functional regulatory agency for advancements like these to continue.

In my full statement, I discuss the major provisions of the new PDUFA agreement. I would like to highlight one of these, the review enhancements for new molecular entities, or NMEs, which will have an immediate impact on Pfizer and medicines in our pipeline. A good example of the benefit of an effective NME review process is Xalkori, which was approved by FDA last August. Xalkori is an NME and is the first lung cancer drug approved by the FDA in more than 6 years. This scientific innovation is also one of the first personalized medicines targeting a genetic abnormality shared by only 3 to 5 percent of the 200,000 lung cancer patients

diagnosed in the United States each year. Xalkori was a fast-track product that was given priority review by FDA. The goal was to review in 6 months. FDA reviewed it in 4 months. While Xalkori's approval is an example of getting it right, the challenge we have is making sure that situations like Xalkori are the rule and not the exception. The NME review process enhancements will help achieve that goal. These enhancements embody what we consider to be the foundation of a successful review: communication and transparency.

The improved process will encourage better issue identification and resolution at the fine stages of the review cycle. Further, these enhancements will have a direct impact on the dozens of NMEs at various stages of development in our pipeline. These are potential new treatments and therapeutic areas such as oncology, pain, cardiovascular disease and vaccines.

The ability of Pfizer to do its job depends on the ability of FDA to do its job, and PDUFA provides a framework and resources for that to happen. PDUFA is must-pass legislation. It is must-pass for Pfizer and the biopharmaceutical industry. It is must-pass for FDA, but most importantly, it is must-pass for patients and society as a whole.

Thank you for this opportunity to testify. I look forward to answering any questions you may have and hearing your views.

[The prepared statement of Mr. Germano follows:]

Testimony of Mr. Geno Germano
President and General Manager
Specialty Care and Oncology
Pfizer Inc.
Before the House Energy & Commerce Subcommittee on Health
Reauthorization of the Prescription Drug User Fee Act (PDUFA)
February 1, 2012

Chairman Pitts, Chairman Upton, Ranking Member Pallone, Ranking Member Waxman and members of the Subcommittee, my name is Geno Germano. I am President and General Manager of the Specialty Care and Oncology businesses at Pfizer. Founded in 1849 in New York City, we have grown to become the world's largest biopharmaceutical company, providing treatments for myriad diseases that afflict people around the world.

I appreciate the opportunity to testify on behalf of Pfizer and our 40,000 U.S. based colleagues, to unequivocally support the reauthorization of the Prescription Drug User Fee Act (PDUFA).

Behind the acronym PDUFA is another acronym: R&D. Research and Development. R&D is the lifeblood of Pfizer. It is the lifeblood of our industry. And it is the lifeblood of great American innovation.

Today, it takes on average more than $1 billion and 12-15 years to research and develop a new medicine. Approximately 1-in-10,000 compounds that enter the drug discovery phase is ever approved by the Food and Drug Administration (FDA) and made available to patients.

Our R&D is ultimately codified in our patents. Patents represent our license to move forward and are a fundamental legal basis for our existence.

It is important to remember that we file our patents on compounds in the very early stages of development, often a decade or more before the review process begins at the FDA. Therefore, by the time we have submitted an application to the FDA, the patent life has already eroded to a meaningful extent, making an effective and efficient process with the FDA imperative for the firm investing in this innovation.

Biopharmaceutical companies like Pfizer typically have at most between 11-14 years to recoup our investment in a new compound before generic competition enters the market; however, the public health value of our investment continues for generations to come.

It is through this foundational work in R&D and manufacturing that the biopharmaceutical industry supports more than three million U.S. jobs, nearly $300 billion in total output to GDP. PDUFA will help keep R&D and new medicine introductions in the U.S.

The odds, financial commitment, and significant time and resources reflect the uncertainties inherent in our business. The scientific uncertainties are ultimately reduced to the core question:

Does the benefit of the drug outweigh the risk?

This is a question we and the FDA seek to answer and it will vary depending on the treatment and the intended patient population. Regulatory uncertainties can complicate this dynamic if the review process at the FDA is ambiguous and inefficient. This is why a strong partnership and communication with the FDA are essential.

R&D at Pfizer

Before discussing the provisions of PDUFA, it's important to provide additional background on the R&D process at Pfizer. My business is focused on developing and providing therapies of a specialized nature. This means treatments for rare diseases, for many forms of cancer, and vaccines that help prevent people from getting infectious diseases like pneumonia or meningitis.

As the head of a business, I am intimately engaged in the development of our medicines pipeline. The business and R&D share the goal of investing in the right therapeutic areas. That means making sure the compounds progressing have a reasonable chance of making it through the entire development process and gaining efficient and successful review by the FDA. We also look beyond that to ensure that payers recognize the value of the product.

One of our main focuses at Pfizer is to always improve the performance of our innovative core – the nexus where strong R&D leads to valuable products. Over the past year, there has been a steady cadence of progress in our late stage pipeline that includes positive clinical data presentations, submission of marketing applications, regulatory approvals, and new product launches, as well as the emergence of a promising mix of early to mid-stage assets.

We have a number of products that we're very excited about.

First is Prevnar 13, a vaccine for the prevention of pneumococcal disease which is approved for use in children 6 weeks through 5 years old, and in December of last year, received approval for adults 50 years of age and older. This new approval is very important given that the most common manifestation of the disease in adults is pneumococcal pneumonia, which occurs in about 440,000 Americans 50 and older every year, accounting for about 300,000 hospitalizations and significant related personal and societal costs.

FDA approved Prevnar 13 under the agency's accelerated approval pathway, which allows for earlier approval of certain drug products to treat serious or life-threatening disease which may not be adequately addressed by existing drug products. The approval of the vaccine was based on its effectiveness in relation to a surrogate endpoint that is likely to predict clinical benefit and was granted on the condition that a confirmatory clinical trial be conducted to verify the anticipated clinical benefit. While that confirmatory study is currently underway, today Americans 50 and older have access to an important new option for the prevention of a potentially life-threatening disease.

Second is Xalkori, a New Molecular Entity (NME), which is the first lung cancer drug approved by the FDA in more than six years. This scientific innovation is also one of the first personalized medicines, targeting a genetic abnormality shared by 3% to 5% of the 200,000 lung-cancer patients diagnosed in the U.S. each year.

Xalkori, which was approved last August, was a fast track product and was given priority review by the FDA. The goal for priority review is 6 months - FDA approved it in 4 months. Xalkori and other NME's are the highest priorities for Pfizer and FDA because as new treatments they target unmet medical needs. And while Xalkori's approval is an example of getting it right, the challenge we have is making sure that situations like Xalkori are the rule, not the exception.

Third, we recently received European approval for Vyndaqel (Tafamidis) to treat TTR-FAP, a rare and irreversible, progressive neurodegenerative disease that affects approximately 8,000 patients worldwide. Patients experience debilitating symptoms that usually prove fatal within 10 years, and until now there has been no treatment option other than liver transplant. This product has been submitted to the FDA with a decision expected later this year.

We are also pleased with the results we have seen with tofacitinib in the phase 3 rheumatoid arthritis program and have submitted applications for approval to regulators in both the U.S. and Europe. This represents just some of the near-term opportunities in our growing product pipeline. And while I'm encouraged, I know we have much more work to do.

In 2011, we made a strategic decision to narrow our therapeutic areas of focus, took steps to identify failures earlier in the development cycle, advanced the most promising compounds within our pipeline, and continued to invest in our R&D network and the capabilities needed to drive biomedical innovation.

We are allocating the majority of our R&D efforts to the areas that represent the intersection between unmet medical needs, our strength in biology and chemistry, and the willingness and ability of patients and payors to value our innovation. We are focusing on the areas where we believe we have the right elements for success -- Neuroscience, Cardiovascular, Oncology, Inflammation and Immunology, Vaccines, Pain and Sensory Disorders and Biosimilars.

In addition, in 2011, we established an enhanced focus on rare diseases; an area in which Pfizer has a strong legacy with more than 17 approved orphan indications. Rare diseases are among the most serious of all illnesses and impact greater than 50 million patients in the U.S. and the EU, yet fewer than 5% of the estimated 7,000 rare diseases have approved treatments. We believe that patients suffering from a rare disease deserve equal access to an approved treatment so we are actively expanding development in this space for conditions like sickle cell anemia, hemophilia, cystic fibrosis and muscular dystrophy.

We are prioritizing the R&D portfolio. We are focusing our internal capabilities in the areas where we offer unique value such as clinical trial design and overseeing the end-to-end strategy for our clinical assets. We have turned to external partners to manage the areas that don't drive competitive value for us such as clinical trial implementation. This makes it easier to scale activity up or down based on the needs of the portfolio.

We have made tough but necessary capital allocation decisions regarding our global R&D site network. We are laying the foundation for a new MIT-sponsored research site in Cambridge, MA, that will focus on cardiovascular, metabolic and neuroscience research. By locating in science and technology hubs we have better access to a highly skilled talent base that will enrich our capabilities in the biologic sciences and increase our opportunities for external partnerships.

We have invested in new technologies within our focus areas.

For example, in Oncology we are investing in Antibody-Drug Conjugates (ADC) which combine the best features of two proven cancer therapies – antibodies and cytotoxic drugs.

Through our Centers for Therapeutic Innovation we are partnering with 19 leading academic medical institutions located in Boston, New York, San Francisco and San Diego to tap into the research expertise of academics in diseases, targets and patient populations to help bridge the gap between early scientific discovery and the translation into new medicines.

We are adopting a Precision Medicine approach to research, integrating clinical and molecular information to understand the biological basis of disease. This leads to better selection of disease targets and the identification of patient populations that demonstrate better clinical outcomes.

We expect that in 5 years most of our Phase 3 clinical trial starts will reflect a Precision Medicine R&D approach.

Supporting all our actions is a more rigorous governance model across all of R&D and the Business Units that has clear metrics and a process for establishing that a compound will meet a clear medical need, be valued by payers and patients and have a strong rationale that the product would be approved by regulators prior to starting a proof of concept study. We revalidate the value needs and regulatory rationale at every step of the development path with increased rigor prior to starting our final pivotal Phase 3 trials needed for regulatory submissions and for an approval decision point.

I believe that through all the actions we are taking there is a greater sense of urgency, accountability and results focused across R&D.

All of the work that I described above means nothing without an efficient, well funded FDA that is able to keep pace with the evolving science needed to review drug applications efficiently and effectively.

Why PDUFA Matters to Pfizer

So why does PDUFA matter to Pfizer?

As I mentioned, to develop a single new medicine for patients, Pfizer will invest more than $1 billion and more than ten years identifying new molecules, establishing tolerability, and confirming safety and effectiveness in large numbers of patients. PDUFA is part of the gateway between such R&D and the many patients needing these medicines. The performance metrics and process requirements within PDUFA help ensure that the FDA is efficient, transparent and predictable.

Each of the PDUFA three main focus areas helps enable Pfizer and FDA to improve transparency in the drug approval process. Here is how.

1. Enhancements to the Drug Review Process

New Molecular Entity (NME) Review Program: PDUFA V will increase predictability, transparency, and scientific communication during FDA's review of NME's (drugs containing no active molecules previously approved by the FDA in any other application) for new applications.

Under PDUFA V, the NME review program will help identify and resolve issues earlier in the review process and thereby shorten the time to a review decision – potentially providing patients with earlier access to needed treatment.

Communication during drug development: Interaction between the FDA and drug sponsors during drug development is critical, and this program will help sponsors and the FDA engage more efficiently and productively.

At times, such interactions require a formal meeting; at other times, a response can be provided without a formal meeting. However, obtaining FDA responses to questions outside the formal meeting process has been challenging due to FDA staff workload and competing demands.

The PDUFA V performance goals propose funding an agency communication and training staff that will focus on improving communication between the FDA and drug sponsors during development.

Benefit/risk assessment: When safety issues arise, the confidence of patients and the public may be shaken. Benefit/Risk assessment measures a drug's benefits and risks and then assesses whether the balance of these factors is favorable. This analysis is critical to ensure patient confidence in their medicine.

PDUFA V would facilitate continued development and implementation of a structured benefit-risk framework in the drug evaluation process to increase transparency and objectivity.

E-submission and data standards: Pfizer alone sends about 10,000 submissions a year to the FDA and has been a leader as the industry moves toward digitization, which allows FDA reviewers to have an entire product submission in electronic form. This new proposal will require that all applications be submitted to the FDA in standardized electronic format – bringing still greater efficiency and predictability to the review process. Additionally, the FDA would begin a public process to standardize clinical data terminology for certain therapeutic indications.

2. Modernizing Regulatory Science

Advances in regulatory science will help make the evaluation and approval process more efficient, helping deliver safe and effective new products to patients faster and strengthening the ability to monitor product use and improve performance, thus enhancing patient outcomes.

PDUFA V's enhancements will affect Pfizer in each of the regulatory science provisions:

Meta-analysis: Meta-analysis is the technique of pooling data from different clinical trials on a particular drug. FDA needs the ability to review and respond to meta-analyses, conducted by third parties to determine if they were in fact conducted appropriately. There a number of these analyses conducted on Pfizer products and it is crucial that we and the FDA have an accurate way to interpret the results of them to better inform patients.

PDUFA V addresses this issue by requiring FDA to develop a scientific method to determine how to best use the information from a meta-analysis. Doing so will help give the FDA the tools it needs to provide appropriate guidance on the results of meta-analysis.

Biomarkers & pharmacogenomics: A biomarker is anything that can be measured as an indicator of biological activity, such as a blood pressure count or DNA sequence. Pharmacogenomics is the study of how genes affect a person's response to drugs. Biomarkers and Pharmacogenomics can be predictors of many things, such as the natural course of a tumor, and enable doctors to decide which patients are likely to respond to a given drug and at what dose.

PDUFA V will enhance FDA's ability to address the increasing workload of applications that involve biomarkers and thereby allow innovative new treatments to get to patients sooner.

Patient-reported outcome tools: Many quality-of-life problems go unnoticed as patients don't always tell their doctors how they are feeling. The only real way to get the patient's perspective is to ask the patient directly. However, FDA staff is already overloaded and timely patient-reported outcome reviews are difficult to ensure – sometimes taking months.

PDUFA V would increase FDA's review capacity, ensuring that agency reviewers have access to every tool needed to support claims within a specific drug context.

Rare disease drug development: Pfizer has a strong legacy in rare diseases, with more than 17 approved orphan indications, and is actively expanding its activity in the space.

PDUFA V will continue to ensure that regulatory evaluations of orphan drugs are conducted flexibly to take account of the specific issues facing that particular rare disease. The small number of patients suffering from a given rare disease often makes it difficult to enroll a sufficient number of patients in a clinical trial. The rarity of the condition results in smaller set of data on efficacy and safety compared to more common diseases, and often the evidence will include case histories, registry data and studies from distant countries.

But the standards for safety and efficacy should not be lower, so regulatory agencies need to have evidence and flexible approaches to assessment that take into account the rarity of the condition, the degree of fundamental understanding of the natural history of the disease, the limitations in identification and diagnosis of patients, and the urgency of patient need.

PDUFA V will enhance development of new drugs for rare diseases though FDA policy development and training of review staff on scientific issues unique to rare diseases, and will support outreach to industry, patients, and the scientific investigator communities.

3. Strengthening Post-Market Safety Surveillance

As part of its mission to protect and promote the public health, the FDA has always kept a keen focus on the safety of drugs and other medical products. Once a drug is approved and reaches the marketplace, FDA and drug sponsors maintain a system of post-marketing surveillance and risk assessment programs to identify adverse events that may not have been detected during the drug approval process.

Under PDUFA V, two safety enhancements are being proposed, both of which would affect Pfizer.

The Sentinel Initiative: FDA's Sentinel Initiative would access national electronic data systems to actively monitor medical product safety in real time – a development Pfizer supports as a powerful public health resource that may greatly improve drug safety reporting. FDA's phased approach to Sentinel implementation, emphasizing success over speed, is appropriate.

As Sentinel advances, FDA must ensure it has the financial resources and the IT infrastructure to build a distributed system on such a large scale. Also, Sentinel governance and operating frameworks must ensure timely and effective company access to product safety data and to signal detection and analysis methods – both of which will be critical to maintaining company involvement over product safety and risk management. It is extremely important that Sentinel not be used as a method for comparative effectiveness.

Standardizing risk evaluation and mitigation strategies (REMS): FDA has the authority to require REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks over the longer-term. However, industry has expressed concerns regarding the ability of REMS programs to mitigate risk and the burden REMS places on providers, patients, pharmacists, and the healthcare delivery system.

It is vital that FDA consider REMS' impact on their ability to meet PDUFA review performance metrics and expedite patients' access to safe and effective new medicines. Pfizer supports PDUFA V's goal of improving REMS approval times by providing better clarity during development meetings and holding public meetings on how to reduce the burden of implementing REMS.

Fees

The PDFUA V agreement includes an additional 129 full time equivalents (FTE) to support additional activities at FDA. The additional FTE is dedicated to support the provisions on modernizing regulatory science. We believe the current level of FTE dedicated to the review of applications and to perform post marketing safety activities can be accomplished with existing resources.

User fees to fund drug review activities at FDA are approaching 70% of the total budget. While Pfizer understands the current economic situation, this level of support nonetheless concerns us. It is important Congress and the Administration devote additional government resources to supplement the fees paid by our industry.

Reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research and Equity Act (PREA)

Pfizer strongly supports the reauthorization of BPCA and PREA. They work together by providing biopharmaceutical companies like Pfizer an incentive, six months of additional exclusivity, to study our products in the pediatric populations and ensuring that drugs are appropriately studied and labeled for pediatric populations. While BPCA and PREA are working, Pfizer supports making them both permanent in order to provide us with the certainty that is important in the R&D and regulatory process.

Supply Chain Safety

Pfizer has comprehensive systems and processes in place to manage our global supply chain, starting with the raw materials we use to manufacture our products and ending when consumers receive our products. Our processes help us to prevent, detect, and respond to threats so that we protect the quality and safety of our products and ensure that our patients are receiving the life-saving and sustaining drugs they expect.

Pfizer recognizes that the Committee may be considering supply chain security provisions for inclusion in the PDUFA legislation. A number of proposals addressing upstream and downstream drug supply safety as well as a national track and trace system are being discussed. As we have put in place strong measures to ensure the integrity of our materials and the quality of our suppliers and distributors, we look forward to working with members of Congress who have put forward proposals to address these issues.

Conclusion

PDUFA represents the best kind of collaborative leadership: where government and business come together with rigor and excellence to ensure that patients have timely access to the critical medicines they and their families deserve. The ability of Pfizer to do its job depends on the ability of FDA to do its job, and PDUFA provides a framework and resources for that to happen. PDUFA is must pass legislation. It is must pass for Pfizer and the biopharmaceutical industry. Must pass for FDA. And most importantly it is must pass for patients and society as a whole.

Again, thank you for the opportunity to testify. I look forward to answering any questions you may have and hearing your views.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman, Dr. Gollaher, for 5 minutes for an opening statement.

STATEMENT OF DAVID L. GOLLAHER

Mr. GOLLAHER. Thank you, Chairman Pitts and Ranking Member Pallone. My name is David Gollaher, and I am President and CEO of the California Healthcare Institute. California has by far the largest cluster of innovative research institutions and biotechnology companies in the world. Today there are about 270,000 jobs directly connected to biomedical R&D in California.

My purpose today is first to support the reauthorization of PDUFA, then to explain why PDUFA is critical to drug innovation, and then briefly to review work that CHI, our institute, has been conducting with the Boston Consulting Group, BCG, together and analyzed data that accurately reflect FDA performance.

I know there has been a lot of criticism of the FDA, but all of us agree that a strong, efficient FDA is important to our industry and to patients, an agency that performs well, encourages medical innovation and a regulatory system that has clear rules, that operates transparently, builds confidence among investors, and confidence is key because patients need to be confident that their drugs meet the highest standards of safety and effectiveness while industry needs to be confident that the FDA is abreast of the latest science and is applying it reasonably to innovative products.

The first point I would like to make is about the relationship of advanced science to regulation. We live in an unprecedented age of biological sciences. After the human genome project was completed in 2003, our ability to understand diseases at the level of genes and cells is racing ahead. Still, though, if we compare the past several years to the period during the 1980s and 1990s when there was so many pioneering biotech drugs along with breakthrough drugs for HIV/AIDS, we can see that today drug development has lagged. It hasn't kept up with science.

The reasons for this are complicated. For one thing, our bodies are the most complex organisms in nature, and developing drugs that have powerful effects on disease without harming healthy cells and tissue turns out to be extremely difficult. So difficult, in fact, that developing a new medicine now costs well over a billion dollars.

In trying to become more efficient and reduce development costs, the drug industry is searching for the optimum model for R&D but the most productive model and scale for biotech research remains a quest in progress.

The problem is that we continue to see high failure rates for drugs that enter the regulatory pipeline. Only 5 to 8 percent of new molecular entities that start out as drug candidates make it all the way to the market. Commissioner Hamburg has pointed out that we are investing between industry and academia about $100 billion in research today and not getting our fair share of new medicines. But this isn't true across the board. In 2011, the FDA issued a report citing 35 innovative treatments for hepatitis C, prostate cancer, lupus, pneumonia and other serious disorders. This report showed how the FDA used expedited approval authority, flexible clinical study requirements, and resources collected under PDUFA

to improve the rate of approvals. Oncology, for instance, emerged as a particularly bright spot, and our recent work with BCG found that cancer drugs experience rapid review on the order of 10 to 15 months. But there were other areas—cardiovascular, central nervous system, gastrointestinal—that stretched almost twice as long.

The point is, there are major differences in timelines depending on a drug's therapeutic area, and in our view, this suggests an opportunity, namely, for the FDA to learn from its own best practices and then replicate those practices across the agency. To accomplish this, though, will require more data than we have had in the past but timely, accurate data would prove equally valuable for internal FDA benchmarking and for industry management.

It is hard to overstate the importance of good data. A time-honored principle of management is that what gets measured gets done. Our work with BCG over the past 2 years, mining the agency phone data in order to gain a better understanding of how it operates, suggests a few things to us. First, that we meet regularly together and analyze the best possible data and that there is an opportunity to provide longitudinal data over the next PDUFA cycle so that 5 years from now FDA, industry and Congress can share the understanding of real trends over time. It is ironic that for an agency that regulates more than 20 percent of U.S. GDP and relies increasingly on industry user fees that there has been so little in the way of consistent tracking.

In addition, better data may help the agency, Congress and industry to develop a better understanding of benefits versus risks. Virtually all medicines carry some capacity for harm, and a zero-risk mentality would shut down development of beneficial drugs altogether. But more attention needs to be devoted to how the FDA's policies and operations encourage or discourage investment in different therapeutic areas. In other words, how should we measure risk if the agency's demands for data become so intense that investors avoid that therapeutic area altogether. This is happening today in areas like diabetes and obesity.

I would like to conclude by observing that PDUFA has been a remarkable success. For this legislation to move science forward, it needs to remain highly focused on enabling the agency to promote innovation, on encouraging it to address areas of inefficiency, on balancing its mission to protect public health with the importance of attracting robust private sector investment into new drugs and biologics. Ultimately, public health and economic competitiveness are two sides of the same coin. Without investment, the next generation of breakthroughs will never materialize nor will the jobs to manufacture them. Commissioner Hamburg wrote an op-ed last year calling FDA America's innovation agency. I think this is more an aspiration than a historical fact, but it is an aspiration that we all share, and PDUFA V is an important step toward accomplishing it.

Thank you, and I would be happy to answer any questions.

[The prepared statement of Mr. Gollaher follows:]

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CALIFORNIA HEALTHCARE INSTITUTE

TESTIMONY OF DAVID L. GOLLAHER, PH.D.
PRESIDENT AND CEO, CALIFORNIA HEALTHCARE INSTITUTE
HOUSE COMMITTEE ON ENERGY AND COMMERCE, SUBCOMMITTEE ON HEALTH
HEARING ON "REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS"
FEBRUARY 1, 2012

Chairmen Upton and Pitts, and Ranking Members Waxman and Pallone, my name is David Gollaher and I am the President and CEO of the California Healthcare Institute – CHI. I am honored to testify today on behalf of our organization, which represents some 300 biopharmaceutical and medical technology companies, along with California's leading academic medical centers and private research institutions. FDA's Prescription Drug User Fee Act (PDUFA) program has special importance to California because the biomedical industry is among our state's leading high-tech employers, directly accounting for about 270,000 jobs whose salaries average $76,000 a year. The purpose of my testimony today is to support the reauthorization of PDUFA, to underscore its critical role in drug innovation, and briefly to review a project CHI has been pursuing with the Boston Consulting Group (BCG) to gather and analyze data that accurately reflect FDA performance.

While the FDA has frequently been the target of criticism, I want to emphasize that CHI and our industry are committed to strengthening the partnership with the Agency. A strong, efficient FDA is equally important to industry and to the patients we serve. We believe that positive policy and operational improvements at the FDA, along with constructive legislation, will encourage biopharmaceutical innovation. A predictable and transparent regulatory process is an essential component of our biomedical innovation ecosystem. Since its inception, PDUFA has been a notable success. By working together, Congress, the Agency, industry and other

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stakeholders can maintain the high standards of safety and effectiveness that physicians, patients and their families expect while also enhancing the biomedical sector's ability to attract the capital essential to secure U.S. global leadership in life sciences.

1. EFFICIENT REGULATION IS ESSENTIAL TO REALIZING THE PROMISE OF ADVANCED SCIENCE

In an era of increasing global competition, the United States remains the world leader in basic biological sciences and in translating laboratory breakthroughs into new medicines for patients. Since the mid-twentieth century, America's competitive advantage in biomedical innovation has been driven by federal investment in basic research, principally through the National Institutes of Health (NIH). In the 1970s, NIH funding fueled the discovery of recombinant DNA at the University of California – San Francisco. This made possible genetic engineering and led to the creation of a whole new industry called biotechnology. More recently, in 2003, scientists at the NIH and in the private sector completed the sequencing of the human genome. The Human Genome Project took fourteen years and cost more than one billion dollars. Yet the pace of scientific advance is so rapid that today you can have your personal genome sequenced for about a thousand dollars -- a million-fold drop in price in just nine years. Low-cost human genomics has two implications. First, it enables scientists to correlate genes with diseases, and we are discovering that a great many disorders have a genetic basis. Second, it opens the way to personalized medicine, allowing physicians to determine in advance how various medicines may affect an individual. There is already a genetic test for women with breast cancer, for example, that accurately predicts whether or not a patient will respond to a targeted monoclonal antibody therapy. Only patients who test positive for a specific genetic mutation are treated with the drug.

Our expanding ability to understand diseases at the levels of genes and cells means that there has never been a time in history when the science of human health has

been so promising. Still, after a period during the 1980s and 1990s that saw the introduction of many breakthrough biotechnology drugs, along with remarkable medicines for HIV/AIDS and other infectious diseases, drug development has not kept pace with science. The reasons for this are understandable. The human body is the most complicated organism in nature, and developing drugs that have powerful effects on disease without undue side effects turns out to be extremely difficult. At the same time, faced with drug development costs that average well in excess of a billion dollars, industry is searching for the optimum model for R&D. The most productive organizational model and scale for drug research remains a quest in progress.

Beginning in the early 1980s, much of the work of translating basic scientific inventions into commercial products for patients was the province of biotechnology startups. Here the classic pattern involved a basic research discovery, say, in a university laboratory which the university patented and then licensed the invention to a company funded by venture capital. Hundreds of companies began this way, creating tens of thousands of jobs. But this model began to run into trouble after the dotcom bubble burst in 2000. The global financial crisis beginning in 2008 has further pressured venture capital, sharply reducing the reservoir of funds available for new firms. In addition, volatility in the financial markets stemming from the global contraction and European debt crisis has heightened investors' sensitivity to risk.

Risk is the necessary framework for understanding how the FDA influences drug development. Whether from the viewpoint of venture capitalists or drug company executives, regulation has always weighed as a key risk factor in decisions about capital allocation. In the drug discovery pipeline, Phase I trials are first used to evaluate if a new drug is safe, then Phase II trials are done to assess the drug's efficacy, and finally Phase III trials are performed in a larger population to confirm

the safety and efficacy of the drug. Each consecutive phase includes more people to refine the results obtained in the previous phase. Since the 1990s, the trend has shifted toward a higher and higher failure rate. The odds of drug candidates -- a new molecular entity (NME) – making it all the way through three phases of clinical trials is between five and eight percent.

Since most new drug candidates fail, in a capital-constrained environment, regulatory risk increases exponentially. As Joseph DiMasi at the Tufts Center for the Study of Drug Development observed, "Longer development times increase R&D costs and shorten the period during which drug companies can earn the returns they need to make investments financially viable. . . . longer development times reduce innovation incentives." Significantly, a study by CHI and BCG, *Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry* (February 2011), found that from the time PDUFA was first authorized in 1992 until 2007 there were clear improvements in FDA drug review performance. But comparing submissions for NMEs from 2003-2007 with 2008, there was a 28 percent increase in the number of months to approval (from an average of 14.7 months to 18.9 months). One result of longer review times at the FDA was a new drug lag, with a number of new drugs approved in Europe ahead of the U.S. from 2007-2010.

A slowdown at the FDA was frustrating to industry because it widened that gap between fresh knowledge emerging from the engine of biosciences research (much of it funded by government), on the one hand, and the application of this knowledge to human health, on the other. Meanwhile, the relationship between industry and the Agency was strained by unpredictability, by unexplained regulatory delays, by a lack of clear standards for what clinical data would ultimately be sufficient for product approval, and by a bureaucracy whose communications were inconsistent. It is worth noting that many, if not most, of industry's criticisms focused less on

matters governed by the Agency's statutory authority than on those that were the prerogatives of Agency management.

2. FDA PERFORMANCE DISPARITIES AMONG THERAPEUTIC AREAS

In 2011, there is evidence that the FDA began to address drug approval timelines. In November 2011, for example, the Agency issued a report, *Innovative Drug Approvals,* citing 35 innovative drugs that represented advances in treatment for hepatitis C, late-stage prostate cancer, lupus, drug resistant skin infections, pneumonia, and other serious disorders. This report detailed how the FDA used expedited approval authorities, flexible clinical trial requirements and resources collected under PDUFA to improve the rate of approvals. Earlier, a study from the Friends of Cancer Research noted that for oncology over the past decade, most innovative medicines were approved in the U.S. in advance of the European Union.

This is an important finding, and evidently, among therapeutic areas within the FDA, oncology is a bright spot. But recent analysis of FDA data by BCG suggests a more nuanced picture. The FDA is not a monolith; there are significant deviations in average review times, depending on a product's therapeutic area. Oncology and anti-infective drugs, for example, experience the fastest reviews, on the order of 10-15 months. For other categories – cardiovascular, central nervous system, gastro-intestinal, respiratory, etc. – average review times stretch from 20 to 30 months. As a consequence, a drug's therapeutic area influences both the time it spends under review and the probability of its being approved first in the U.S. or Europe.

It is unclear what explains differences in performance from one therapeutic area to another. Some fields may be inherently more complicated, with fewer biomarkers or with poorly understood mechanisms of action for novel drugs. Alternatively, certain therapeutic areas may be understaffed or may reflect differences in managerial priorities or effectiveness. Oncology, for example, remains a field in which there are

comparatively few effective drugs, while prevalence of cancer and public concern runs high. The same may be said of infectious diseases. Unsurprisingly, the Agency performs comparatively well in both areas.

In some ways, variations in FDA performance in different therapeutic areas suggest an opportunity. That is, the Agency is in a position to learn from its own best practices, and to replicate them across different areas. To accomplish this will require more data than we have had in the past; data that would prove equally useful for internal FDA benchmarking and for industry management.

Ideally, recognizing that the FDA must set priorities and that not all disorders pose equal threats, one would hope for basic alignment between regulation and public health. Yet, to some degree, things have gotten out of balance. Diabetes, obesity, and cardiovascular disease exert enormous, and growing, damage on health. Unfortunately, though, regulatory pathways in these areas are fraught with uncertainty. And the result is that fewer large pharmaceutical manufacturers are developing products for these indications, while venture funding for startups has all but disappeared. Within industry and the venture community alike, the common wisdom is that the Agency has, in these areas, tightened its benefit-risk calculation, demanding more data over longer periods, thus increasing the cost of clinical trials to the breaking point.

There is broad agreement between industry and the FDA about the importance of building a better shared understanding of benefits and risks. Virtually all medicines bear some capacity for harm. A zero-risk approach would shut down the development of beneficial drugs. In this regard, however, the Agency focuses almost exclusively on the *direct* risks of drugs: side effects, adverse events and so forth. These are comparatively discrete and measurable. But *indirect* risks are both difficult to observe and subject to a much longer time horizon. Where are data that

allow one to calculate the harm to public health if investors avoid an important disease because the FDA's demands for data are so extensive and its standards for drug approval so uncertain?

We are encouraged that the Agency has begun to address this challenge. Its report, *Driving Biomedical Innovation: Initiatives to Improve Products for Patients* (October, 2011), acknowledged that despite more than $95 billion invested into biomedical R&D between the NIH and industry, "these investments have not translated into a parallel increase in novel products" (p. 3). As Commissioner Margaret Hamburg's Innovation Initiative starts to unriddle the reasons for this, we hope that a top priority will be a more transparent elaboration of how the Agency manages its benefit-risk calculations, including an appreciation of indirect risk. Indeed we also acknowledge and laud PDUFA V provisions to enhance benefit-risk assessment as well as a concentration on patient-focused drug development.

3. THE IMPORTANCE OF RELIABLE DATA

A time-honored principle of management is that what gets measured gets done. We have learned a great deal in working over the past two years with BCG and the FDA, mining the Agency's data in order to gain a better understanding of how it operates, and how its performance metrics have changed over time. So we believe that there is great value in (a) regularly gathering and analyzing the best possible data; (b) updating performance metrics during the next PDUFA cycle in order to track performance consistently and longitudinally; and (c) ensuring that there is agreement among the FDA, industry, and congress that the data and how they are reported are the most accurate possible measures of agency performance. It seems ironic that for an agency that regulates more than 20 percent of American production, and depends increasingly on industry user fees, there has been so little in the way of consistent tracking mechanisms. In this vein, we believe all would

benefit from more granular information from the division review level in order to understand where things are working and where they need improvement.

4. CONCLUSION

PDUFA V represents the next step in a successful, ongoing partnership between the FDA and industry. It is important for the legislation to remain highly focused: to support the Agency in its efforts to promote biomedical innovation; to encourage it to address areas of inefficiency; to balance its imperative to protect public safety with the importance of continuing robust private-sector investment into new drugs and biologics. In the long view, public health and the economic health and competitiveness of the biomedical industry are two sides of the same coin. Without immense investment, the next generation of breakthroughs for our greatest healthcare needs will never materialize. Nor will the jobs to produce them. Commissioner Hamburg has called the FDA "America's Innovation Agency" (*Wall Street Journal*, August 1, 2011), which might be considered more an aspiration than historical fact. But it is an aspiration we share, and believe that PDUFA V will be an important step in accomplishing it.

Thank you again for the opportunity to testify. And I would now be pleased to answer any questions you may have.

Mr. PITTS. The chair thanks the gentleman and recognizes Mr. Pops for 5 minutes for an opening statement.

STATEMENT OF RICHARD F. POPS

Mr. POPS. Thank you, Chairman Pitts and Ranking Member Pallone. I appreciate the opportunity to be here today. I am Richard Pops, Chairman and CEO of Alkermes, and I am here testifying on behalf of the Biotechnology Industry Organization, or BIO. I coordinated BIO's engagement on the PDUFA V discussions with FDA, and I have got more than 20 years of experience in managing biotechnology companies and successfully developing new therapies for patients. So I know firsthand the impact that PDUFA has had on patients and on medical innovation.

BIO, in summary, supports a swift enactment of PDUFA V recommendations that improve this regulatory process and provide patients and doctors with earlier access to breakthrough therapies that we focus our lives on developing. So at Alkermes, our company, we are in a very exciting phase of growth with a diversified portfolio of commercial products that have already made it through the FDA process, so we have had that experience, but also new medications in development where we are in the midst of the regulatory process addressing central nervous system disorders such as addiction, schizophrenia and depression.

We began as a raw startup in labs next to MIT up in Massachusetts, and today we employ over 1,200 individuals in Massachusetts, Georgia, Ohio and worldwide, and we operate large manufacturing facilities in both Ohio and in Georgia as well.

The key to our success and I think the success of the industry in general is a reliable and predictable FDA, and the PDUFA program is an incredibly important part of that.

The PDUFA V recommendations are based on the principles that a science-based transparent and well-managed review process that appropriately balances benefit and risk can enhance the public trust and increase patient access to new medicines. Industry and FDA agreed upon a set of enhancements under PDUFA V designed to reinforce FDA's review performance and get back to basics for patients. These proposals have also been informed by an unprecedented level of public input, which has further strengthened the technical agreement. These enhancement include a new molecular entity, or NME, review program that we hope will lead to further review cycles and earlier patient access to needed treatments, enhanced communication during drug development, regulatory science modernization and robust safety and postmarket surveillance capacities.

While BIO, of course, supports the entirety of the technology agreement, today I would like to focus primarily on the enhanced communication in PDUFA V. This initiative is based on the philosophy that timely interactive communication with biotechnology and life science companies during drug Venezuela should be a core agency activity. While many biotechnology companies operate on the cutting edge of biomedical science and develop new therapies, science is a collaborative process. It doesn't occur in a vacuum. And it is critical to promote interactive scientist-to-scientist communications between FDA and sponsors.

In the course of drug development, we often have simple clarifying questions, the responses of which could have a significant impact on the development program but are not extensive enough to warrant formal meetings with FDA. To obtain timely responses to such questions, we currently often have to engage in lengthy exchange of multiple formal letters with FDA, which is an inefficient and cumbersome use of both FDA's and sponsors' time. For small biotechnology companies reliant on limited venture capital funding sources, these delays can create significant impediments to development programs and therefore innovation.

So as part of the enhanced communication program, FDA will establish best practices for this type of interactive dialog and train staff on communication. Independent reports commissioned by FDA have demonstrated that enhanced communication during drug development ultimately results in higher quality applications which can improve efficiency for FDA reviewers. This proposal was a top BIO priority and we are pleased that it was included in the agreement.

In addition to the enhanced communication features, the PDUFA V agreement makes new resources available to modernize regulatory science in the areas of personalized medicine and rare disease drug research. Modern approaches to drug development and evaluation will introduce new efficiencies in the drug development process and provide FDA with additional tools to evaluate the benefits and the risks of pharmaceutical products. These proposals will also integrate more structured and systematic approaches to addressing benefits and risks and allow FDA to conduct outreach to patients and hold workshops to better understand patient perspectives on disease severity and unmet medical need.

BIO looks forward to working with the committee and the FDA to implement PDUFA V, and I want to thank you again for having us here today.

[The prepared statement of Mr. Pops follows:]

TESTIMONY OF RICHARD F. POPS
CHAIRMAN AND CHIEF EXECUTIVE OFFICER, ALKERMES.
HOUSE COMMITTEE ON ENERGY & COMMERCE, SUBCOMMITTEE ON HEALTH
HEARING ON "REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS"

FEBRUARY 1, 2012

Chairmen Upton and Pitts, and Ranking Members Waxman and Pallone, it is my privilege to provide testimony before this Subcommittee today. My name is Richard Pops and I am Chairman and CEO of Alkermes. I am here testifying on behalf of the Biotechnology Industry Organization where I serve on BIO's Health Section Governing Board and coordinated BIO's strategic engagement in the Prescription Drug User Fee Act (PDUFA V) technical discussions with FDA. BIO represents over 1,100 members involved in the research and development of innovative healthcare, agricultural, industrial, and environmental technologies. As an entrepreneur with more than twenty years experience managing biotechnology companies and successfully developing novel therapies for patients, I would like to speak to the positive impact that the PDUFA program has had on patients and medical innovation, and highlight the challenges we seek to address under PDUFA V.

In short, BIO supports quick enactment of the PDUFA V recommendations as we believe they can enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance. Most importantly, from the standpoint of young, innovative companies, our hope is that PDUFA V will provide patients and doctors with earlier access to breakthrough therapies.

I. BIOMEDICAL INNOVATION REQUIRES A RELIABLE, PREDICTABLE, SCIENCE-BASED REGULATORY ENVIRONMENT

At Alkermes, we have a steadfast commitment to develop innovative medicines based on our imaginative science and proven technologies. We are inspired by real patient needs as we develop products to help patients and physicians better manage diseases. We are in an exciting phase of growth, with our diversified portfolio of commercial products that address central nervous system (CNS) disorders such as addiction, schizophrenia and depression, and an exciting late-stage pipeline. We began as a raw start up in rented labs next to MIT, and today Alkermes employs 1,200 individuals in Massachusetts, Georgia, Ohio and world-wide.

The U.S. biotechnology industry is poised to be a major driver in an innovation-driven economy. Biotechnology offers real solutions to our most pressing health care needs: curing disease, reducing costs, increasing quality, and ensuring that people enjoy not only longer lives, but better and more productive lives. A key to Alkermes' success and the future of the U.S. biotechnology industry is a reliable, predictable, and science-based regulatory environment, and the PDUFA program represents an important element of our nation's overall innovation eco-system. A fundamental part of biotechnology companies' ability to innovate and raise private investment is having an FDA with the resources and infrastructure required to review and approve innovative products effectively, consistently, and in a timely manner based on the best available science. Since 1992 Congress, FDA, and the biopharmaceutical industry have supported a carefully structured user fee program to help fund FDA's human drug review activities. This program has contributed to the approval of more than 1,200 new medicines and, initially, reduced review times for the newest, most innovative drugs by more than a year. In the past year alone, biopharmaceutical companies have successfully brought to market remarkable therapies to treat

hepatitis C, melanoma, lung cancer, lupus, and rare genetic disorders. Last week, after a decade of development, FDA approved an exciting new diabetes drug, which only needs to be administered once a week, developed by us and our partners. These advancements in patient care represent the leading edge of the next generation of biotechnology innovations.

But the pace of biotech innovation—and, more specifically, the pace at which new pharmaceutical treatments reach patients who need them—is not keeping up with our nation's healthcare needs. Developing innovative treatments and cures is a time- and capital-intensive endeavor, and the average time between treatment discovery and availability to sick and suffering patients is between 10 to 15 years. That is much too long. Additionally, new scientific and regulatory complexities in the FDA's drug review process have stressed our ability to speed safe and effective new treatments to patients. Unpredictability and inconsistency in the review process, suboptimal communication with sponsors, and decreased FDA performance not only hinders patient access to new treatments, but also negatively affects the ability of biotechnology companies to raise funding to support clinical development and ongoing innovation. This undermines economic growth in the biotechnology sector as well as biomedical research into key public health priorities.

II. PDUFA V: GETTING BACK TO BASICS FOR PATIENTS

Just as we have witnessed a revolution in genomics and our understanding of the molecular and biological basis of disease, we also must pursue new regulatory paradigms and modern approaches to how we assess the safety and effectiveness of novel therapies. When we began the process of organizing for our discussions of PDUFA V, we in the industry started with a simple

set of principles that could provide the foundation for our discussions with FDA and other stakeholders. These were that a *science-based*, *transparent*, and *well-managed* review process that appropriately *balances benefits and risks* can enhance public trust and increase patient access to new medicines.

With these principles in mind, industry and FDA agreed upon a set of enhancements under PDUFA V that seek to reinforce FDA's review performance and get back-to-basics for patients. These proposals also have been informed by an unprecedented level of public input through workshops, meetings, and stakeholder outreach, which further strengthened the technical agreement. These enhancements include:

- **New Molecular Entity (NME) Review Program:** Historically, nearly 80% of all NME applications submitted to FDA are ultimately approved, but fewer than half are approved on the first submission.[i] Sponsors and FDA can and must do better for patients. By strengthening scientific dialogue and transparency between FDA and Sponsors under the proposed review program for novel drugs and biologics, we can minimize the potential review issues that can delay patient access to needed treatments. Increased FDA-Sponsor scientific dialogue and transparency, such as a mid-cycle communication, exchange of discipline review letters and advisory committee information, and a significant new late-cycle meeting, will help to identify and resolve issues earlier in the review. This represents a significant paradigm shift in FDA's review process while maintaining FDA's high standards for safety and efficacy. An additional two-month validation period during the review period will help to ensure FDA has all the information it needs at the

beginning of the process to perform a complete review. Finally, a robust third-party evaluation will provide data on whether we have been successful in this program of leading to fewer review cycles, shorter approval times, and earlier patient access to needed treatment.

- **Enhanced Communication during Drug Development**: To help advance American innovation and promote the development of the next generation of modern medicines, FDA has also committed to a philosophy under PDUFA V that timely, interactive communication with biotechnology and life science companies during drug development is a core Agency activity.

FDA's recent report on driving biomedical innovation highlights that "the private sector is the engine of innovation, and much of this innovation begins with small business."[ii] Indeed, many small biotechnology companies operate on the cutting edge of biomedical science to develop new therapies for devastating diseases. Yet we must acknowledge that the scientific method does not operate in a vacuum, and it is critical to promote interactive, scientist-to-scientist communication between FDA and Sponsors. In the course of drug development, Sponsors sometimes have simple or clarifying questions, the responses to which could have a significant impact on the development program, but which are not extensive enough to warrant formal meetings. To obtain timely responses to such questions, Sponsors currently often have to engage in a lengthy exchange of multiple formal letters with FDA, which is an inefficient and cumbersome use of both FDA's and the Sponsor's time. For small biotechnology companies reliant on limited

venture capital, these delays can create significant impediments to development programs.

Additionally, independent reports commissioned by FDA have also demonstrated that enhanced communication during drug development ultimately results in higher quality applications, which can improve efficiency for FDA reviewers.[iii]

BIO fully supports the PDUFA V proposal to promote innovation through enhanced communication between FDA and Sponsors during drug development, which will establish best practices for this type of interactive dialogue, train staff on communication practices, and provide the Agency with additional staff capacity to respond to sponsor inquiries in a timely manner.

- **Modernizing Regulatory Science:** Additionally, the PDUFA V agreement makes new resources available to modernize regulatory science, for example, in the areas of personalized medicine and rare disease drug research. Modern approaches to drug development and evaluation, such as through the application of new tools for rare disease drug development, flexibility with regard to creative study designs and new endpoints, greater utilization of biomarkers and patient reported outcome tools will introduce new efficiencies in the drug development enterprise and provide FDA with additional tools to evaluate the benefits and risks of pharmaceutical products. These proposals will also integrate more structured and systematic approaches to assessing benefits and risks of

therapies, and allow FDA to conduct outreach to patients and hold workshops to understand better patient perspectives on disease severity and unmet medical need.

- **Robust Drug Safety and Post-Market Surveillance Capacity:** PDUFA V continues industry's commitment to a lifecycle approach to product evaluation by strengthening FDA's post-market surveillance and benefit/risk management capacity. Earlier discussion of risk management strategies, standardized approaches to REMS, and further validation of the Sentinel Network will promote patient confidence in drug and biologics.

Under the PDUFA V agreement, industry has reinforced its commitment to a well-funded drug and biologics program that supports sound, science-based regulation consistent with FDA's public health mission. However, user fees are intended to support limited FDA activities around the drug review process and were never intended to supplant a sound base of appropriations. User fees currently account for nearly two-thirds of the cost of human drug review. We urge Congress to support FDA's mission and fund the Agency at the Administration's FY12 requested levels.

Additionally, it is critical for PDUFA to be reauthorized well in advance of PDUFA IV's expiration in September 2012, to avoid a reduction in force at the FDA. Even the threat of a downsizing at the FDA would be devastating to the Agency's public health mission and its ability to review new drugs and biologics.

BIO looks forward to working with Congress and FDA to fully implement these enhancements under PDUFA V.

III. PEDIATRIC DRUG DEVELOPMENT

The Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) have been remarkably successful in ensuring that the medications used in children are tested and labeled appropriately for their use. BPCA and PREA have generated a wealth of pediatric drug information for physicians and parents, contributing to improved health outcomes for pediatric patients. Working in tandem, BPCA and PREA have resulted in nearly 425 pediatric labeling changes since 1998, according to the FDA. Congress should recognize the success of these programs and:

1. Reauthorize the existing framework and incentive for ongoing pediatric research, and
2. Make the programs permanent by eliminating their sunset provisions.

The five year sunset periods for BPCA and PREA result in an uncertain regulatory environment for pediatric drug development. Since the average pediatric clinical research program spans 6 years, most clinical programs will span two reauthorization periods in which the ground-rules for pediatric research are subject to change. This uncertainty makes it difficult for companies to invest in infrastructure to support development of products for children, and practically impossible for the FDA to issue guidance to promote understanding of the current regulatory framework.

Since their enactment, BPCA and PREA, working together, have been widely acknowledged as effective in promoting pediatric drug research. There is no logical reason to continue to allow such important legislation to sunset, as the ambiguity associated with this situation has the potential for limiting or endangering the pediatric research infrastructure that companies have been endeavoring to build and expand.

IV. REFORM OF ADVISORY COMMITTEE CONFLICT OF INTEREST POLICIES

As a pre-eminent science-based regulatory agency, it is critical that FDA have access to the most knowledgeable and most qualified scientific minds to help inform key public health decisions and evaluate the safety and effectiveness of innovative new cures and treatments for patients. BIO thanks Representative Burgess for his work on this issue and for introducing legislation that will enhance FDA's ability to empanel highly-qualified external scientific advisors, while maintaining the highest levels of integrity for these proceedings.

In recent years, arbitrary limits and unnecessarily restrictive interpretations of conflict of interest rules have created barriers that have prevented FDA from consistently recruiting highly qualified scientific advisors. Consequently, advisory committee vacancies are at an all-time high, the quality of the scientific discourse on such panels has suffered, and FDA has at times had to rely on scientific advice from panel members lacking relevant expertise, particularly with respect to rare diseases and cutting-edge technologies where the pool of available experts can be quite small.

BIO believes that FDA should have greater flexibility and discretion to select the most appropriate advisors, consistent with the rules that apply to other federal agencies. Such changes will help to ensure that FDA decisions are informed by the best available scientific experts and in the best interest of patients.

V. FDA MISSION STATEMENT

FDA's mission, as amended by the Food and Drug Administration Modernization Act of 1997 and set forth in section 903 of the Federal Food, Drug, and Cosmetic Act (FFDCA), is to promote and protect the public health. However, the FDA mission statement does not reflect the Agency's critical role in incorporating modern scientific advances into review practices to ensure that innovative treatments and therapies are made available to the patients who need them.

The pathway for such long-sought health technology advances as personalized medicine, health applications of nanotechnology, and other cutting-edge developments to reach patients and to improve healthcare in the United States goes through FDA. The Agency has a critical role in facilitating healthcare innovation, but this fact is not formally and forcefully recognized in FDA's legislative mandate. BIO applauds Congressman Mike Rogers for introducing legislation and advancing a dialogue on updating the FDA's mission for the 21st century.

VI. SUPPLY CHAIN INTEGRITY & ADOPTION OF A NATIONAL PHARMACEUTICAL TRACEABILTY SYSTEM

Due to the nature of the United States' closed and highly regulated pharmaceutical supply chain, American patients have high confidence in the integrity of the drugs and biologics they are prescribed. BIO member companies believe the quality and safety of their products is their responsibility to the patients they serve, and is their first priority. BIO supports the initiatives that FDA has already implemented to expand the Agency's global presence through foreign offices; expand the foreign inspectorate and part of a risk-based inspectional strategy; and modernize registration and facility tracking systems and information technology infrastructure.

This Committee has also been examining granting the Agency several new regulatory authorities to further secure the supply chain and BIO looks forward to working with the Committee to further strengthen FDA's import programs and oversight. BIO is supportive of well crafted proposals to increase penalties for criminal counterfeiters and adulterers, provide FDA with authority to detain or destroy known counterfeits at our ports, modernize FDA's facility registration and tracking systems, and better leverage the resources of established international regulatory authorities through joint inspections.

In addition to enhancing oversight over the "upstream" supply chain for pharmaceutical ingredients, it is critical to make enhancements to the "downstream" domestic supply chain for finished pharmaceutical products. BIO supports the establishment of strong, uniform, national standards for serialization and tracing systems, rather than relying on the emerging patchwork of individual state mandates. In this case, BIO believes that the Congress should enact laws governing drug product serialization and traceability systems that regulators can leverage to hold supply chain members accountable for ensuring that legitimate product reaches the patient. A national system using existing and proven technologies would best protect supply chain integrity and patient safety.

Specifically, this approach would standardize efforts nationwide and provide immediate measures to increase supply chain security. Such an approach would enable the identification and adoption of a consensus and technology neutral standard for a traceability system achieved through a progressive process where each system advancement is predicated upon clearly defined triggers and benefits analysis. Such a system should be sufficiently flexible to allow the

end-state to reflect the realization of the project's goal—facilitating the identification of and preventing the introduction of counterfeit, diverted, substandard, adulterated, misbranded or expired drugs from the supply chain and improving the efficiency and effectiveness of recalls.

VII. CONCLUSION

Thank you for the opportunity to offer BIO's support for the PDUFA V recommendations. We believe that these are common sense recommendations that will help advance innovative new cures for patients. We call on Congress to fully support FDA's appropriated budget and to pass PDUFA V as expeditiously as possible. I would be pleased to answer any questions from the committee.

REFERENCES

[i] FY10 PDUFA Performance Report, p.4, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf

[ii] FDA, *Driving Biomedical Innovation: Initiatives for Improving Products for Patients*, October 2011, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM274464.pdf

[iii] Booz Allen Hamilton, *Independent Evaluation of FDA's First Cycle Review Performance — Final Report* July 2008, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127117.htm

Mr. PITTS. The chair thanks the gentleman and recognizes Dr. Wheadon for 5 minutes for an opening statement.

STATEMENT OF DAVID E. WHEADON

Mr. WHEADON. Thank you. Chairman Pitts Ranking Member Pallone and members of the subcommittee, good afternoon. I am David Wheadon, Senior Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, better known as PhRMA. PhRMA appreciates this opportunity to testify today and share our views on the fifth reauthorization of the Prescription Drug User Fee Act, PDUFA, and the reauthorization of the Best Pharmaceuticals for Children Act, BPCA, and the Pediatric Research Equity Act, PREA.

PhRMA and its member companies, the country's leading pharmaceutical research and biotechnology companies, strongly support the original goals of PDUFA, namely to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the agency's regulatory oversight. PDUFA has advanced public health by accelerating the availability of innovative medicines to patients while helping to ensure patient safety.

Furthermore, PDUFA has helped to improve America's competitiveness around the world. Since the passage of the original Prescription Drug User Fee Act in 1992, the United States has become the world leader in bringing new medicines to patients first. Ensuring that the United States maintains a policy and regulatory environment that encourages an efficient, consistent and predictable drug review process is key to keeping America competitive in today's global economy.

PhRMA strongly endorses the recommendation of PDUFA V performance goals letter, which was created with unprecedented transparency and input from diverse stakeholders. This agreement will provide FDA with the resources and the tools required to further enhance the timeliness, completeness and efficiency of the drug review process including provisions to advance regulatory science and modernize drug development, to improve benefit-risk decision making, and to further strengthen FDA's focus on patient safety.

I would like to focus for a moment on one specific provision in the PDUFA V agreement. PDUFA V will improve the review process for new molecular entity, NME, drug and biologic applications which will be particularly significant for patients because NMEs are novel compounds that have the potential to address unmet medical needs and advance patient care. Specifically, it is anticipated that earlier and more comprehensive communication between the agency and drug sponsors as required in this enhanced review program will improve the rate of on-time first-cycle successes. The success of the new review program and of the agency's ability to achieve its drug review goals will be independently assessed and reported in 2015 and 2017. PDUFA V will continue to provide FDA with the resources and tools that are essential to support patient safety and promote medical innovation through enhanced timeliness, completeness and efficiency of the drug review process.

PhRMA encourages Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA V performance goals and to minimize the inclusion of additional provisions that may have the unintended consequence of distracting from the act's original intent.

The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients. According to the FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative. Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care in the face of rising research costs. Since their initial enactment and subsequent reauthorizations, BPCA and PREA have been subject to a sunset clause under which their provisions expire after 5 years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children, Congress should permanently reauthorize BPCA and PREA.

In closing, I would like to use this opportunity to briefly discuss the issue of pharmaceutical supply chain integrity. PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk. We support providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risk they present and believe relying on set criteria such as compliance history, time since last inspection, and volume of type of products produced will enhance the FDA's ability to target its inspection resources efficiently and effectively. A more detailed description of additional recommendations on how to strengthen the integrity of the supply chain can be found in PhRMA's written testimony. We look forward to continuing to work with this committee, FDA and other stakeholders on these important issues.

Chairman Pitts and members of the subcommittee, thank you for the opportunity to testify. I am happy to answer any questions.

[The prepared statement of Mr. Wheadon follows:]

"Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients"

David E. Wheadon, M.D.
Senior Vice President, Scientific and Regulatory Affairs
Pharmaceutical Research and Manufacturers of America (PhRMA)
Summary of Testimony

- **The Prescription Drug User Fee Act (PDUFA).** PDUFA has been a great success for patients since its initial passage in 1992. The PDUFA user fee program has provided FDA with the additional staffing and resources it needed to significantly reduce the timeframe for the review of new medicines, while protecting public health by assuring the safety of these products.
- The PDUFA-V performance goals letter is the result of extensive negotiations between the FDA and the innovative biopharmaceutical industry. FDA's process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.
- A number of important new commitments are detailed in the PDUFA-V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, to advance regulatory science and to modernize drug development, to improve benefit/risk decision-making, and to further strengthen FDA's focus on patient safety. PhRMA strongly endorses the recommendations of the PDUFA-V performance goals letter.
- Since the passage of PDUFA-I in 1992, the U.S. has become the word leader in bringing new medicines to patients first and PDUFA has helped to improve America's competitiveness around the world. The reauthorization of PDUFA is an important factor in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth.
- Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the FDA and impede patients' access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.
- **Advancing Pediatric Drug Development.** The Best Pharmaceuticals for Children Act (BPCA). BPCA was established in 1997 as part of FDAMA to provide incentives to encourage manufacturers to conduct pediatric studies of medicines with the potential for use in children. The legislation grants pharmaceutical companies an additional six-month period of pediatric exclusivity upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.
- The Pediatric Research and Equity Act (PREA) gave FDA the authority to require manufacturers to conduct pediatric studies for certain new drugs and biologics approved for use in adults where the indication for use in children would be comparable to that for adults and to produce formulations appropriate for children, *e.g.* liquid or chewable tablets.
- BPCA and PREA have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients.
- Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care. Since their initial enactment and subsequent reauthorizations, BPCA and PREA have been subject to a "sunset clause" under which their provisions expire after five years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children, Congress should permanently reauthorize BPCA and PREA.
- **Supply Chain Security.** The U.S. ensures drug safety in part by maintaining a closed system for the distribution of prescription medicines. Supply chain security is the responsibility of all parties involved in the distribution of medicines to patients in the U.S.
- PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk by providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risks they present.

Statement PhRMA

TESTIMONY OF DAVID E. WHEADON, M.D.
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HEARING ON "REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS, INNOVATION, AND PATIENTS"
FEBRUARY 1, 2012

Chairman Pitts, Ranking Member Pallone, Members of the Subcommittee, good afternoon. I am David Wheadon, Senior Vice President, Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA appreciates the opportunity to testify today and share our views on the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) and the reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

Reauthorization of the Prescription Drug User Fee Act (PDUFA-V)

PDUFA has been a great success for patients – the tens of millions of Americans who rely on innovative drugs and biologics to treat disease and to extend and improve the quality of their lives. The PDUFA user fee program has provided the U.S. Food and Drug Administration (FDA) with additional staffing and resources needed to significantly reduce the timeframe for review of new medicines, while protecting public health by assuring the safety of these products. Furthermore, PDUFA has helped to improve America's competitiveness around the world. Since the passage of the original PDUFA in 1992, the U.S. has become the word leader in bringing new medicines to patients first.

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The PDUFA-V performance goals letter is the result of extensive negotiations between the FDA and the innovative biopharmaceutical industry and is intended to improve FDA's ability to conduct thorough and efficient reviews of new medicines for patients. FDA's process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.

PhRMA and its members, the country's leading pharmaceutical research and biotechnology companies, strongly support the original goals of PDUFA, namely to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

PhRMA strongly endorses the recommendations of the PDUFA-V performance goals letter. This agreement will provide FDA with the resources and tools required to further enhance the timeliness, completeness and efficiency of the drug review process.

The Role of PDUFA in Encouraging Innovation and Economic Growth

Ensuring that the U.S. maintains a policy and regulatory environment that encourages an efficient, consistent and predictable drug review process is key to keeping America competitive in today's global economy. A 2011 report by *Battelle*[1] found that the U.S. biopharmaceutical industry "is well recognized as a dynamic and innovative business sector generating high quality jobs and powering economic output and exports for the U.S. economy." According to the report, nationwide the sector supported a total of four million jobs in 2009, including 674,192 direct

[1] Battelle Technology Partnership Practice, The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation, July 2011, Battelle Memorial Institute, Prepared for the Pharmaceutical Research and Manufacturers of America.

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jobs. The total economic output from the sector's direct, indirect and induced impacts was $918 billion. Because PDUFA has injected greater consistency, transparency and predictability into the FDA's drug review process, its reauthorization is an important factor in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth. Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the Agency and impede patients' access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.

There are a number of important new commitments in the carefully negotiated PDUFA-V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, to advance regulatory science and to modernize drug development, to improve benefit/risk decision-making, and to further strengthen FDA's focus on patient safety.

Below I will discuss these significant enhancements contained in the PDUFA-V performance goals letter.

Enhanced NME Review Program

PDUFA-V will improve the review process for new molecular entity (NME) drug and biologic applications which will be particularly significant for patients, because NMEs are novel compounds that have the potential to address unmet medical needs and advance patient care. The enhanced NME review model addresses the increasing complexity of reviewing new drug applications (NDAs) and biologic license applications (BLAs), and provides for increased communication between FDA and drug sponsors prior to and during the drug review process. A

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validation period will help FDA plan activities such as inspections and advisory committee meetings, and will accommodate iterative interactions between sponsors and the Agency. As a result, the NME review program is expected to improve the efficiency of the review process and reduce the overall time until new medicines become available to patients. Specifically, it is anticipated that earlier and more comprehensive communication between the Agency and drug sponsors will improve the rate of "on-time, first-cycle" successes – the number of new medicines that are fully reviewed and for which definitive regulatory action is taken within the target timeframe following initial submission. The success of the new review program and of the Agency's ability to achieve its drug review goals will be independently assessed and publicly reported in 2015 and 2017.

Advancements in Regulatory Science

Several new provisions in the PDUFA-V performance goals letter will afford FDA with appropriate staffing and resources to develop, through public input, new tools and methods to integrate emerging scientific data and techniques into the drug development and review process. These advancements in regulatory science will rely on engagement with industry, academia and other stakeholders to identify best practices so the Agency can provide appropriate guidance to stakeholders involved in drug development.

Provisions to enhance FDA's regulatory review capabilities include:

- The use of pharmacogenomics and biomarkers to decrease drug development time by helping demonstrate therapeutic benefits more rapidly, and identifying patients who are likely to benefit from treatment, as well as those at increased risk for serious adverse events;

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- Avenues for accelerating drug development for rare and orphan diseases and provide FDA with the necessary regulatory flexibility to encourage and advance research into novel treatments for patients with significant unmet needs today;
- Standards for and validation of patient-reported outcomes and other assessment tools that may assist regulators in evaluating treatment benefits and potential risks from the patient's point of view; and
- The evaluation of the use of meta-analyses in regulatory review and decision-making, highlighting best practice and potential limitations.

Systematic Approach to Benefit-Risk Assessment

A key provision in the PDUFA-V performance goals letter recognizes that the drug review process could be improved by a more systematic and consistent approach to benefit-risk assessment that fairly considers disease severity and unmet medical needs. During PDUFA-V, the Agency will implement a structured benefit-risk framework, and hold public meetings to assess the application of such frameworks in the regulatory environment. In addition, over the course of PDUFA-V the Agency will hold a series of public meetings with the patient advocacy community to identify disease states that – from the patient perspective – have considerable unmet needs. Development and implementation of a patient-focused, structured framework for evaluating benefits and risks of new treatments will help inform the drug development process as well as ensure that regulatory decisions are consistent, appropriately balanced and based on best science.

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Modernizing the U.S. Drug Safety System

Finally, further enhancement and modernization of the FDA drug safety system under PDUFA-V will ensure that patient safety remains paramount. The PDUFA-V performance goals letter provides for a public process to help standardize risk evaluation and mitigation strategies (REMS), with the intent to assess and reduce burden on healthcare providers and patients. Additionally, FDA will continue to evaluate the feasibility of using the Agency's Sentinel Initiative to actively evaluate post-marketing drug safety issues.

PDUFA has advanced public health by accelerating the availability of innovative medicines to patients while helping to ensure patient safety. The PDUFA program has strengthened the scientific basis of FDA's regulatory review process through the development and application of new tools, standards and approaches that facilitate assessment of the safety and efficacy of innovative drugs and biologics. PDUFA-V will continue to provide FDA with the resources and tools that are essential to support patient safety and promote medical innovation through enhanced timeliness, completeness and efficiency of the drug review process. PhRMA encourages Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA-V performance goals and to minimize the inclusion of additional provisions that may have the unintended consequence of distracting from the Act's original intent - to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

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Reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research and Equity Act (PREA)

Prior to passage of the pediatric exclusivity provisions in the Food and Drug Modernization Act (FDAMA) of 1997, there were significant disincentives for biopharmaceutical companies to conduct clinical trials for pediatric use - generally speaking, in patients under the age of 18 - for medicines developed primarily for adults. At the same time, there were concerns that many FDA-approved drugs had not been clinically tested in children. For example, at that time about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.[2]

Growing recognition of the need for pediatric-specific information prompted action by Congress and the FDA. Congress responded by establishing BPCA to provide incentives to encourage manufacturers to conduct pediatric studies of medicines with the potential for use in children as part of FDAMA. The legislation included a provision that granted pharmaceutical companies an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.
In addition to BPCA, PREA gave FDA the authority to require manufacturers to conduct pediatric studies for certain new drugs and biologics approved for use in adults where the indication for use in children would be comparable to that for adults and produce formulations appropriate for children, *e.g.* liquid or chewable tablets.

[2] U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

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Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in BPCA and PREA in 2002, and again in 2007 as part of the Food and Drug Administration Amendments Act (FDAAA). Similarly, there are provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if the sponsor submits pediatric studies in accordance with a written request from FDA. BPCA and PREA both sunset on September 30, 2012, unless reauthorized or made permanent.

BPCA and PREA have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients. According to the FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.[3] As of 2008, an estimated 50 to 60 percent of prescription drugs used to treat children have been studied in some part of the pediatric population.[4] Since 1998, BPCA and PREA have resulted in 426 pediatric labeling changes,[5] and a GAO report released in May 2011 states that pediatric studies conducted in the past five years represent 16 different therapeutic areas including oncology, endocrinology, hematology, cardiovascular disease, infectious disease and neurology.

A recent issue of *NIH MedlinePlus* magazine notes the importance of pediatric clinical trials and cites several examples of how clinical trial knowledge has improved the lives of children. The

[3] Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.
[4] FDA, "Giving Medication to Children: Q&A With Dianne Murphy, MD," June 2009.
[5] FDA, http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf

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article states that, among other examples of great progress in innovative pediatric drug development, "as a result of repeated clinical trials in children with cancer, most children who develop leukemia survive" compared to 50 years ago when "acute leukemia was almost universally fatal in young children". Additionally, clinical trials in young children "showed that surfactant - a substance that keeps air sacs in the lungs inflated - helps premature infants breathe" and with this knowledge "the lives of thousands of babies who would otherwise die of respiratory failure are saved each year".[6]

Permanent Reauthorization of BPCA and PREA is Key to Ensuring Innovation in Pediatric Research

Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care in the face of rising research costs. Since their initial enactment and subsequent reauthorizations, the pediatric exclusivity incentive and PREA have been subject to a "sunset clause" under which their provisions expire after five years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children over the past fifteen years, Congress should permanently reauthorize BPCA and PREA.

Permanent reauthorization of these provisions would provide greater certainty to companies by allowing a more predictable regulatory path and would help spur increased pediatric research. Pediatric product development would also benefit from updated regulatory guidance to assist both industry and FDA review staff in achieving a common understanding of the requirements

[6] NIH Medline Plus, "Developing Safe and Effective Medicines for Children," Winter 2012, < http://www.fnlm.org/Program_MLP/MLP_intro.html>

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under the Federal Food, Drug, and Cosmetic Act (FDCA). Because of the five-year BPCA/PREA sunset and reauthorization cycle, no such current guidance exists, since every reauthorization has brought new changes to the law. The lack of current FDA guidance creates additional challenges for sponsors involved in pediatric product development to incorporate any differences into its plans due to changes in statutory requirements. If Congress were to reauthorize BPCA and PREA permanently, it would enable the FDA to publish and maintain up-to-date regulatory guidance for companies that seek to develop pediatric treatments.

Further, making BPCA and PREA permanent would allow sponsors to build upon the existing pediatric research infrastructure and expand their capacity to conduct clinical studies. Uncertainty about whether incentives will continue could deter this vital investment. A similar pediatric incentive was successfully introduced in the European Union (EU) in 2007, and while the regulation is subject to review, the EU's pediatric incentive is permanent. The permanent incentive in the EU has enabled the European Medicines Agency (EMA) to publish clear guidelines for industry and regulators making the process more efficient, transparent and predictable.

Given the undisputed success of BPCA and PREA, we urge Congress to permanently reauthorize BPCA and PREA in their current forms to allow pediatric research to thrive and create more options for our most vulnerable population: children.

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Maintaining Pharmaceutical Supply Chain Integrity

In addition to the Subcommittee's focus on the reauthorization of PDUFA, BPCA, and PREA, PhRMA shares the Subcommittee's longstanding interest in helping to assure the safety of the U.S. pharmaceutical supply.

The U.S. ensures drug safety in part by maintaining a closed system for the distribution of prescription medicines. In addition to the existing standards that require an NDA or a BLA and maintenance of current Good Manufacturing Practice (cGMP), the U.S. closed prescription distribution system helps provide assurance regarding the quality, safety and integrity of the products lawfully sold in the U.S., and helps minimize the possibility that a consumer receives a counterfeit medicine. Even with FDA's comprehensive regulatory system, increasing globalization of pharmaceutical supply chains presents challenges that require biopharmaceutical companies and the FDA to be more adaptive and flexible in the review and oversight of entities located around the world. Relying on risk-based approaches will help achieve these goals.

Supply chain security is the responsibility of all parties involved in the distribution of medicines to patients in the U.S. We appreciate the Subcommittee's long-standing commitment to these issues and Congressman Dingell's particular focus on these topics. As you know, PhRMA has constructively engaged with this Subcommittee, with the full Committee and other stakeholders on all aspects of supply chain security, and appreciates the opportunity to continue to be part of this important dialogue.

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As part of this discussion, we are pleased to provide the following preliminary comments, and look forward to an ongoing dialogue on these important issues.

Enhancements to FDA's Inspection Regime – Adoption of Risk-Based Inspection Intervals

PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk. The use of risk-based approaches to regulation, and in particular, to cGMP inspections is not a new concept.[7] We support providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risks they present, and believe relying on set criteria such as compliance history, time since last inspection, and volume and type of products produced, will enhance the FDA's ability to target its inspection resources efficiently and effectively.

Leverage FDA's Inspection Resources by Allowing Use of Foreign Inspection Reports or Accredited Third Parties as Appropriate

In recognition of the fact that the Agency does not have unlimited resources and in order to help ensure that foreign inspections occur on a more regular basis, Congress should consider allowing FDA to rely on the inspection results of other foreign regulatory bodies with similarly robust drug regulatory oversight systems, or to use accredited third parties to conduct certain foreign inspections, such as inspections of facilities considered moderate to low risk based on appropriate criteria. These inspections would not take the place of FDA inspections, which are a necessary and important part of the Agency's mandate; however, they would provide FDA with the flexibility to leverage the work of foreign regulatory bodies of similar standing and maximize

[7] See *e.g.*, "FDA Guidance: Risk-Based Method for Prioritizing GMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model," (Sept. 2004).

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its resources, all without foreclosing its ability to inspect any facility. FDA recently acknowledged and embraced the concept of relying on "public and private third parties to conduct audits and other oversight activities on behalf of FDA."[8]

A risk-based approach to inspections and reliance on third parties inherently contemplate that limited sharing of inspection-related information may be a necessary component of these proposals. In those circumstances, we must also protect confidential commercial and trade secret information, including information related to manufacturing methods and processes. It will be critical for FDA to have in place written agreements with relevant foreign governments setting out the scope of information that can be shared and obtaining assurances from those foreign governments that the pharmaceutical sector's innovation and ingenuity will be protected from public disclosure. Continued innovation of developing and manufacturing tomorrow's new medicines depends on this information being adequately protected.

When considering the issues of supply chain security, another enhancement that could be considered would include requiring all foreign facilities manufacturing prescription drug products or components destined for import into the U.S. to register with FDA and list their products, to the extent they are not already required to do so under current law. By requiring such facilities to register, the FDA will be able to establish a single database that will contain information on all facilities that manufacture products or components of products that are sold in the U.S.

[8] "Pathway to Global Product Safety and Quality: Special Report," Food and Drug Administration, (July 7, 2011), available at: <http://www.fda.gov/AboutFDA/CentersOffices/OC/GlobalProductPathway/default.htm>.

Finally, as we consider whether new authorities are needed to help strengthen our existing prescription drug supply chain, we must also consider the appropriateness of including new burdens on the import of materials for use in preclinical and clinical investigations. The continued, uninterrupted access to preclinical research and clinical trial materials, including active pharmaceutical ingredients (APIs), is essential to ensure that vital research into innovative, life-saving and life-enhancing new treatments is not hindered in any way. Materials and articles used in preclinical research activities are not used in the treatment of patients, but instead are used in laboratory testing as scientists try to understand the pharmaceutical properties and initial safety profile of the test article. Thus, we strongly encourage the inclusion of an exemption for APIs, investigational drugs and other materials intended for use in preclinical testing and clinical trials that comply with FDA's stringent requirements relating to the proper use of investigational material, including labeling and import of investigational products and materials for use in clinical trials under an Investigational New Drug application (IND), into any new provisions related to securing our pharmaceutical supply chain.

We commend the Subcommittee for its focus on and commitment to the issue of securing the pharmaceutical supply chain. The U.S. system of prescription drug supply chain security today is of a very high standard, but even good systems can be improved upon. We look forward to continuing to work with the Committee, FDA and other stakeholders on these important issues.

Thank you for the opportunity to testify today and I welcome any questions you may have.

Pharmaceutical Research and Manufacturers of America
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Mr. PITTS. The chair thanks the gentleman and recognizes Mr. Coukell for 5 minutes for an opening statement.

STATEMENT OF ALLAN COUKELL

Mr. COUKELL. Chairman Pitts, Ranking Member Pallone and committee members, thank you for the opportunity to be here today.

My name is Allan Coukell. I am the Director of Medical Programs with the Pew Health Group, which seeks to improve the health and wellbeing of Americans by supporting policies that foster innovation and reduce risks to consumers. I am here today to talk about the safety of the U.S. drug supply. Pew has focused on this for the last 4 years as has this committee.

In recent years, pharmaceutical manufacturing has been transformed. What was once a domestic industry is now global. Forty percent of our finished drugs and 80 percent of the active ingredients now originate outside our borders. Much of the supply is purchased in India and China. The number of non-U.S. plants that supply the United States has doubled in just the past decade. Yet the Food, Drug, and Cosmetic Act remains overwhelmingly domestically focused. This puts consumers at risk and American manufacturers on an uneven playing field. While the leading companies are already doing thorough assessments of their supply chains, we have to make sure that there is no incentive for the weaker actors to gain a competitive advantage by cutting corners.

Just 4 years ago, hundreds of American patients were sickened and some died after they received a blood-thinning drug, heparin, that had been adulterated during manufacture in China. This was a U.S. company that was reliant on an upstream network of suppliers that it didn't know and couldn't control. Since that tragedy, this committee has held nine hearings and heard from more than 60 witnesses. You have conducted a careful and thorough investigation that has identified serious gaps in the system. We don't know who adulterated that heparin from China but we certainly know how to reduce the risk that someone else will adulterate some other imported drug in the future.

Congress needs to act to protect Americans. We need a system that reduces risks, that rewards companies that have proper quality systems in place, promotes an even playing field, and uses taxpayer dollars efficiently. Pew's "After Heparin" report identifies the risks and suggests some pragmatic solutions. Let me make three key points.

First, inspections. Not that far from here is one of the U.S.'s largest pharmaceutical manufacturing facilities. It is a Mylan facility in West Virginia that employs a lot of people, and like any other domestic manufacturing facility, it can expect an FDA inspection about every 2 years. That company's competitors in India and China also making drugs for the U.S. market face nowhere near that level of scrutiny. A plant outside the United States knows that FDA may visit only once before the product is first approved and then may never return, and that reduces the incentive to make ongoing investments in quality. The FDA should inspect plants both domestic and overseas based on risk, and no company should go uninspected for more than 4 years. We support the call by Mylan

and others in industry for a level playing field to ensure safety regardless of where the drugs come from.

Inspections are one part of the solution. Let me talk for a moment about supplier quality. Pfizer, represented here today on this panel, has invested heavily in supply chain integrity from production and ingredient sourcing to distribution security. Let me quote from previous testimony by Pfizer. They said "Companies in emerging markets are operating in a developing regulatory environment with a novice inspector. Many have rudimentary quality systems, or none at all. Before a U.S. pharmaceutical firm can considering sourcing from these suppliers, it is imperative that the firm work with suppliers to upgrade their quality systems and standards."

The Pew report outlines well-documented cases of suppliers concealing the actual sources of drug ingredients, in some cases bringing in chemical materials that were not intended for pharmaceutical use. We call for modernizing current regulations to ensure that every company has appropriate measures in place to ensure quality standards at their suppliers.

And finally, we need to make sure that the FDA has the tools that are appropriate for today's global paradigm. For example, companies with high quality systems and an established track record shouldn't face delays at the border. Companies that don't have those things should face heightened scrutiny. We need to make sure that the FDA has the clear authority at the border to refuse products when the plant that made them has denied an FDA inspection.

The proposed generic user fee agreement will provide FDA with new resources for increased inspections of overseas generic manufacturing. It is an important step, and the PDUFA reauthorization is the opportunity to bring the FDA into the 21st century to give Americans a greater assurance of safety.

Let me conclude with something that we heard often over the course of our research. If there are feasible practical steps that we don't take, it is not a question of if there is another tragedy, it is a question of when.

Thank you, and I welcome any questions.

[The prepared statement of Mr. Coukell follows:]

ONE PAGE SUMMARY

Testimony before the

House Committee on Energy and Commerce, Subcommittee on Health

United States House of Representatives

February 1, 2012

Allan Coukell, Director, Medical Programs, Pew Health Group, The Pew Charitable Trusts

The safety of the U.S. pharmaceutical supply system, a focus for Pew for the past four years, has also been a matter of sustained interest to this Committee. Nevertheless, many Americans would be surprised by the rapid and profound changes in how our prescription drugs are made – and the new risks that brings. Today, 40% of all finished pharmaceuticals, and 80% of the active ingredients and bulk chemicals in U.S. drugs, are now sourced by industry from foreign countries.

Despite this shift, FDA oversight of manufacturing is overwhelmingly domestically-focused. This puts consumers at risk and American manufacturers on an uneven playing field. While the best companies are already doing thorough assessments of their supply chains, we must make sure there is no incentive for the weaker actors to gain a competitive advantage by cutting corners.

Pew has been working to identify the risks to the drug supply and advance pragmatic solutions. In July of 2011, we released a report entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs." The report was informed by a two-day conference we hosted in March 2011 that included representatives of brand and generic pharmaceutical manufacturers, active drug ingredient makers, major and secondary pharmaceutical wholesalers, chain and independent pharmacies, consumer and health professional organizations, the U.S. Food and Drug Administration (FDA), state regulators and independent supply chain experts.

One of the most striking outcomes of this conference was the amount of consensus among stakeholders about risks and the need to address them. The stakeholders all acknowledged the geographic disparities in FDA oversight of drug manufacturing. In addition, Pew's research underscored again and again how important it is that companies know their suppliers and have systems in place to ensure the production quality throughout their supply chains. Finally, FDA needs regulatory systems that are appropriate for today's global paradigm. For example, we should ensure that companies with high-quality systems in place don't face delays at the border. We also need to ensure that the FDA has the clear authority to refuse products when the plant that made them has denied an FDA inspection.

The authorization of the Prescription Drug User Fee Act (PDUFA) and other user fee programs this year offers an opportunity for Congress to tackle the risks of the global supply chain. Numerous stakeholders agree on the path forward here. They also agree that without action, we will face another disaster. Now is the time for this Committee to Act on what it has learned over the past four years.

Testimony before the

House Committee on Energy and Commerce, Subcommittee on Health

United States House of Representatives

February 1, 2012

Allan Coukell, Director of Medical Programs, Pew Health Group, The Pew Charitable Trusts

Chairman Pitts, Ranking Member Pallone and members of the Health Subcommittee, thank you for the opportunity to submit testimony about the essential steps Congress must take to protect Americans and ensure the integrity of our drug supply.

Based on research and critical analysis, the Pew Health Group seeks to improve the health and well-being of all Americans by reducing unnecessary risks to the safety of medical and other consumer products and supporting medical innovation. Pew applies a rigorous, analytical approach to improve public policy, inform the public and stimulate civic life.

The safety of the U.S. pharmaceutical supply system, a focus for Pew for the past four years, has also been a matter of sustained interest to this Committee. Nevertheless, many Americans would be surprised by the rapid and profound changes in how our prescription drugs are made – and the new risks that brings. Today, 40 percent of all finished pharmaceuticals,[1] and 80 percent of the active ingredients and bulk chemicals in U.S. drugs, are now sourced by industry from foreign countries.[2] Up to half are purchased from plants in India and China.[3] The number of non-U.S. plants we depend on has doubled in just the past decade.[4]

Despite this shift, FDA oversight of manufacturing is overwhelmingly domestically-focused. This puts consumers at risk and American manufacturers on an uneven playing field. While leading companies are already doing thorough assessments of their supply chains, we must make sure there is no incentive for the weaker actors to gain a competitive advantage by cutting corners.

In 2008, hundreds of American patients were sickened, and some died, after they received a blood thinning drug, heparin, that had been adulterated during the manufacturing process in China.

Since that time, this committee has held nine hearings and heard from more than 60 witnesses, in this Congress and those prior. You have conducted a careful and thorough investigation that has identified serious gaps in the system. We do not know who intentionally adulterated Chinese made heparin in 2008 but we certainly know how to make it much less likely that that kind of adulteration can happen again. Congress needs to act now to protect American consumers.

An ideal system will reduce risks, reward companies with good quality systems, promote an even playing field and use taxpayer dollars efficiently.

Pew has been working to identify the risks to the drug supply and advance pragmatic solutions. In July of 2011, we released a report entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs."[5] The report, which underwent extensive external review, was based upon information from regulatory and public documents, peer-reviewed journal articles and interviews with dozens of supply chain experts from numerous perspectives. It was informed by a two-day conference we hosted in March 2011 that included representatives of brand and generic pharmaceutical manufacturers, active drug ingredient makers, major and secondary pharmaceutical wholesalers, chain and independent pharmacies, consumer and health professional organizations, the U.S. Food and Drug Administration (FDA), state regulators and independent supply chain experts.

One of the most striking outcomes of this conference was the amount of consensus among stakeholders about risks and the need to address them. Leaders within industry that adhere to high standards of quality management and supply chain oversight understandably want all makers of drugs to be held to maintain and ensure drug quality.

Stakeholders at the Pew meeting acknowledged the geographic disparities in FDA oversight of drug manufacturing. Not far from here is a pharmaceutical manufacturing plant in West Virginia, operated by Mylan, the largest U.S. producer of generic drug products. Like every other domestic facility, it faces FDA inspections at least every two years. But as Heather Bresch, the company's president has noted, her competitors in China receive nowhere near this level of scrutiny. She has written that:

> "Every consumer should have the peace of mind in knowing that every prescription

> purchased in the U.S. is held to the same standard of quality regardless of whether the product or its ingredients originated in the U.S. or outside its borders."[6]

While FDA inspections alone are not enough to ensure quality, the expectation of inspection is a critical driver of quality compliance by makers of drugs and their ingredients. A plant outside the U.S. knows FDA may visit only once, before the product is first approved, and then never return. That reduces the incentive to make ongoing investments in quality. The FDA should inspect plants, both domestic and overseas, based on risk, which will permit the Agency to make much more efficient use of its limited resources. However, no plant should go indefinitely without an inspection. A minimum frequency of 4 or 5 years should thus also be established.

Second, Pew's research underscored again and again how important it is that companies know their suppliers and have systems in place to ensure the production quality throughout their supply chains. Pfizer, who joins us on this witness panel, has invested heavily in supply chain integrity, creating overarching systems that cover all company functions – from production and ingredient sourcing to distribution security. Pfizer has said in testimony:

> "Companies in emerging markets are operating in a developing regulatory environment with a novice inspectorate. Many have rudimentary quality systems or none at all. Before a US pharmaceutical firm can consider sourcing from these suppliers, it is imperative that the firm works with the suppliers to upgrade their quality systems and standards. To accomplish this, Pfizer and other companies have taken steps to Educate, Evaluate and for lack of a better word, Enforce appropriate quality standards."[7]

Pew supports updating current regulations to ensure all companies implement quality systems to manage their supply chains. These systems should include robust supplier assessment. Companies that do not adequately monitor and control suppliers may not only be ignorant of quality problems, they may be deliberately deceived. There have been well-documented cases of suppliers concealing the actual source of drug ingredients, in some cases bringing in chemical materials that were not intended for pharmaceutical use.

Martin VanTrieste, Vice President for Quality at Amgen and a founder of an industry pharmaceutical quality consortium called Rx-360 has said:

> "Rx-360 members recognize that we are responsible for our suppliers and supply chains and have a responsibility to tackle head-on the challenges associated with a global supply chain."[8]

Finally, we need to ensure FDA regulatory systems are appropriate for today's global paradigm. We should ensure that companies with high-quality systems in place don't face delays at the border. We need a system that benefits those companies and allows FDA to focus resources on firms that can't show a record of inspections or compliance with best practices. Indeed, FDA has conducted pilot programs in this area, and is also implementing a new risk-based screening system for imports to increase the efficiency of targeting. We also need to ensure that the FDA has the clear authority to refuse products when the plant that made them has denied an FDA inspection.

This year's authorization of the Prescription Drug User Fee Act (PDUFA) and other user fee programs offers an opportunity for Congress to tackle the risks of the global supply chain. We are greatly encouraged that the Generic Drug User Fee agreement, which will provide the FDA with new resources to conduct increased inspections of overseas generic manufacturing facilities – reaching parity with US inspections within five years. The additional changes to bring the FDCA into the 21st Century are feasible, practical and germane to the user fee renewal.

Numerous stakeholders agree on the path forward. They also agree that without action, we will face another disaster like that of the adulterated heparin four years ago. We have heard over and over the mantra, "it is not if, but when." Now is the time for this Committee to act on what it has learned over the past four years.

Thank you, and I welcome your questions.

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[1] Hamburg, Margaret. Commissioner, U.S. Food and Drug Administration. Testimony before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations. April 13, 2011. http://republicans.energycommerce.house.gov/Media/file/Hearings/Oversight/041311/Hamburg.pdf. Accessed April 27, 2011.

[2] U.S. Government Accountability Office (March 1998). Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program (Publication No. GAO/HEHS-98-21).

[3] NSD Bio Group. *Potential Health & Safety Impacts from Phormaceuticals and Supplements Containing Chinese-Sourced Raw Ingredients*. Prepared for the United States China Economic and Security Review Commission. April 2010.

[4] Woodcock, Janet. Director, Center for Drug Evaluation and Research, Food and Drug Administration. "The FDA's Response to Biogenerics, QA and Globalization." Unbranding Medicines: The Politics, Promise, and Challenge of Generic Drugs. Harvard Interfaculty Initiative on Medications and Society. December 12, 2008

[5] Pew Health Group. "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs." (2011) http://www.prescriptionproject.org/after_heparin_report

[6] Bresch, Heather. President, Mylan Inc. Submission to Docket No. FDA-2010-N-0381 Re: Generic Drug User Fee, FDA Request for Comments. October 17, 2010

[7] Migliaccio, Gerry , Vice President, Quality, Pfizer Inc. "Restoring FDA's Ability to Keep America's Families Safe". Testimony before the Senate Health, Education, Labor, and Pensions Committee, April 24, 2008.

[8] VanTrieste, Martin. "Securing the Pharmaceutical Supply Chain". Testimony before the Senate Health, Education, Labor, and Pensions Committee. Wednesday, September 14, 2011

Mr. PITTS. The chair thanks the gentleman and recognizes Ms. Dorman for 5 minutes for an opening statement.

STATEMENT OF DIANE EDQUIST DORMAN

Ms. DORMAN. Thank you, Mr. Chairman. Thank you, Ranking Member Pallone. Thank you for the opportunity to testify before you today. I am Diane Dorman, Vice President for Public Policy for NORD, the National Organization for Rare Disorders.

Since 1983, NORD has served as a leading voice and advocate for the approximately 30 million men, women and children with rare diseases in the United States. NORD's mission is to foster a social, political and financial culture of innovation that supports the basic and translational research necessary to develop new diagnostic tests and therapies for all rare disorders. This requires a regulatory environment that encourages the development and timely approval of new, safe and effective treatments for rare disorders.

Reauthorizing PDUFA presents an opportunity for Congress to achieve that goal. Greater clarity and predictability for the review of novel therapies for rare disorders can be achieved by allocating some of the PDUFA resources to support the enhancement of regulatory science. Of special significance in the draft agreement is the rare disease initiative that will enhance development of drugs and biologics for the treatment of rare conditions. We support these efforts and look forward to the opportunity to work with the agency and with Congress to guarantee the success of this initiative.

The rare disease community was heartened recently when the drug approval summary for 2011 was announced. Of the 35 innovative drugs approved in 2011, ten were orphan drugs. We hope and expect that further investment in orphan products will lead to continued development of therapies that address the unmet medical needs of patients. We are encouraged that the Orphan Drug Act has brought about such successful innovation in the market for rare disease therapies.

The reality is that we have barely started the journey. There is still approximately 6,800 rare diseases that lack an FDA-approved therapy. The reauthorization of PDUFA offers hope that we may build on previous successes by strengthening the review process still further and by creating an environment that encourages innovation and investment. We believe that the rare disease program will enhance the regulatory science needed to accelerate development of new therapies. This initiative allocates a small fraction of user fees to support the existing rare disease program and CDER. The agreement completes the current staffing and implementation plan and establishes a rare disease liaison within the Center for Biologics.

Last October, NORD released a landmark study that looked at all drugs for diseases other than cancer approved as orphans since 1983 to identify whether and when FDA exercised flexibility in the review process. Of the 135 drug approvals studied, NORD concluded that the FDA demonstrated flexibility in the review of effectiveness data on orphan drug therapies for two out of every three orphan drugs approved. FDA clearly has demonstrated in its actions on orphan products over the past three decades that it recognizes the importance of therapies for people with rare disorders.

NORD believes it would be helpful for such flexibility to be recognized in a formal FDA policy and for officials to incorporate flexibility in a systematic way in their evaluations of each new therapy.

While the statutory standard for safety and efficacy should be the same for all medical products, enhancement of the rare disease program will allow FDA to provide greater clarity in how it applies the standards for safety and effectiveness to orphan products. A formal policy setting forth the agency's view of flexibility in conducting orphan product review is likely to provide more certainty to innovators seeking to develop rare disease therapies. Further, we would like to see the proposed public meeting and staff training implementation dates moved forward to occur no later than 2013.

PDUFA V will provide FDA with the resources needed to maintain a strong professional staff that is necessary for the development of clear guidelines and the expedited review of innovative therapies.

In addition to the rare disease program, there are two other policy considerations that we feel are worthy of your consideration: current conflict-of-interest provisions and patient participation in risk assessment. First, during FDAAA negotiations, NORD argued that because patient populations are very small and the number of researchers who study a particular rare disease is limited, identifying experts not financially conflicted to sit on an advisory committee would be difficult, if not impossible. Those concerns were realized in 2008 when it took the FDA nearly 6 months to identify an expert to review a life-saving therapy to treat infantile spasms. While conflict-of-interest considerations are clearly necessary, our view is that the existing provisions in the Federal Advisory Committee Act and the Ethics in Government Act of 1978 are adequate to safeguard against conflicts of interest. A separate standard is not needed.

Second, NORD, working with like-minded patient organizations, has developed a proposal submitted to the FDA to allow the patient community to communicate on a more frequent and periodic basis with medical reviewers and other relevant FDA staff to make risk tolerance and other decisions. We advocate that more systematic processes be established at FDA to enable contributions from the patient community at the time that critical decisions on risk tolerance are being made. We do not seek to create a burdensome or time-consuming process; rather, we want to be sure that patients have the opportunity to share their views.

In closing, I want to thank the committee again for giving NORD the opportunity to testify today regarding the reauthorization of PDUFA. The rare disease community believes that engaging Congress and FDA officials in the process has and will continue to lead to practical, detailed improvements to the regulatory process that will accelerate the development of orphan products from concept to access.

Thank you very much.

[The prepared statement of Ms. Dorman follows:]

Testimony of Diane Edquist Dorman
Vice President, Public Policy
National Organization for Rare Disorders (NORD)

Before the
United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

February 1, 2012

Mr. Chairman, ranking member Pallone, distinguished members of the Subcommittee, I want to thank you for the opportunity to testify before you today. I am Diane Dorman, Vice President for Public Policy of the National Organization for Rare Disorders, or NORD.

Since 1983, the National Organization for Rare Disorders has served as the leading voice and advocate for the approximately 30 million men, women and children with rare diseases in the United States. NORD is a '501(c)(3)' nonprofit federation of voluntary health organizations dedicated to helping Americans with rare 'orphan' diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

NORD's mission is to foster a social, political, and financial culture of innovation that supports the basic and translational research necessary to develop new diagnostic tests and therapies for all rare disorders. This requires a regulatory environment that encourages the development of and timely approval of new safe and effective treatments for rare disorders.

To that end, reauthorizing the Prescription Drug User Fee Act (PDUFA) presents an opportunity for Congress to achieve that goal. In particular, some of the resources generated by the user fee program should be allocated to support the enhancement of regulatory science, to create greater clarity and predictibility for the review of novel therapies for rare disorders, and to empower patients to fully participate in the regulatory decision-making process where questions of benefit-risk assessment arise.

Of special significance in the draft agreement is the rare disease initiative that will enhance the development of drugs and biologics for the treatment of rare conditions. NORD supports these

efforts and looks forward to the opportunity to work with the Agency and Congress to guarantee the success of this initiative.

RARE DISEASE PROGRAM INITIATIVE

The Food & Drug Administration (FDA) has facilitated a series of open meetings for patient stakeholders, providing a forum for input from patients and consumers regarding the human drug and biologic review programs. NORD has been active participant in this process, voicing the concerns and priorities of patients with rare diseases.

Mr. Chairman, everyone within the rare disease community was heartened recently when the drug approvals summary for FY2011 was announced. Of the 35 innovative drugs approved by the FDA in FY2011, 10 were orphan drugs that treat rare diseases with few or no treatment options[1]. We hope and expect that further investment in orphan products will lead to continued development of therapies that address the unmet medical needs of patients with rare diseases.

We are encouraged that the Orphan Drug Act has brought about such successful innovation in the market for rare disease therapies. The reality is that we have barely started on the journey. There are still approximately 6,800 rare diseases that lack an FDA approved therapy. The reauthorization of PDUFA offers hope that we may build on previous successes by strengthening the review process still further and by creating an environment that encourages innovation and investment.

Particularly, we believe that the Rare Disease Program Initiative in the agreed upon PDUFA reauthorization performance goals will enhance the regulatory science needed to accelerate development of new therapies that treat rare diseases. This initiative allocates a small fraction of user fees for the expansion of the existing Rare Disease Program in the FDA's Center for Drug Evaluation and Research (CDER). In brief, the agreement completes the current staffing and implementation plan for the CDER Rare Disease Program in the Office of New Drugs, and establishes a rare disease liaison within the Office of the Center Director of the Center for Biologics Evaluation and Research (CBER). The patient community supports this initiative.

A key ingredient to successful innovation is how FDA views drugs for rare diseases. Last October, NORD released a landmark study that looked at all drugs for diseases other than cancer approved as orphans since 1983 to identify whether and when FDA exercised flexibility in the review process. Of the 135 drug approvals studied, NORD concluded that the FDA demonstrated flexibility in the review of effectiveness data on orphan drug therapies for two of every three orphan drugs approved. FDA clearly has demonstrated in its actions on orphan products over the past three decades that it recognizes the importance of therapies for people

[1] See report, "FY2011 Innovative Drug Approvals," US FDA, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm.

with rare disorders. (Several examples of flexibility in orphan product review are included in Appendix A).

NORD believes it would be helpful for such flexibility and importance to be recognized in a formal FDA policy, and for FDA officials to incorporate flexibility in a systematic way in their evaluations of each new therapy in development and under FDA review for Americans with any rare disease.

While NORD believes that the statutory standard for safety and efficacy should be the same for medical products for both rare disorders and prevalent diseases, enhancement of the Rare Disease Program will allow FDA to provide greater clarity in how it applies the standards for safety and effectiveness to orphan products. A formal policy setting forth the agency's view of flexibility in conducting orphan product review is likely to provide more certainty to innovators seeking to develop orphan products.

Missing in the draft agreement is increased coordination between CDER and CBER and two other key FDA Centers. Although the regulatory schemes differ between CDER, CBER, CDRH and CFSAN, there are underlying themes of commonality – geographically dispersed small patient populations and, of course, the challenges of trial design. Because humanitarian use devices and medical foods for inborn errors of metabolism and other rare conditions are equally critical to rare disease patients, increased collaboration and education of reviewers in CDER and CBER with CDRH and CFSAN is strongly supported by NORD.

Further, we would like to see the proposed public meeting and staff training implementation dates in the PDUFA reauthorization performance goals moved forward, to occur no later than the end of FY 2013.

Additionally, we think that the American public is served well by a strong FDA that continues to review safe and effective therapies and approve them for marketing in the United States first, faster than in Europe, (as demonstrated by a recent study of new oncology therapy approvals at the FDA and the European EMA[2]). Likewise, our own analysis comparing orphan drug approvals over the last decade indicates that a total of 106 more orphan products have been brought to market in the United States compared to the European Union, (see Appendix B).

PDUFA V will provide FDA with the resources needed to maintain a strong professional staff that is necessary for the development of clear guidances and the expedited review of innovative drugs.

ADVISORY COMMITTEES AND CONFLICT OF INTEREST

During FDAAA negotiations, NORD argued that because patient populations are very small, and the number of researchers who study a particular rare disease is limited, identifying experts not

[2] This study, by Friends of Cancer Research, indicates that a sizeable majority of new cancer therapies approved for marketing by both the US FDA and European EMA from 2003-2010 were approved by FDA first.

financially conflicted to sit on an Advisory Committee would be difficult, if not impossible. Those concerns were realized in 2008 when it took the FDA nearly six months to identify an expert to review a life-saving therapy to treat infantile spasms[3].

To address those concerns, NORD has joined forces with over 50 organizations who are deeply concerned about the current conflicts-of-interest statutory provisions and their impact on the appointment of experts, particularly researchers and patients, as Special Government Employees on FDA Advisory Committees and as otherwise needed. As a group, the organizations promote efforts to bring better treatments and cures to those struggling with diseases. Many of these conditions have no adequate treatments and, therefore, it is imperative that we challenge hurdles that impede the quality and efficiency of the treatment development process.

It is our belief that protections must be in place when persons are appointed to positions where their own financial interests might influence their service to the federal government. However, it is also our strong belief that the current conflict-of-interest statutes that apply to the FDA have resulted in a system that is out of balance to the point that conflict avoidance is the primary driver of who serves on Advisory Committees, regardless of the extent of the conflict, the uniqueness of their expertise, or the government's need for their services.

As you know, FDA SGE's are subject to an additional layer of statutory conflict-of-interest provisions beyond those that already govern SGE's for all other departments and agencies in the executive branch. Specifically, under current law, the FDA must analyze potential committee members pursuant to Section 712 of the Food, Drug, & Cosmetic Act (FDCA), in addition to the government-wide provisions found in the Federal Advisory Committee Act and the Ethics in Government Act of 1978. This additional FDA-specific provision appears to drive the FDA to look only for individuals to serve as SGE's who have virtually no financial ties to any issue that might be addressed by a given Advisory Committee.

While that may sound wise at first glance, in fact those with expertise in a given area often have foreseeable and unavoidable ties to the community as a result of their expertise. Yet, under the current structure, the FDA is not allowing those individuals to serve as SGE's, despite the fact that by doing so the FDA is being deprived of expertise by those who are best qualified. Accordingly, we support any effort to eliminate the additional conflicts of interest restrictions that apply only to the FDA[4].

Our view is that the existing provisions in the Federal Advisory Committee Act and the Ethics in Government Act of 1978 are adequate to safeguard against conflicts of interest, while still

[3] The details of this delay are outlined in an article appearing in Pink Sheet Daily, August 27, 2008. See references.

[4] http://www.accessdata.fda.gov/FDATrack/track?program=advisory-committees&id=AdvComm-waivers&fy=all. While FDCA does give the FDA authority to issue waivers for those with conflicts of interest (with an annual cap on the number) it frequently selects for SGE service those who need no waivers, often meaning they have little direct involvement in an issue or a field.

allowing those with the necessary expertise and perspective to serve on these very important committees. In fact, the specific standard for SGE's found in 18 U.S.C. 208(b)(3) recognizes that potential SGE's may have conflicts-of-interest, but allows for their service nevertheless when the need for their services outweighs the potential for a conflict-of-interest created by the financial interest involved.

That standard is clear, reasonable, and balanced and appropriately recognizes that some potential SGE's may come to the FDA with ties to the community that may pose some conflict-of-interest, but that the primary issue must be the government's need for their services. The main goal of these committees, after all, is to help the FDA to make the best decisions possible. The FDA can only do that if it has the best, most well-informed researchers, clinicians, and patients advising it.

RISK TOLERANCE IN THE PATIENT COMMUNITY

Early this year, NORD convened a meeting of like-minded members of the patient community to discuss the willingness or reluctance of patients and their families to tolerate a greater degree of risk in the use of therapies to treat chronic and rare conditions. Our goal was to develop a proposal to be submitted to the FDA as to how the patient community can communicate on a more frequent and periodic basis with medical reviewers and other relevant FDA staff as they are making risk tolerance and other decisions regarding specific product applications or making policy decisions.

The 32 organizations who signed the letter submitted to CDER on September 27, 2011[5], are in full agreement that it is essential that patients have the opportunity to provide such input to product and policy decisions made by the FDA, particularly with regard to risk tolerance associated with the use of specific products. Mechanisms currently exist for patients and other external audiences to provide input to the FDA – e.g., at the public sessions of advisory committees – but the input does not necessarily occur at the time that risk tolerance and other critical issues are being deliberated, and does not necessarily represent a broad spectrum of patient views.

As the FDA commits to a more patient-centric posture, and as patients themselves become more knowledgeable and sophisticated about diseases and their treatment options, we advocate that more systematic processes be established at FDA to enable contributions from the patient community at the time that critical decisions on risk tolerance are being made, and from a representative sample of patient views.

We believe the process should be well-defined and well-understood within the review divisions, and provide a universally applied opportunity for patients to make such input. We are conscious that FDA reviewers and other relevant FDA staff have many demands on their time, but strongly

[5] A copy of the letter may be found on NORD's website:
http://www.rarediseases.org/docs/policy/MullinRiskToleranceletter..pdf

believe that a new process for input will improve product analysis and approval and access to necessary treatments in a timely manner.

We recognize that risk tolerance and other critical decisions are made at many points during the regulatory life cycle of a product - from initial clinical trials through marketing. However, at some points of the review process when risk assessments are made, patient contributions would be of value to the FDA decision-makers.

We also recognize that continuous interaction with the patient community is not feasible. At the same time, the patient community believes that specific milestone events should be designated at the times at which FDA, as a matter of policy, seeks formal input from the patient community.

We do not seek to create a burdensome or time-consuming process. Rather, we want to be sure that patients across the country, whether they belong to a patient organization or not, have the opportunity to share their views with the FDA.

Our hope and expectation is that the kinds of information that patients and patient organizations can share with the FDA will contribute toward its decision-making in assessing the benefit-risk equation of new products as well as the amount of risk patients at various stages of their condition are willing to take, the quality-of-life challenges they face, the ways they receive information about the proper use of their therapies, how often they see and receive information from their physicians, and other information that FDA medical reviewers and other relevant FDA staff may benefit from knowing directly from patients.

CLOSING

In closing, I want to thank the Subcommittee again for giving NORD the opportunity to testify today regarding the reauthorization of the Prescription Drug User Fee Act. The rare disease community believes that engaging Congress and FDA officials in the process has, and will continue to lead to practical, detailed improvements to the regulatory process that will accelerate the development of orphan products– from concept to access.

Thank you.

Respectfully Submitted,

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Appendix A

Selected CDER Rare Disease Product Approvals from 2007 to 2012

1. Voraxaze (glucapidase) – New Biologic

On January 17, 2012 FDA approved Voraxaze (glucarpidase) to treat patients with toxic levels of methotrexate in their blood due to kidney failure.

Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. However, patients receiving high doses of methotrexate may develop kidney failure. Voraxaze is an enzyme that rapidly reduces methotrexate levels by breaking this chemotherapy drug down to smaller, inactive components that can be eliminated from the body by the liver. Voraxaze is administered as a single injection directly into a patient's vein (intravenously). Prior to approval of Voraxaze, there were no effective therapies for treatment of toxic methotrexate levels in patients with renal failure.

The effectiveness of Voraxaze was established in 22 patients from a single clinical study, in which all patients received Voraxaze treatment (open-label, single-arm trial). Patients ranged in age from 5 to 84 years, and the most common cancers being treated were a form of bone cancer (osteogenic sarcoma) and blood cancers (leukemia and lymphoma). The treatment was considered successful if the methotrexate level fell below a critical level within 15 minutes and stayed below the critical level for eight days. Ten of the 22 patients achieved this standard. Although not all patients experienced this result, Voraxaze reduced methotrexate levels by more than 95 percent in all patients.

Voraxaze was given a priority review by FDA, which is a shortened review time of 6 months for drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists, instead of the standard review time of 10 months for other drugs. FDA exercised regulatory flexibility in evaluating efficacy based on rapid and sustained clearance of toxic methotrexate blood levels, a novel endpoint for drug approval. The use of this endpoint in a selected patient population allowed efficacy to be demonstrated in a single arm study.

2. Erwinaze (asparaginase) – New Biologic

On November 18, 2011 FDA approved Erwinaze (asparaginase) to treat patients with a form of blood cancer, acute lymphoblastic leukemia (ALL). Erwinaze is a component of multi-agent chemotherapeutic regimens for the treatment of ALL.

ALL is a malignancy arising in the bone marrow, and most commonly affects children. Epidemiologic data from 2004-2008 show that the median age at diagnosis for ALL was 13 years of age, and 60% of newly diagnosed patients are under age 20.

The effectiveness of Erwinaze was established in one trial in 58 patients, in which all patients received Erwinaze treatment (open-label, single-arm trial). All patients were enrolled in NCI-sponsored cooperative group trials conducted by the Children's Oncology Group. Patients in the study ranged in age from 2 to 18 years (median 10 years). The main outcome measure in the trial was the level of asparaginase activity in serum, an accepted surrogate measure for clinical benefit, which supported a full approval for Erwinaze.

3. Zelboraf (vemurafenib) – New Molecular Entity (NME)

On August 17, 2011 FDA approved Zelboraf (vemurafenib) to treat patients with metastatic melanoma that has a specific abnormality of a gene know as BRAF. It also required coordination with CDRH on the simultaneous approval of a diagnostic test for the gene abnormality, which was the first-ever approval by FDA of a drug + a "companion diagnostic".

Zelboraf's effectiveness and safety were established in one Phase 3 randomized, open-label (not blinded to treatment) trial and one Phase 2 open-label, single-arm trial. In the Phase 3 trial, patients were randomized to Zelboraf or treatment with the chemotherapeutic agent dacarbazine. The results showed an increase in median overall survival (OS) and progression-free survival in patients treated with Zelboraf vs. dacarbazine, and an overall response rate of 48% in the Zelboraf group vs. 6% in the dacarbazine group.

Due to the results of these studies showing a significant benefit in overall survival in patients with melanoma with the BRAF mutation, Zelboraf was given a priority review. In addition, because of the paucity of effective therapies for patients with this disease, this application was given an expedited review and approved by FDA more than 2 months ahead of the PDUFA priority review goal date.

This application is also notable in that FDA became aware of preliminary results in the sponsor's Phase 2 study as well as published results of the Phase 1 study with Zelboraf that showed impressive objective response rates of >50% in this patient population. In published literature reports of patients with metastatic melanoma treated with a variety of chemotherapy agents, objective response rates ranged from 11% to 24%. Given these noteworthy results with Zelboraf, FDA proactively communicated with the applicant to modify the statistical plan for the Phase 3 trial, adapting the impressive observed activity of Zelboraf in the Phase 1 and 2 studies. With this adaptation, the applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial.

4. Carbaglu (carglumic acid) – New Molecular Entity (NME)

On March 18, 2010 FDA approved Carbaglu (carglumic acid) for the treatment of NAGS deficiency, a rare, serious inherited disorder. Less than 20 patients in the US are known to have NAGS deficiency.

NAGS deficiency is one of a group of diseases known as urea cycle disorders. Urea cycle disorders most commonly present in infancy and early childhood. The urea cycle is responsible for removing ammonia from the blood stream. Ammonia is toxic, and high levels in the blood can cause brain damage and death. NAGS is a required cofactor which combines with an enzyme in the first step in the urea cycle, and a deficiency in NAGS results in severe impairment in the urea cycle. Carbaglu is a closely related drug to the naturally occurring NAGS, and acts as a replacement for the deficient cofactor.

Carbaglu's effectiveness and safety were demonstrated in a retrospective case series in which the clinical course of 23 patients with NAGS deficiency who were treated with Carbaglu for a median of 8 years (range 0.6 months to 21 years) was evaluated. Patients included in the analysis started Carbaglu treatment at ages ranging from less than 1 year to 13 years. This retrospective analysis was unblinded and had no concurrent control group, so no meaningful statistical analysis could be performed. The results showed stable or favorable neurological outcomes in most patients over time, which was notable when compared to historical descriptions of the clinical course of the disease ("historical control"). In 13 of the 23 patients, laboratory data on blood ammonia levels was available, which showed decreases in ammonia levels in both short-term (1 day) and long-term (median 6 years) follow-up.

Carbaglu was given a priority review of 6 months. Although non-specific treatments for urea cycles have been available for many years in the US, prior to the approval of Carbaglu, no targeted and specific treatment was approved for NAGS deficiency. Carbaglu represented an advance in treatment for NAGS deficiency patients.

5. Arcalyst (rilonacept) – New Biologic

On February 27, 2008 FDA approved Arcalyst (rilonacept) for the treatment of cryopryin-associated periodic syndromes (CAPS), a group of rare inherited disorders affecting approximately 200-300 patients in the US.

CAPS is a deficiency in a protein "cryopyrin", which is part of the innate immune response. Deficiency in cryopyrin results the body's over-production of another protein, IL-1, which leads to the development of recurrent rashes, fever and chills, joint pain and other symptoms. In severe forms, it can lead severe organ damage, such as deafness, protein accumulation in vital organs, joint and bone deformities, and nervous system impairment. Depending on disease type, CAPS can manifest in neonates, children or adults. Arcalyst is a protein product, which was developed to interfere with IL-1, and hence, to decrease the signs and symptoms of the disease.

Arcalyst's safety and effectiveness profiles were described in one randomized, double-blind, placebo-controlled trial in 47 patients. The effectiveness of Arcalyst was evaluated using a daily symptom questionnaire, which was a novel endpoint developed for this study with the drug developer and FDA working in collaboration.

Arcalyst was given a priority review. Prior to the approval of Arcalyst, there were no targeted products approved for the treatment of CAPS, and Arcalyst represented an advance in the treatment of this disorder.

6. Soliris (eculizumab) – New Biologic

On March 16, 2007, FDA approved Soliris (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare, serious, acquired disorder estimated to affect several thousand people (or fewer) in the US.

PNH is a deficiency in a blood component "terminal complement inhibitor", which results in an over-activation of other proteins in the complement system. This over-activation leads to the breaking apart of red blood cells in the blood stream (hemolysis). Hemolysis can lead to blood clots, abdominal pain and other signs and symptoms. The formation of blood clots is the most serious manifestation of the disease and can lead to death and severe complications, such as stroke or liver failure. Soliris is a monoclonal antibody, which was developed to specifically target the over-activation of one protein in the complement system (C5). Soliris' mechanism of action is intended to result in less hemolysis and longer red blood cell survival.

Soliris' safety and effectiveness were demonstrated in one randomized, double-blind, placebo-controlled trial in 87 patients, with supporting evidence provided by a second, open-label study in which 97 patients all received treatment with Soliris. Soliris' effectiveness was assessed in the first study by changes in laboratory values, including stabilization in measures of red blood cells (e.g., hemoglobin) and whether blood transfusion could be avoided. These endpoints were significantly improved with treatment with Soliris.

Soliris was given a priority review. Prior to the approval of Soliris, there were no targeted products approved for the treatment of PNH, and Soliris represents an advance in the treatment of this disorder.

Appendix B

Year	EU Orphan Marketing Authoriziations	US Orphan Drug Approvals
2001	8	6
2002	7	14
2003	4	12
2004	6	13
2005	3	20
2006	8	23
2007	15	16
2008	6	14
2009	8	20
2010	4	15
2011	4	26
TOTAL	73	179

These data taken from publically available database access, FDA & EMA, 27 Jan. 2012.

Mr. PITTS. The chair thanks the gentlelady and recognizes Dr. Frattarelli for 5 minutes for an opening statement.

STATEMENT OF DANIEL A.C. FRATTARELLI

Mr. FRATTARELLI. Thank you. Mr. Chairman, members of the subcommittee, my name is Dr. Daniel Frattarelli. I am a practicing pediatrician and Chair of Pediatrics at Oakwood Hospital in beautiful Dearborn, Michigan. I am here today representing the American Academy of Pediatrics in my official capacity as Chair of the AAP's Committee on Drugs.

The testimony I give you today is supported and endorsed by the Elizabeth Glazer Pediatric AIDS Foundation, and I am here today to discuss the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, and I would like to begin just by amplifying something that Dr. Wheadon said. When we are looking at BPCA and PREA, we can really say unequivocally that these two laws have added more pediatric-specific information to the labels of drugs and biologics than we have been able to in the 70 years prior to their enactment, and it is vitally important for infants, children and adolescents that these laws be reauthorized.

I wish to extend the academy's sincerest thanks to Representative Anna Eshoo for her longstanding support and for championing these important laws for children, and although not the subject of today's hearing, the academy also wishes to acknowledge and thank Representatives Mike Rogers and Ed Markey, who together authored the Pediatric Medical Device Safety and Improvement Act of 2007.

Now, as a pediatrician, I see firsthand the need for all children to have medicines that are studied for their use, and thankfully, we have gone from a time back when I trained when about 80 percent of the drugs that we used didn't have any specific pediatric labeling, to today, where that number is down to about 50 percent, and this success is a direct result of BPCA and PREA. Since 1997, 426 labels have been updated with new pediatric information, and in many cases, studies have altered the dosages or formulation we give our patients, and in others, drugs that were previously thought to be safe or effective in children have proved not to be.

The 2007 reauthorization led to several improvements in the function of these laws. All BPCA and PREA studies now result in label changes, and the number of times companies have declined BPCA studies has gone down tremendously while the number of products studied under BPCA and PREA has gone up, and the consistency and quality of pediatric studies has improved significantly, largely through the hard work of the FDA's internal pediatric review committee.

Based on what we have learned about these laws since 1997, the academy offers five recommendations for improvements to BPCA and PREA in 2012. The first of these is to do pediatric study plans earlier. Now, PREA is a premarket requirement for safety and effectiveness. However, the law does not require the submission of a plan for pediatric studies until a company submits its drug application to the FDA. Submission of this plan so late in the process can lead to insufficient planning and potentially avoidable delays in getting important pediatric data. The AAP therefore recommends

amending PREA to require the submission of a pediatric study plan by the end of phase II.

The second recommendation is to improve accountability. We heard this already also that 78 percent of PREA studies due after September 27, 2007, are currently late or were completed late. While many of these studies might be delayed for good reason such as difficulty recruiting patients, FDA's publicly available data do not distinguish between the reasonable and the unreasonable delays. We feel the FDA should have the authority to grant extensions when there is a good cause, but in cases where there isn't a good cause, FDA should have added enforcement tools comparable to those it has for postmarketing commitments involving adults.

Third recommendation is to promote studies in younger age groups. Now, the neonatologists, the people who take care of babies from birth to age one month, report that almost 90 percent of the drugs that they use routinely have never been labeled for this population, and neonatal drug research faces some unique hurdles. The AAP believes that the FDA should be required to ensure that BPCA and PREA written requests includes neonates whenever possible, and if they are not, explain the rationale why. PREA should be triggered when a company decides to expand to a new age group so that pediatricians will have data for an age group that is as young as the FDA determines necessary. The GAO also identified a lack of neonatal expertise at the FDA, and we feel that a dedicated neonatologists added at FDA would assist in reviewing divisions in thinking through these neonatal drug studies.

Fourth recommendation is to increase transparency. As we learned in the 2007 amendments, increased transparency benefits policymakers and researchers. Building on this, the AAP also recommends that new written requests under BPCA be made public at the time they are accepted or declined.

And our fifth recommendation is to make PREA permanent. We call upon Congress to make PREA permanent in 2012. The FDA currently has permanent authority to ensure the safety and efficacy of drugs used in adults, and children deserve the same. As part of this legislation, Congress should also reauthorize the important program at the National Institutes of Health to fund the study of older drugs no longer subject to BPCA and PREA.

I would like to thank the committee again for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for the reauthorization of BPCA and PREA, and would be happy to answer any questions that you have.

[The prepared statement of Mr. Frattarelli follows:]

American Academy of Pediatrics

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Testimony of
Daniel A.C. Frattarelli MD FAAP

On behalf of the
American Academy of Pediatrics

Before the
Energy and Commerce Committee
Health Subcommittee

February 1, 2012

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Daniel A.C. Frattarelli, MD FAAP
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February 1, 2012

Mr. Chairman, members of the subcommittee, I am Daniel Frattarelli MD FAAP, a practicing pediatrician and Chair of Pediatrics at Oakwood Hospital and Medical Center in Dearborn, MI. I am here today representing the American Academy of Pediatrics (AAP) in my official capacity as chair of the AAP Committee on Drugs. The AAP is a non-profit professional organization of 62,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. As a pediatrician, I see first-hand the need for all children to have medicines that are studied for their use and are in dosage forms that are made for their size and stages of development.

The testimony I give today is supported and endorsed by the Elizabeth Glaser Pediatric AIDS Foundation. More than two decades ago, Elizabeth Glaser began lobbying the halls of Congress to call for more research for drugs to treat HIV/AIDS in children. The Elizabeth Glaser Pediatric AIDS Foundation carries on her work today, advocating for children in the U.S. and around the world to have access to the best prevention and care that science and medicine have to offer.

THE ACCOMPLISHMENTS OF BPCA AND PREA

I am here today on behalf of the AAP to discuss the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which represent critical public policy successes for children. I thank this subcommittee and full committee for its strong support of these programs throughout the years. I begin my testimony today by saying enthusiastically and without reservation that through BPCA and PREA we have gained more useful information on drugs and biologics used in children than we had in the seventy years prior to their enactment.

I wish to extend the Academy's sincerest thanks to Representative Anna Eshoo for her long-standing support and for championing these important laws for children. Although not the subject of today's hearing the Academy also wishes to acknowledge and thank Representatives Mike Rogers and Ed Markey who authored the Pediatric Medical Device Safety and Improvement Act of 2007. The Academy sees these three laws as a complementary package of vital pediatric drug and device laws and all three should be reauthorized together this year. We also recognize Senators Jack Reed and Patty Murray for their outstanding leadership in championing these laws in the Senate.

BPCA and PREA have advanced medical therapies for infants, children, and adolescents by generating substantial new information on the safety and efficacy of pediatric pharmaceuticals where previously there was little. It is vitally important for these pediatric subpopulations that these laws be reauthorized.

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In a 1977 landmark statement, the AAP's Committee on Drugs, which I now have the privilege of chairing, said that it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children. The Committee also said that it is not only ethical, but also imperative that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who need them.

In the time since that statement was published, we have gone from a situation where about eighty percent of time, the drugs we were using in children did not have FDA-approved pediatric labeling to today where that number is down to about fifty percent. That success is a direct result of BPCA and PREA. However, because half of drugs used in children still lack pediatric labeling, off-label use remains an unfortunate but necessary practice. As Congress considers legislation related to prescription drugs, such as drug shortages, the Academy asks policymakers to ensure that off-label uses of therapeutic agents be part of the discussion since it is the standard of care for our patient population.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. BPCA provides a voluntary incentive to drug manufacturers of an additional six months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children. PREA provides FDA the authority to require pediatric studies of drugs when their use in children is for the same indication as for adults.

BPCA was first enacted in 1997 and later reauthorized by Congress in 2002. PREA was passed in 2003 and reauthorized together with BPCA for the first time in 2007, creating a unified approach to pediatric drug testing and labeling at the FDA. In 2010, Congress extended BPCA to biologics for the first time. Since 1997, 426 drug labels have been updated with pediatric information including 147 under BPCA, 181 under PREA, 50 under both BPCA and PREA, and 48 under the precursor to PREA, the Pediatric Rule.

As a clinician, I cannot overstate the importance of what we've learned through the pediatric studies generated by these laws. Pediatric studies conducted under BPCA and PREA challenged what was previously thought about therapeutics in children. In many cases, studies and resultant labeling altered the dosages we give our patients. In others, drugs previously thought to be safe and effective in children proved not to be. And, pediatric studies have led to more effective formulations that are more palatable for children. To put it simply, the more we learn, the more we realize what we didn't know.

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CHANGES TO BPCA AND PREA IN 2007 MAKING AN IMPORTANT IMPACT

In 2007, BPCA and PREA were reauthorized for the first time together. Congress took advantage of that historic opportunity and created the most integrated, well-coordinated system at FDA to pursue pediatric safety and efficacy labeling that we have seen to date.

In 2007, the AAP argued that every drug label should reflect when a pediatric study was done (either through BPCA or PREA) and the results of the study, whether the results are positive, negative, or inconclusive. Prior to 2007, there were studies in which families chose to enroll their children for which resultant data does not appear in a products label. I am proud to report that based on data from the Government Accountability Office (GAO), all pediatric studies completed under BPCA and PREA from 2007 until 2010 resulted in labeling changes that included important pediatric information.

Since the 2007 reauthorization, the number of drugs and biologics studied in children rose dramatically: 130 products between 2007 and 2010, compared with 250 products between 1997 and 2007. The incentive under BPCA is well-targeted and is increasingly more popular over time. According to GAO, the number of declined pediatric studies under BPCA fell from 19% between 2002 and 2005 to 5% between 2007 and 2010. Drugs and biological products studied under BPCA and PREA represent a wide range of diseases in children, including those that are common or life-threatening such as cancer, HIV/AIDS, diabetes, allergy and asthma.

The 2007 reauthorization of PREA established the Pediatric Review Committee (PeRC), an internal FDA committee that is providing assistance in the review of pediatric study results and increasing the consistency and quality of such reviews across the agency. The PeRC has played a vital role in helping to better integrate BPCA and PREA and pediatrics generally within FDA and should continue to be supported and strengthened.

BUILDING ON WHAT WE'VE LEARNED FOR FUTURE IMPROVEMENTS

With each reauthorization of BPCA and PREA, we have learned how truly essential it is for children that these laws exist and evolve. Congress has made changes to these programs that have monumentally improved how they function. Based on what we've learned about these laws since 1997, the Academy offers several recommendations for improvements to BPCA and PREA in 2012.

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Remove barriers to earlier pediatric studies

PREA is a premarket requirement for safety and effectiveness. However, the law does not require the submission of a plan for pediatric studies until the time a company submits its application or supplement, which is at the end of the adult drug development process. The precursor to PREA, the Pediatric Rule, required that drug companies discuss and plan for pediatric studies no later than the end of phase 2. The laws of the European Union require the submission of a pediatric investigational plan at end of phase 1. It is important to remember that under PREA, failure to submit a pediatric plan at the time of the submission of a drug application cannot delay the approval of the drug in adults.

Submission of a pediatric plan so late in the process can lead to insufficient and inappropriate study plans and delays of important pediatric data. Pediatricians and families will get better quality pediatric data if discussions with FDA's PeRC happen earlier in the drug development process. And, by giving companies more time to work with FDA on a realistic pediatric plan, we will reduce the need to rely on deferrals, too many of which are well past their agreed-upon due date.

In the PREA retrospective review required by Congress in the 2007 reauthorization, FDA found that with 17 review divisions within the Center for Drug Evaluation and Research (CDER) and few or no pediatricians in some divisions, "approaches in the implementation of PREA, including the level of detail in reviewing pediatric protocol plans, were quite variable." FDA said that many of the pediatric postmarketing requirements listed in the approval letters were described in general terms in "one to three sentences".

FDA found that in cases where PREA studies did not demonstrate efficacy, it is possible that the process could have benefitted from a more detailed pediatric plan being submitted by the applicant before approval. FDA went on to say, "where there was evidence of specific discussion and documentation of the studies needed to fulfill PREA requirements before commencement and/or submission of the studies, the PREA assessments generally were of higher quality."

AAP recommends amending PREA to require the submission of a proposed pediatric study plan at the end of phase 2 that includes a description of the study objectives, age groups, study design, relevant endpoints, statistical approach, and timeline for expected completion of the study. Within a reasonable timeframe, the PeRC should approve or reject the proposed pediatric study plan.

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Improve accountability

Based on the data available today from FDA, within CDER, 78% of PREA studies that were due after September 27, 2007 are still pending today or were completed after their agreed-upon due date. Within CBER, 54% of PREA studies that were due after September 27, 2007 are still pending today or were completed after their agreed-upon due date, including several childhood and flu vaccines. These numbers only include studies that were deferred after September 27, 2007 and do not include studies that were deferred prior to 2007.
Under current law, FDA is prohibited from delaying the approval of a drug or biologic in adults even if the applicant or sponsor has failed to comply with its PREA requirement. AAP supports the principle that adults should not be denied access to effective therapies while studies in children are underway. However, it cannot be the case that delays in studies become permanent once a drug is approved for marketing. Once a product is approved, FDA treats PREA requirements as post-marketing requirements. PREA prohibits FDA from using any existing enforcement mechanisms under section 303 of Federal Food, Drug and Cosmetic Act even though those enforcement mechanisms explicitly pertain to post-marketing requirements that involve adult populations. While we hope enforcement action would never have to be taken, FDA should have enforcement tools for children comparable to those for post-market requirements in adults to ensure that pediatric data is gathered as soon as possible. Congress may also want to consider whether the benefits of BPCA's market exclusivity remain available for companies who are ignore their PREA requirements or have not worked with FDA to establish a new completion date and other necessary amendments for their studies.

There are reasons why pediatric studies might take longer than anticipated. For instance, companies may encounter problems with patient enrollment. However, FDA currently does not distinguish between delays that are for good, justifiable cause and those that are not. The AAP recommends giving FDA the authority to grant deferral extensions when there is good cause.

Promote studies in younger age groups

Premature babies and babies born with congenital or genetic conditions routinely require numerous drugs and other medical interventions to survive their first days, weeks and months. AAP's neonatologists report that almost 90% of the agents that are routinely administered to neonates (babies from birth to age 1 month) have never been adequately studied for safety, dosing, or efficacy in this unique population. As such, these tiny children, remain second-class citizens when it comes to drug safety and efficacy information. While neonatal drug research faces many barriers that are scientific and ethical, GAO and other experts have identified that greater neonatology expertise at the FDA would aid drug development for this population. AAP recommends that a dedicated neonatologist be added to FDA's Office of Pediatric Therapeutics. AAP also believes that FDA should be required to ensure that BPCA written requests include

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neonates wherever possible and if they are not included, the written request should include a statement describing the rationale why. Lastly, PREA requirements are triggered when an applicant submits an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. We believe new age group should be added to this list so that pediatricians would have data for as young an age group as the FDA determines necessary.

Increase transparency

As we learned in the 2007 amendments, increased transparency benefits policymakers, families, researchers and other stakeholders. Currently, pediatric researchers cannot access information on what drugs are currently being studied under BPCA and cannot access written requests and the corresponding medical, statistical, and clinical pharmacology reviews for drug studies completed under BPCA prior to 2007. In some cases prior to 2007 where a company was awarded 6 months of exclusivity for conducting pediatric studies, the labeling does not reflect the results of those studies. The reviews of those studies should be made available to the public just like they have been for studies conducted after 2007.

AAP also recommends that BPCA written requests be made public at the time they are accepted or declined rather than at the time exclusivity is granted. At present, BPCA study requests that are declined by drug companies are never made public. Declined BPCA study requests represent an important gap in pediatric data and companies should have the opportunity to state their reasons for declining the study request.

Make PREA permanent

The AAP commends the House of Representatives for making PREA permanent as part of the FDA reform bill it passed in 2007 and we call upon Congress to make PREA permanent in 2012. The FDA currently has the permanent authority to ensure the safety of drugs used in adults. Children deserve the same. Congress need not debate every few years whether we should continue to require safety and efficacy information on drugs used in children. It is useful, however, to reevaluate the exclusivity program periodically to ensure that the incentive offered achieves its desired goal despite changes in the dynamic pharmaceuticals market. Congress should have the opportunity through a 5-year sunset to analyze whether BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive to maintain the number and quality of pediatric studies for on-patent drugs.

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February 1, 2012

Continue promising pediatric study program at NICHD

BPCA and PREA work well for new drugs and other on-patent drugs for which additional market exclusivity provides an incentive. However, some of the most commonly-used drugs in children are off-patent and beyond the traditional reach of these programs. To address this need, BPCA tasked the National Institute for Child Health and Human Development (NICHD) and the National Institutes of Health (NIH) with creating a priority list of pediatric therapeutic needs in off-patent products and conducting those needed studies. NICHD's program has grown into a promising effort to increase pediatric labeling, with more than a dozen clinical trials completed or ongoing and dozens more awaiting funding to initiate the trials. AAP recommends that NICHD's program continue and be reauthorized without changes at its fiscal year 2008 authorized level of $200 million.

By contrast, the Foundation for the National Institutes of Health (FNIH) which is given authority to collect donations from pharmaceutical companies to fund declined BPCA studies has collected no such donations to enable it to complete any BPCA studies in the history of its involvement with BPCA studies. Therefore, its mandate to conduct pediatric studies of on-patent drugs only serves as a barrier to NICHD conducting those studies and, as such, should be eliminated. However, the Academy recommends retaining the legal authority of FNIH to maintain an emphasis on children and raise money for important pediatric needs, such as training pediatric clinical investigators, building pediatric research networks, and studying pediatric disease mechanisms.

CHILDHOOD CANCER AND OTHER RARE DISEASES

Experts in pediatric oncology have suggested that PREA would better serve the needs of children with cancer if it was allowed to require the study of a drug in children even if it is intended to treat a cancer—like lung cancer—that does not occur in children. The AAP believes this idea has merit and deserves serious consideration by Congress.

The AAP also underscores the importance of the Orphan Drug Act in stimulating drug development for populations with rare diseases, half of which are children. Families with children facing these devastating diseases require the special consideration the Orphan Drug Act, BPCA and PREA provide.

Daniel A.C. Frattarelli, MD FAAP
American Academy of Pediatrics
Energy and Commerce Health Subcommittee
February 1, 2012

CONCLUSION

I would like to thank the subcommittee again for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for reauthorization of BPCA and PREA. For the health and well-being of all children, we urge their renewal, as well as the renewal of the Pediatric Medical Device Safety and Improvement Act, as part of the package of FDA bills under consideration by the subcommittee.

I would be happy to answer any question you may have.

Mr. PITTS. The chair thanks the gentleman, and I will now begin questioning and recognize myself for 5 minutes for that purpose.

Mr. Germano, will you explain how the PDUFA agreement will help improve predictability and transparency of the drug review process, why this is important to American patients and jobs?

Mr. GERMANO. I think that the measure that I spoke of in my testimony was a measure that is particularly important. The PDUFA provisions allow for a review process that has a number of important enhancements. Most notably, as the number of interactions that now would be mandatory for communication and transparency between the agency and the sponsor companies, I think very often issues that arise during the review process are not clearly understood or not consistently understood between the agency and the sponsor company, and I think that this enhanced level of communication and transparency is likely to result in a greater level of understanding and issue resolution and consistency in the review process leading to, you know, review times that likely could be shortened, and, you know, a clarity on expectations between the two parties. If we can get through the process more efficiently, we can bring new products to the market more quickly and benefit patients, and it is good all around for the FDA, for the company and for physicians and patients who need our medicines.

Mr. PITTS. Thank you.

I will just down the line. Dr. Gollaher, in your testimony you make a connection between differences in FDA review times across therapeutic areas and how that affects development decisions by investors and companies, and can you speak to that issue a little further? You also mentioned the adage that you can't manage what you don't measure, and PDUFA has long required the agency to report on numerous performance measurements. You suggest that performance would benefit from some more granular reporting at the review division level. Can you elaborate on that?

Mr. GOLLAHER. Sure. I think those two are related. Investors in large companies like Pfizer but even more venture capitalists who are looking at funding new ventures consider the time to market for their inventions, for their investments, and as we have seen, for example, in diabetes and in cardiovascular, venture investment has almost completely dried up because the time for review and the cost of clinical studies is so great. So the FDA exists in an ecosystem. It exists in a market in which it sends signals about its standards, about times and so forth, and those signals are extraordinarily important for the amount of investment that flows into new inventions and innovative products.

On the data question, you know, we just heard the Commissioner talking about moving to electronic submissions and basically taking the FDA from the analog era that it has inhabited to the digital age, and that is really important, but at bottom, FDA is really a data management agency. I mean, it collects data from industry, it analyzes the data and makes decisions. The opportunity for a better assessment of some of the metrics that people have been talking about, for example, transparency, communication and so forth, and how the agency is performing against those can be measured and I think should be part of the ongoing assessment of agency performance.

Mr. PITTS. Thank you.

Mr. Germano, you had mentioned in your testimony that one of your vaccines got approved through the accelerated approval pathway. Can you give us background on the importance of the accelerated approval pathway, why it is important to get the vaccine to patients as soon as possible?

Mr. GERMANO. Yes. Just last December, our vaccine Prevnar 13 was approved for prevention of pneumococcal disease in individuals 50 years of age and older under this accelerated review process, and the accelerated review process is a measure that the FDA can use when they deem a medicine or, in this case, a vaccine to be appropriate to satisfy a significant unmet medical need for a serious disease or a serious condition, and in this case, just to give you some understanding of the seriousness of pneumococcal disease, pneumococcal pneumonia accounts for over 300,000 hospitalizations a year in the United States and over 25,000 deaths, so it is a very significant disease state and a high burden of both disease and high burden of cost for society. So the FDA utilized the accelerated review process to review and approve this medicine and now really that there is only one other hurdle to get through to bring this vaccine to patients or to society really and that is a CDC recommendation for usage, and we are hopeful that we will get a CDC recommendation later this month when their advisory council on immunization practices meets, and then we will be able to bring the vaccine to the American public.

Mr. PITTS. Thank you.

I think we are going to have to do a second round. My time is up. I will recognize the ranking member, Mr. Pallone, for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask this question, I guess of Mr. Germano and I guess Mr. Pops and Dr. Wheadon, the three of you could answer. We heard from Dr. Hamburg this morning that the FDA rarely, if ever, meets the waiver caps related to the number of persons with a conflict of interest that can serve on an FDA advisory panel. At the same time, we know there are concerns from the public about FDA panelists having conflicts of interest related to the issues they are reviewing. About 3 weeks ago, the Wall Street Journal published an article highlighting the conflict of interest three panelists had one panel had in relation to a product they were reviewing. You know, I know it is a concern, I mean, we are concerned because we want to have the best experts possible on the panels but we need to help the FDA get such experts and get them in a timely manner.

But I am having difficulty seeing how removing the waiver caps will solve anything when FDA is not meeting these caps, and my question is, given that the waiver caps are not routinely reached, can you explain how removing the caps would improve the current situation, if you believe it would, and are there any other fixes you would suggest in addition to or instead of removing the waiver caps? Let us start with Mr. Germano.

Mr. GERMANO. OK. I will start. And I think this is a particularly important area for Pfizer. As I mentioned in my testimony, we are focused on bringing new medicines in the rare disease and orphan

disease area, and this is an area where oftentimes there are a small number of highly expert opinion leaders and physicians.

Mr. PALLONE. I don't have a lot of time, so what do you think? I mean, should we be removing them?

Mr. GERMANO. Well, I think that we—you know, our view is that there is a need to improve the process of the advisory committees, particularly in areas where there is a paucity of experts, and I don't know if it is additional waivers or better utilization of the waivers that exist. I am not familiar enough with the issues, but there is a need for improvement.

Mr. PALLONE. Would either of the other two of you like to answer?

Mr. POPS. Just being directly responsive to your question, I don't think removal of the waivers does a whole lot for the reasons you cited. I think FDA has different standards than other agencies of the government with respect to conflict. My own view is that I think they are too restrictive. And coming at it from the innovators' point of view, the most important thing for us when we convene a panel is that the people sitting at the panel are expert in the disease because they are the best suited to make the decision between risk and benefit that are so critical for patients.

Mr. PALLONE. OK. Dr. Wheadon?

Mr. WHEADON. Thank you, Representative Pallone. I think in addition to what Mr. Pops just added——

Mr. PITTS. Is your mic on?

Mr. WHEADON. I think it is. Can you hear me?

Mr. PALLONE. Yes, I can hear you. Maybe talk closer to it.

Mr. WHEADON. I think it is also important for us to consider broadening the question and looking at it from perhaps a different perspective from just waiver caps, and that might be recognizing that both FDA and industry have a vested interest in working with the best expertise. Should there be a penalty for FDA because industry has engaged that expertise and helping it develop its plan for investigation and research and vice versa, should industry not be allowed to engage that expertise because FDA may be planning to use that individual in an advisory committee. And in the case of rare diseases, it is even more of a particular issue because there could be so few experts for both industry and FDA to engage.

Mr. PALLONE. All right. Thanks.

Let me get a second question in here. We talked about how in today's world drug manufacturing is a global affair and outsourcing is common, and robust supply chain management is best practice for industry including supplier qualification and assessment. So I wanted to ask Mr. Germano again, Pfizer has underscored in previous testimony the importance of ensuring the quality of suppliers, particularly those in emerging economies. Can you tell me what Pfizer is doing to ensure supplier quality? Do you believe that every company knows their suppliers and knows the quality system in place?

Mr. GERMANO. Well, I mean, you know, product supply quality is the highest interest to Pfizer and I think that we have put a number of important measures in place to ensure the integrity of our supply, and you know, some of those measures include risk assessments of potential suppliers, you know, contractual measures

to ensure the effectiveness and quality of those suppliers. We go into some of the suppliers and work with them to upgrade their systems. We have audits on a routine basis. So we employ quite an array of measures to ensure the quality and integrity of our suppliers.

Mr. PALLONE. I was going to ask Mr. Coukell but I guess I am out of time, Mr. Chairman. Thanks.

Mr. PITTS. The chair thanks the gentleman and recognizes Dr. Burgess for 5 minutes for questioning.

Mr. BURGESS. Thank you, Mr. Chairman.

Ms. Dorman, let us stay on the issue of the conflicts because you referenced that in your prepared testimony, and I do believe it is extremely important. In fact, when this reauthorization occurred in 2007, I was way down at the kids' table on the minority side and wasn't really able to make the point as effectively as it needed to be made, but we have got vacancies on the advisory panels. Now, we have got waivers that can be applied and there are caps on the waivers. Do you think the system itself creates an environment where otherwise qualified people say you know what, I don't need that, I'm not going to go through that. So have we created a hostile environment to the researchers and the people who might be knowledgeable about these products because of the restrictions placed on the advisory panels in the 2007 reauthorization?

Ms. DORMAN. I don't know if I would say that there is a hostile environment per se but some of the restrictions, especially related to, you know, their finances and their investments and things like that, could be a deterrent to some people to expose themselves to that type of level of scrutiny. I will say, there is something that really does need to be done. A colleague of mine is president of the Friedrich's Ataxia Research Association, and he was asked by the FDA to apply to sit on an advisory committee, and he was turned down because of perceived conflicts, and this is a man whose child died of Friedrich's ataxia, so there are real concerns that really need to be looked at, and we feel as if it should be—FDA should not held to an even higher standard than all other federal agencies.

Mr. BURGESS. Well, as I recall, during the discussion, the reference to the Institute of Medicine said no more than 40 percent of the advisory panel should be made up of people who potentially had a conflict, and I thought that was an OK number. That means you still have—as you correctly alluded to, the universe of people who have an understanding of the diseases and the treatments proposed is vanishingly small with some of these, and if you exclude even one individual, that may be a significant percentage of the population, the scientific population that actually understands the studies at hand.

Ms. DORMAN. That is correct. I mean, the patient population—the rare disease community is very, very small. Patient organizations work with researchers. They work with companies to encourage the development of these orphan products. So yes, in the rare disease community, basically everyone is pretty conflicted.

Mr. BURGESS. Well, are all conflicts equal? In the real world, are all conflicts equal?

Ms. DORMAN. No, I don't think so.

Mr. BURGESS. Yes, I don't either.

Let me ask you this. Do you think we have actually—that the advisory conflict policy has hindered bringing new products to market?

Ms. DORMAN. No. It may have delayed like in the case of Savril but I don't think it has, in my opinion.

Mr. BURGESS. In my opinion, hindered and delayed would be identical, but I will accept your answer.

Well, would you support loosening some of these restrictions?

Ms. DORMAN. Excuse me?

Mr. BURGESS. Would you support the loosening of some of these restrictions that were placed in the 2007 reauthorization?

Ms. DORMAN. Yes, we would.

Mr. BURGESS. In the interest of full disclosure, I have a bill out there, 3206, which attempts to undo some of these restrictions. Have you had an opportunity to look at that legislation?

Ms. DORMAN. Yes, I have, and I have spoken with your staff.

Mr. BURGESS. And Dr. Hamburg implied that she didn't need a legislative fix, but in your estimation, would a legislative fix expedite the solution to this problem in your world?

Ms. DORMAN. That has been our position, yes.

Mr. BURGESS. And no great surprise, my position too.

Dr. Wheadon, let me ask you a question. Dr. Hamburg referenced coming into the electronic age for some of the applications for the premarket approval process, and I guess I am surprised that that is not farther along. Do you have a sense as to what is the volume of new product applications, new drug applications that are sitting on paper applications in boxes in the basement of someone's warehouse?

Mr. WHEADON. Well, I think we may be talking about two different things. Most sponsors, if not all, certainly the member companies that we represent now submit what is called an electronic document. So everything is electronic. It is no longer boxes in U–Haul trucks as it used to be 20 years ago.

I think what Dr. Hamburg was referring to and what we reference in the PDUFA agreement is an attempt to have more of a common template such that that electronic data is collected in a common format regardless of who the sponsor may be. The ultimate benefit of that is, when the agency needs to look across products, across sponsors, the data is collected in a similar way. It is much easier to collate, much easier to do analyses and come to some robust conclusions. Right now, it is all over the place and it makes it much more difficult for the agency to do that type of analysis. So I don't think Dr. Hamburg was intending to imply that they are still collecting data on a paper format. That is not the case. It is just doing it more physically such that the agency can carry out its job much more effectively.

Mr. BURGESS. Thank you.

Thank you, Mr. Chairman. I will yield back the time.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member emeritus, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy.

First, welcome to Dr. Daniel Frattarelli. He is a constituent of mine from Oakwood Hospital and from Dearborn Medical Center in

Dearborn, Michigan, my hometown. Doctor, it is a pleasure to welcome you. Thank you for being here.

Mr. FRATTARELLI. Thank you.

Mr. DINGELL. As members of the committee well know, I have long believed that the FDA does not have the people, the funding or the authorities it needs to properly oversee an increasingly global drug supply chain. That has been supported by testimony and evidence submitted in hearings before this committee for a number of years. So in support of that posture, I would like to direct my questions to you, Mr. Germano of Pfizer, and please answer to the following questions yes or no. Do you agree that both FDA and industry have a responsibility to ensure the security of our drug supply chain? Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. Do you agree that the knowledge of your suppliers is important? Yes or no.

Mr. GERMANO. I am sorry. The knowledge about suppliers?

Mr. DINGELL. Yes, your knowledge and experience with them as to their behavior and the quality of the goods that they are delivering you. Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. Thank you. There are no traps here.

Mr. GERMANO. I just want to make sure I understand the question.

Mr. DINGELL. Just give the answers and you will be satisfied and so will I.

Mr. GERMANO. OK.

Mr. DINGELL. Does Pfizer have systems in place so that they can know and understand their suppliers and monitor the manufacturing quality of these suppliers? Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. Should all companies making drugs in the United States know their suppliers and have quality systems in place there to assure that they are getting safe supplies from their suppliers? Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. Now, I must assume, however, though, that there would be some instances where additional help would be needed by American suppliers, i.e., in the heparin case where raw materials or components for the heparin were clearly not safe and the result was American manufacturers were put at risk. Should FDA have additional authorities to provide that kind of support for American manufacturers? Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. No traps here. I want you to be comfortable.

Should the companies be using risk analysis to target safety risks? Yes or no.

Mr. GERMANO. Yes.

Mr. DINGELL. And that is not a standalone basis. Obviously they would have to use other things.

Now, these are for Dr. Wheadon of PhRMA. Doctor, I want you to be comfortable with these, and I am not trying to lay any traps for anybody here. I want to focus on inspections. Do you agree that requiring FDA to conduct comparable inspections of domestic and

foreign drug facilities is important to ensuring a level playing field for our drug manufacturers? Yes or no.

Mr. WHEADON. Certainly, the answer is yes based on——

Mr. DINGELL. Sorry?

Mr. WHEADON. I am sorry. Certainly, the answer is yes based on the ability to assess risk.

Mr. DINGELL. Good. I have very limited time, Doctor, and I beg your cooperation here.

Mr. WHEADON. I understand.

Mr. DINGELL. Do you agree that conducting comparable inspections of domestic and foreign facilities is important to public health? Yes or no.

Mr. WHEADON. That is a yes.

Mr. DINGELL. And of course, it is important to the fairness with which we treat our manufacturers. Is that not so?

Mr. WHEADON. I think it is important to be fair across the board.

Mr. DINGELL. Now, do you agree that FDA needs adequate resources to conduct comparable inspections of domestic and foreign drug manufacturers? Yes or no.

Mr. WHEADON. I believe the agency should have adequate resources.

Mr. DINGELL. Now, if FDA does not treat manufacturers alike, it is very liable to be unfair to U.S. manufacturers because of its inability to impose equal burdens upon both domestic and foreign manufacturers who are outside of our borders and outside the capabilities of FDA to reach them. Isn't that so?

Mr. WHEADON. I think FDA has ability to impact foreign manufacturers if they are importing drugs into the United States.

Mr. DINGELL. But you would advocate that FDA do have such authority?

Mr. WHEADON. I think FDA has that ability to impact those manufacturers——

Mr. DINGELL. Please answer my question.

Mr. WHEADON. And they should, yes, sir.

Mr. DINGELL. OK. Does the prescription drug user fee agreement currently provide resources for preapproval inspection? Yes or no.

Mr. WHEADON. Yes, it does.

Mr. DINGELL. Does the prescription drug user fee agreement currently provide resources for any inspections beyond the preapproval inspection? Yes or no.

Mr. WHEADON. That is a qualified yes, it does.

Mr. DINGELL. Qualified? But it should be "yes", shouldn't it? Because FDA should have that authority, should they not?

Mr. WHEADON. FDA has the ability to inspect facilities with resources——

Mr. DINGELL. That is one of the questions we are going to be going into, Doctor.

The generic drug user fee agreement provides additional resources for FDA to conduct GMP inspections of both domestic and foreign drug facilities. Would you support providing similar resources to FDA for inspections of facilities manufacturing innovator drugs? Yes or no.

Mr. WHEADON. No.

Mr. DINGELL. Do you agree that a risk-based inspection schedule for domestic and foreign drugs facilities based, for example, on compliance history, time since last inspection, volume and type of product would allow the FDA to better target the use of their resources? Yes or no.

Mr. WHEADON. Yes.

Mr. DINGELL. One obstacle to ensuring comparable inspections of domestic and foreign facilities is the lack of complete and adequate information that FDA has on drug manufacturing establishments. Do you support requiring domestic and foreign drug manufacturing facilities to register with FDA to provide a unique facility identifier and to list their products? Yes or no.

Mr. WHEADON. I think that is one I would have to come back to you with further comment on. I am not prepared to give a specific yes or no on that one.

Mr. DINGELL. Very good. One question then. Why is it that PhRMA does not support additional resources for GMP inspections?

Mr. WHEADON. Well, this is more than a yes or no, right?

Mr. DINGELL. It is a fairly simple question. I know you have a fairly easy to understand answer.

Mr. WHEADON. Right. So as you correctly point out, Representative Dingell, the PDUFA fees that the innovative industry presently pays goes towards preapproval inspections. When an inspector goes into a facility, be it domestic or foreign, they don't only look at the product that is under consideration for approval, they look at the system of that manufacturing establishment. So a GMP inspection is carried out in the context of preapproval inspections.

Mr. DINGELL. Am I somewhat dense in not understanding why we would want to see to it that FDA has the authority that it needs to carry out its responsibilities in the best way possible?

Mr. WHEADON. We certainly agree that FDA should have the resources to carry out their responsibilities very efficiently.

Mr. DINGELL. I note, Mr. Chairman, I have exceeded my time by 3 minutes and 5 seconds. You have my thanks and my apologies.

Mr. PITTS. The chair thanks the gentleman and yields to the gentleman from Illinois, Mr. Shimkus, for 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman, and I apologize for missing the first part. I have a lot of questions about nuclear waste I could offer to you, but it is good to be here on the health panel.

I would also like to go to Ms. Dorman, and can you just elaborate on how the FDA's risk-based, current risk-based analysis is affecting patients?

Ms. DORMAN. Well, it is the feeling of many patient organizations that the FDA has become far more risk averse than it should be, and so we want some way that patients can communicate directly with the reviewers. We have had conversations with the FDA leadership but the reviewers actually looking at the data don't normally hear from the patients or their families.

Mr. SHIMKUS. And what would the patients and the families tell them if they were listening?

Ms. DORMAN. It depends on the disease, I suppose, or the condition, but just let them know what their quality of life is, to know more about the disease, what the risks of the disease are, what the progression of the disease is. I think those are some of the things

that the reviewers would like to hear, and I would like to point out to the committee that Mr. Shimkus was the sponsor of the rare diseases back in 2002. Thank you.

Mr. SHIMKUS. No, thank you, and that is not why I went to you but I appreciate that.

So I think you kind of answered this. How would you improve that risk-based system? What would you want us to do in a public policy arena to try to fix that?

Ms. DORMAN. What we have proposed directly with the FDA, we are working internally with the officials there, what we have proposed, which isn't really written in stone, would allow patients in an unburdensome way, maybe through a portal there on their Web site that would communicate some of those things. We don't want it to be a burdensome process for the agency at all. But to empower patients in some way, shape or form to feel as if they have more control over approval of a product.

Mr. SHIMKUS. And technologically, that shouldn't be real difficult, should it?

Ms. DORMAN. I am a real techno dweeb but I would say it is probably not all that difficult to do.

Mr. SHIMKUS. I would also agree with you.

Let me stay with you and ask about the FDA's vacancies on their advisory committees. Do you know how many there are, and what does that mean in this discussion that we are having?

Ms. DORMAN. I really don't know what the numbers might be.

Mr. SHIMKUS. And what is the problem with vacancies?

Ms. DORMAN. Well, the problem is that it can delay consideration of products if they are unable to find someone who is expert, especially in the rare disease world where, you know, there are not of people expert in their conditions. Usually the patients know more about their conditions than their doctors do, so——

Mr. SHIMKUS. Say that again. I mean, just reiterate that point.

Ms. DORMAN. I am speaking just from NORD's perspective. I mean, many patients have more knowledge about their condition, about the progression of their disease than some of the physicians do. So it is very important to have their input, and they are anxious to do so.

Mr. SHIMKUS. And I would agree with you there. I mean, they are anxious because either they are suffering themselves or having the life experience. They are also very passionate to try to make the system better for the future, and by being involved in the process, helpful. That gives them a role in this that they would like to be involved in.

Ms. DORMAN. Yes, and it is helping our organizations understand the regulatory process more. So many of them are focused entirely on research at NIH and know very little about the FDA process. But on March 1, they are having a one-day advocacy meeting with patient organizations and over 180 organizations have signed on, so they will give them an opportunity to learn about the FDA and the FDA to learn about their conditions.

Mr. SHIMKUS. Great. Thank you.

And just briefly, Mr. Gollaher, I have been very concerned about capital research fleeing the United States because of the FDA's slowness. We have also heard a lot of testimony about venture cap-

italism. Is that true, if we have research and development, venture capital moving overseas? Where are they going and what does this mean for U.S. jobs?

Mr. GOLLAHER. To some degree, and this is less true in the drug industry than the medical device industry, there has been a shift of first in human trials and of middle-stage and late-stage research to Europe and the device field has a faster and more user-friendly regulatory system. And we have certainly seen in California, we have seen across the country that most venture capitalists will not look at a business plan for a device company that doesn't have a European strategy. That is a tremendous change in the last 10 years.

Mr. SHIMKUS. And that would really affect jobs and the economy. I mean, if they get the approval in Europe, they are most likely going to start there.

Mr. GOLLAHER. Well, no, that is right, and there are also a number of sequelae. So for example, if you introduce a product in Germany before here, the doctors learn to use it. Some of the factors that are involved in early-stage manufacturing may go there as well. And you also teach your competition how to make the product. So it is a real issue.

Mr. SHIMKUS. Thank you very much. I yield back my time, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from California, Mr. Waxman, for 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Frattarelli, in your testimony you provide compelling evidence of the benefits to children that the Best Pharmaceuticals for Children Act provides. As you know, because of studies conducted in response to BPCA and the Pediatric Research Equity Act, we learned invaluable information about the use of drugs in children. However, despite how well it has worked, you point out that the AAP believes that Congress should not remove the BPCA 5-year sunset provision because it provides Congress the opportunity to assess whether the BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive. Can you briefly expand on your testimony regarding why Congress should retain that 5-year sunset provision?

Mr. FRATTARELLI. Sure. One of the big issues here is that it is kind of a moving target that we are talking about. The cost that this is going to incur by varying the period of exclusivity these drugs obtain will change over time, and that cost is going to be borne by a lot of groups, private insurance companies and the government as well. So there is a financial side to this, but the other part is, every 5 years having the opportunity to look at these again, revise them, gives us some real benefits. If we go through, you know, what happened last time we went and reauthorized these, we had some changes made so that, for example, now all the information that we get from these studies results in a label change and the information is more publicly available. Those are two real meaningful and important things to have, and they came about because we had this opportunity to reevaluate.

Mr. WAXMAN. That is a very good argument. The other, of course, is that when we have a 6-month exclusivity, that is a lot of money, and that cost, as you point out, is being carried by the people who pay for these drugs, whether it is government, insurance or private individuals. If you have a 6-month exclusivity, especially if it is a drug like Lipitor where the annual sales are over $5 billion, that just can be a huge cost that is being passed on to others.

And so we need to maintain a balance between providing adequate incentives for developing new indications for pediatric populations and not unduly burdening patients and payers with high drug costs for any longer than is necessary.

During the 2007 reauthorization, we put forward a proposal to trim that 6 months of exclusivity for drugs with very high profit margins, so-called blockbuster drugs. I thought that made sense, but we didn't prevail in including it. I agree, it is critical to retain that sunset provision so we have an opportunity to evaluate these questions, both the balance and the research questions as well.

Ms. Dorman, we have heard concerns from several parties about the development of drugs for rare diseases. I talked in my opening statement about a proposal under consideration that would make changes to FDA's fast-track approval system for orphan drug, the ULTRA Act. Specifically, it would require the FDA to use whatever data was available to evaluate and approve surrogate endpoints for review of these drugs and would prevent FDA from requiring additional clinical data even when FDA considers such additional data necessary to enable it to make an approval decision based on that endpoint. That is a concern to me. My understanding is that under current law, FDA has a great deal of discretion to identify and require appropriate scientific evidence.

NORD recently did a study looking at whether FDA is flexible in its requirements for the approval of orphan drugs. Can you describe the conclusions of this study in more detail? What is NORD's view on the need for legislative changes to FDA's fast-track approval program for orphan drugs, specifically on the ULTRA Act?

Ms. DORMAN. We feel as if ULTRA would require the FDA to rely on surrogate endpoints based on little or no clinical evidence, and it could expose patients to unnecessary risk and in our opinion would lower the approval standards of the FDA, and that is our concern. That study is really a landmark study. Of the 130, you know, products that were reviewed by a former chair, many of them, 90 of the 135, were approved based on administrative flexibility or case-by-case flexibility, and I think the example that Dr. Hamburg gave this morning in her testimony regarding the new therapy for cystic fibrosis, it was approved in 3 months, so they do use that flexibility when something that important comes forward.

Mr. WAXMAN. Well, we all want these drugs on the market as fast as possible but I would be concerned about any proposal to remove FDA's ability to require clinical data when FDA thinks it is essential to assure that these drugs are safe and effective, so I certainly agree with the position NORD has been taking.

Ms. DORMAN. Thank you.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from New Jersey, Mr. Lance, for 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman.

To Mr. Germano, very nice to see you again. In your testimony, you noted that Pfizer's enhanced focus on rare diseases, specifically allocating the majority of your research and development efforts to the areas that represent the intersection between unmet medical needs and your strength in biology and chemistry, given that, could you comment on how the enhancements in regulatory science contained in the goals letter will support the development of products for rare diseases?

Mr. GERMANO. Yes, I think that there are a number of elements of the proposed PDUFA V that will help in the advancement and review and development of medicines for rare diseases. I think the NME review process that I spoke of before will help bring, you know, clarity to the review process, which I think will be helpful. I think that some of the provisions in the, you know, enhancements in regulatory science, you know, specifically for rare diseases, biomarker identification and, you know, other measures that are in the PDUFA V I think are all intended to elevate the capability of the FDA and the potential for better transparency and problem solving and decision making between the company and the FDA.

Mr. LANCE. Thank you. Are there any other changes that you could see that would incentivize innovative biopharmaceutical companies into developing more products for unmet needs?

Mr. GERMANO. Well, I think overall, you know, confidence in the development pathway is a very big part of providing an incentive for a company to take on a project in the development of a new molecular entity in particular. So some of these provisions relate directly to improving confidence in the pathway and agreements that exist between the agency and the sponsor company. Beyond that, I think, you know, intellectual property and exclusivity assurance will give greater confidence to the sponsor to make the investments necessary to bring these kinds of medicines forward.

Mr. LANCE. Thank you very much.

To Mr. Pops, I think it is critical that we ensure a consistent and transparent evaluation of benefit-risk during FDA's review of new drugs. Unfortunately, from my perspective, this evaluation has on occasion kept life-improving, life-saving drugs from patients, and in your opinion, what do we need to do in order to rebalance the analysis?

Mr. POPS. The was one of the real questions that was brought up during the PDUFA V technical negotiations, and I think that what we——

Mr. LANCE. Which I know you were involved.

Mr. POPS. Is that in PDUFA V, and I think the Commissioner mentioned earlier, there is this patient-centric and more formalized risk-benefit evaluation that we are seeking to implement through PDUFA V. I think we have a long way to go but I think the agency has an interest in bringing more rigor and formalization to the risk-benefit analysis.

Mr. LANCE. Thank you.

Is there anyone else on the panel who would like to comment on that? Very good. Thank you very much.

I yield back the balance of my time, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from New York, Mr. Towns, for 5 minutes for questions.

Mr. TOWNS. Thank you very much, Mr. Chairman.

Let me begin by thanking you, Ms. Dorman, for working with my staff and Mr. Stearns on ULTRA. This bill is still a work in progress, and we look forward to receiving NORD's recommendations for changes to the text as your group has promised my staff within the next few weeks. We look forward to continued work with you on that.

Let me go to you, Mr. Germano. Last year, the FDA approved a Pfizer drug under priority review in 4 months. In your experience, is this common for orphan drug review, and what made this one so exceptional?

Mr. GERMANO. This was—I think you are referring to our drug crizotinib, and the brand name is Xalkori. It is a drug for——

Mr. TOWNS. That is correct.

Mr. GERMANO [continuing]. A specific subset of patients with non-small-cell lung cancer, and in this case, there is a genetic marker to identify patients who are most likely to respond to the medication. So we were able to—once the identification of the genetic marker occurred, we were able to work with our partners at Abbott Laboratories to develop a companion diagnostic and complete a clinical trial that demonstrated, you know, fairly clearly the benefit-risk profile of this medicine for this particular patient population. So it is a great example of the benefit of personalized medicine or precision medicine approach to drug development. You know, the more we are able to do this, you know, the more efficient the development process is, the more efficient the review process is and the more quickly we can get new medicines to patients.

So, you know, I can't say it is commonplace. I think we are all working harder and harder to find, you know, genetic markers and biomarkers of activity, whether it is efficacy or safety signals that we are after to help bring more clarity to the benefit-risk profile of our medicines and make it easier for us to develop them and for the agency to review them.

Mr. TOWNS. Let me just say that I really appreciate Pfizer's strong commitment to finding treatments for rare diseases. To the best of your knowledge, have any of Pfizer's recently offered drug approvals been approved under the accelerated approval pathway at FDA?

Mr. GERMANO. Well, this one that we are speaking of, crizotinib, was approved under the accelerated review process.

Mr. TOWNS. Any others?

Mr. GERMANO. We have another drug for a rare disease, a rare polyneuropathy that we have recently filed with the FDA and we are seeking accelerated review of that product as well.

Mr. TOWNS. Do you have any ideas or suggestions as to how we might be able to improve the accelerated approval process? Do you have any ideas or suggestions that you might want to offer?

Mr. GERMANO. Well, I think that some of the provisions of PDUFA V are likely to be helpful. Again, I think the greater

amount of required interaction between the agency and the sponsor, the focus that the agency will put on, you know, risk-benefit framework, biomarker understanding and, you know, rare and orphan disease issues that are components of the PDUFA V should be helpful in improving our ability to bring these kinds of medicines to the market.

Mr. TOWNS. I want to go to a very quick yes or no question. I am very committed to supporting the FDA in their timely approval of safe, effective treatment options, particularly for rare diseases. For this reason, I am proud to be working with my colleague from Florida, Congressman Stearns, on an initiative that I hope will encourage the development of innovative, safe drugs in this space. The goal is to improve access to the FDA's existing accelerated approval pathway for drugs designed to treat patient with life-threatening rare diseases, and this would be a yes or no. Let me ask you, Mr. Germano, and of course Mr. Pops and Ms. Dorman, do you support this goal?

Mr. GERMANO. To——

Mr. TOWNS. Do you support the goal?

Mr. GERMANO. I am sorry?

Mr. TOWNS. Congressman Stearns and I are working on this initiative that I hope will encourage the development of innovative, safe drugs in this space. The goal is to improve access to FDA's existing accelerated approval pathways for drugs designated to treat patients with life-threatening rare diseases. Do you support that?

Mr. GERMANO. Yes, I would support that.

Mr. TOWNS. OK. Ms. Dorman?

Ms. DORMAN. Yes.

Mr. TOWNS. Thank you very much, and I would note, Mr. Chairman, I don't have anything to yield back, but I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes Mr. Guthrie for 5 minutes for questions.

Mr. GUTHRIE. I think the previous two kind of went down the path I was going to go with Ms. Dorman. I think that we do need to make sure that we have a good accelerated program for people with risk, and I have a friend caught up in another situation, and the argument, I always say this. I have bad allergies. I don't want something put out to keep me from sniffling that is going to have adverse effects to me. But when you have a friend who has Lou Gehrig's disease, or ALS, and there is some opportunities for them to go forward, as long as the patient knows the risk and what could be there, I think that we should have a process for them to go forward. So I agree with Mr. Stearns and Mr. Towns and I would like to work with you on that because I think that is important to do.

On the venture capital, which is more medical devices, I gather, a lot of times they are encouraged to go to Europe just because they get approved. If they get approved in the home country where they manufacture, they also get—I think China recognizes it. So the President talked about manufacturing, which is my background, we are in a situation where we have American manufacturers having to locate in Europe because of our regulatory process, which we are not comparing to a country that doesn't have substantial safety concerns. I mean, we are talking about the Euro-

pean Union that we are not competitive with in our approval process.

But I want to get to Mr. Coukell. On this panel, a lot of people say "as a doctor." I don't get to say that, but as a quality control engineer—that was my background before in manufacturing—Pew has done some research on drug pedigree, and just if you can talk about that and particularly I would like the safety of the supply chain, particularly foreign supply chains dealing with third parties or foreign regulators. I mean, if you could talk about what your research has been in the drug pedigree world?

Mr. COUKELL. Thank you for that question, sir. It is an area that I didn't touch on my testimony, but we looked at as drugs move from the manufacturer through distributors to the pharmacy and ultimately to the patients, what is the pedigree system or the absence of. So if I could share one short story. A couple of years ago, there was a tractor-trailer load of insulin that was stolen in North Carolina and disappeared for a while. Insulin is a drug that should be refrigerated. And then it showed up back in pharmacies of a major chain grocery store in a couple of different States. And between there is passed through a couple of different wholesalers. And so the question is, is there a system by which the pharmacy at the end use could have recognized that as stolen product, flagged it, do we have a system that lets you track the product through the system, do we have a unique serial number on the drugs, and the answer is we don't have that. California has law which is scheduled to come into effect in 2015. Our view is that a national standard would be much more preferable.

Mr. GUTHRIE. What about your looking into ingredients, foreign ingredients and the integrity and dealing with foreign regulators or third parties? I think you looked into that in your report as well. And what are solutions? I mean, you said unique serial numbers. Are there other things like working with foreign regulators or third-party groups?

Mr. COUKELL. So let me make two points that I think are important. One is, a manufacturer absolutely has to have confidence that they know who is in their upstream supply chain and that they know what quality standards are in place and that there isn't a risk of sub standard product coming in through the backdoor and making its way into the supply chain.

Mr. GUTHRIE. Did you find that manufacturers didn't know that or didn't have systems in place for that?

Mr. COUKELL. We absolutely found a whole spectrum, and there are great manufacturers in every country, but there are also risks. In our report, there is a photograph from a manufacturing facility in China with a whole wall of 50-gallon drums stacked up about one deep, and the inspectors went in there and said, you know, what is behind those drums; well, nothing. So they climbed over and found behind the drums a whole warehouse full of uncertified active pharmaceutical ingredient that was destined for, in that case, a European supply chain. So it does occur.

On the question of foreign regulators, I think we acknowledged that the FDA is moving in the right direction on this, which is no one country can inspect the whole world, and so we have to deploy

limited resources in a rational way. We do duplicate inspections and rely on other trusted regulators wherever possible.

Mr. GUTHRIE. In automotive manufacturer, you actually hire people to come in and certify and audit your plant, and Ford or GM or Chrysler would accept that. Using third-party auditors that are reputable, that you can—the trick to it was or the issue was that you actually paid them to come to your plant to certify you to Ford's standard, but they had a reputation to uphold as well, and so——

Mr. COUKELL. Absolutely, and I think Congress did some of that for food in the Food Safety Modernization Act a couple of years ago. You know, one of the real leaders in industry on quality, a vice president of quality for one of the big companies has said every supplier and sub-supplier should be audited by somebody, but at the same time, if there is one company that is making, you know, an inactive ingredient like talc or something for tablets and they are supplying 30 companies, you don't need 30 audits.

Mr. GUTHRIE. Right. Common sense.

Thanks. I yield back.

Mr. PITTS. The chair thanks the gentleman.

That concludes the questioning, and I would like to thank the witnesses and members for participating in today's hearing. We have had a lot of very important information come before the committee, and I remind members that they have 10 business days to submit questions for the record. I will ask the witnesses to please respond promptly to those questions. Members should submit their questions by the close of business on Wednesday, February 15th.

With that, without objection, the subcommittee is adjourned.

[Whereupon, at 2:25 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Opening Statement of the Honorable Marsha Blackburn
Subcommittee on Health
Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients
February 1, 2012

Thank you, Mr. Chairman.

Today marks an important step towards ensuring the current drug user fee program is working as effectively as possible and if not, what changes can be brought about for the FDA to meet its commitment to the drug industry and to our nation's public health needs.

It is important for this committee to use the PDUFA opportunity to examine and improve the FDA regulatory process.

The need for these reforms is two-fold.

First, we must ensure that the companies that invest many years and billions of dollars in bringing life saving products to patients are being provided with both transparency and consistency throughout the FDA review process.

Second, we must ensure the regulatory processes at FDA are conducted with certainty and predictability, thus promoting investments in U.S. based innovations which in turn grow the American economy and help get our constituents back to work.

Far too many jobs have moved overseas because of overregulation. The number one priority at the FDA and all Federal agencies needs to be fostering an environment that promotes US based job creation.

I look forward to working to ensure this is in fact the case.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

SEP 10 2012

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the February 1, 2012, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Reauthorization of PDUFA: What it Means for Jobs, Innovation, and Patients." This letter provides responses for the record to questions posed by certain Members of the Committee, which we received on March 9, 2012.

If you have further questions, please let us know.

Sincerely,

Karen Mistry
for

Jeanne Ireland
Associate Commissioner
for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member

We have restated each Member's questions below in bold, followed by FDA's responses.

The Honorable Joseph R. Pitts

1. **The Committee recognizes that FDA's publication of the July 5, 2011, draft NDI guidance was required by law. However it appears that this draft guidance is inconsistent with the new dietary ingredient notification provisions of the Dietary Supplement Health and Education Act of 1994 (DSHEA). We note that, in response to your July 5, 2011, NDI draft guidance, many stakeholders submitted comments that called on the Agency to withdraw the guidance and work with them to come up with an approach that is consistent with the underlying statute. Would you assure the Committee that FDA will not in any way seek to enforce the requirements of the draft NDI guidance document until it is finalized?**

We appreciate and share your concern that the New Dietary Ingredient (NDI) guidance be consistent with DSHEA. FDA welcomes comments from all parties on the draft guidance and takes seriously the concerns that have been raised. We are currently reviewing comments on the draft guidance and will consider all points of view before issuing a final guidance. We have also met with industry groups over the past few months in order to better understand the issues of concern to them.

We do not regard the draft guidance as establishing or signaling a new enforcement posture on the part of FDA. Guidance documents are not enforceable rules or requirements, and they do not establish or modify the legal basis for enforcement actions. They only indicate FDA's current thinking on the subject, and they are intended to provide information and tools to help industry meet the existing statutory obligation to ensure that dietary supplements containing NDIs are safe.

2. **In order for FDA reviewers to make informed decisions regarding a product's safety and efficacy, it is critical these reviewers are well versed in the latest science and clinical practice of their respective disease areas. Unfortunately, we have heard reports of cases where reviewers, while experienced, and competent in other fields, do not possess the adequate expertise in the clinical area of concern to make these judgments. Please inform the Committee of any efforts to ensure that review staff are up to date in the science and clinical practice of their disease areas of focus.**

It is critical that our reviewers are up to date in their respective disease areas. For example, as part of training and continued education, FDA's Center for Drug Evaluation and Research (CDER) has developed key competencies for all disciplines. CDER scientific disciplines must have the ability to use and apply an understanding of the basic science, methods, processes, and procedures in medical and review disciplines related to the drug review process. They are required to use and apply related knowledge in basic science of clinical practice, clinical pharmacology, chemistry, biochemistry,

pharmacology/toxicology, bioequivalence, and statistics. They must comprehend and evaluate the application of pertinent concepts and knowledge from other disciplines in the review process related to product development.

CDER offers continuous education (CE) opportunities for staff to stay abreast of clinical science through training, CE credit, and professional development. FDA staff consistently seek opportunities to enhance mathematical, scientific, technical, or professional expertise. Examples of internal training programs include ongoing biweekly CDER Seminars, biweekly CDER Scientific Rounds, quarterly Office of New Drugs (OND) Clinical Reviewer Education Program lectures, ongoing OND Pharmacology Toxicology scientific lectures, selected lectures in the FDA Scientific Professional Development series, and ongoing subspecialty training for current clinical topics within review divisions. Externally, review staff attend annual professional subspecialty conferences and are members of professional societies that also provide additional specialized learning in their respective fields. Many clinical review staff also continue to participate in patient clinical care through professional development time permitted through the Agency.

The Center for Devices and Radiological Health (CDRH) has implemented two new training programs designed to improve the consistency of medical device reviews by enhancing the skills of those reviewing premarket applications. The Reviewer Certification Program, which began as a pilot in April 2010 with participants from CDRH's Division of Anesthesia, General Hospital, and Infection Control and Dental Devices, launched in September 2011 and includes all new device reviewers. The program includes up to 18 months of training aimed at complementing the skills and knowledge that new reviewers bring to CDRH from fields such as biomedical engineering and health care. Reviewers in the program will complete online training modules, instructor-led courses, and obtain practical experience in the medical device review process. Courses include medical devices, food and drug law and regulatory requirements, the CDRH review process, device design, and the impact of human factors.

CDRH has also developed a pilot Experiential Learning Program (ELP) for premarket reviewers. The program will include visits to academic institutions, manufacturers, research organizations, and health care facilities and is intended to give reviewers a better understanding of how medical devices are designed, manufactured and used. The program will also help new medical device reviewers understand the challenges of technology development and the impact of medical devices on patient care. The ELP was announced to CDRH staff on April 26, 2012, and orientation for the pilot participants was held on May 1 and is being followed by sessions, prior to each site visit, to prepare staff and supervisors with goals and objectives for that visit. Enhancing staff training is one of the 25 action items listed in FDA's Plan of Action for Implementation of 510(k) and Science Recommendations to increase the predictability and transparency of regulatory pathways and to strengthen the 510(k) process. The 510(k) process is the most common pathway to market for medical devices.

FDA's Center for Biologics Evaluation and Research (CBER) also offers CE opportunities for staff to stay abreast of clinical science through training, CE credit, and professional development. CBER staff consistently seek opportunities to enhance mathematical, scientific, technical, or professional expertise. Examples of internal training programs include CBER Case Seminar, Bone Seminar Series, Division of Viral Products Seminar Series, Clinical Trials Seminar, Office of Biostatistics and Epidemiology Seminar Series, Articular Cartilage Seminar Series, Introductory to Genetic Epidemiology Lecture Series, and CBER Health Information Series. There is also ongoing subspecialty training for current clinical topics within review divisions. Externally, review staff attend annual professional subspecialty conferences and are members of professional societies that also provide additional specialized learning in their respective fields. Many clinical review staff also continue to participate in patient clinical care through professional development time permitted through the Agency. In addition, the Agency has scientific reviewers of regulatory applications, including some physicians, who have active laboratory research programs that keep them current with the latest scientific advances.

3. **With respect to tobacco, FDA is now starting to impose fines for retailers that fail tobacco inspections, but they are imposing multiple fines and alleging multiple violations for a single inspection. That seems to be contrary to the provisions of the law establishing the Center for Tobacco Products, which specifically states that retailers must be informed of all previous violations before being charged with another violation. Can you explain how FDA imposing multiple fines for a single inspection is consistent with the law?**

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) provides that a person "may not be charged with a violation at a particular retail outlet unless the Secretary has provided notice to the retailer of all previous violations at that outlet" (section 103(q)(1)(D)). The language in this provision refers to "violations," not to "inspections." FDA has interpreted this to mean that each violation is a separate finable offense, even if several violations are observed within one inspection. We do not interpret the requirement to provide notice of "previous" violations as implying a restriction on charging contemporaneous violations.

That being said, the Tobacco Control Act requires that FDA provide "timely and effective notice by certified or registered mail or personal delivery to the retailer of each alleged violation at a particular retail outlet *prior to conducting a follow-up compliance check...*" (section 103(q)(1)(B)). Following is a description of how FDA complies with this requirement. FDA has contracted with states and U.S. territories to conduct tobacco compliance check inspections of retailers that sell or advertise regulated tobacco products to determine whether those retailers are complying with the Tobacco Control Act and its implementing regulations. Inspectors working under these contracts are commissioned by FDA to conduct such activities on the Agency's behalf. After each inspection is conducted, the commissioned inspector submits observations and inspection results to FDA. FDA then takes appropriate regulatory actions based on its review of the inspection data and evidence. Although FDA is not required to issue a Warning Letter

before taking further regulatory action, the first time FDA identifies violation(s) at a retail outlet, we generally issue a Warning Letter that describes each violation. FDA then issues an assignment to a commissioned inspector to conduct follow-up inspections of this retail establishment. Subsequent violations may result in FDA issuing a complaint seeking civil money penalties. Thus, violations documented during initial inspections by FDA-commissioned inspectors are communicated to retailers via an FDA Warning Letter (not a fine). It is only violations documented during subsequent inspections that have precipitated complaints seeking civil money penalties.

4. **Where is the FDA in the process of updating and finalizing FDA's 2007 draft guidance for obesity drugs? Please provide information on when this guidance will be updated and finalized.**

FDA is working with stakeholders, such as patient and physician groups, to explore the complex issues related to development and approval of drugs to treat obesity. These interactions include an FDA public advisory committee meeting that was held March 28 and 29, 2012, and participation in a series of roundtable meetings spearheaded by George Washington University (GWU) that includes key players in the obesity community. FDA is participating in the GWU-led discussions as an observer, and we will be participating in several roundtable meetings in 2012. These meetings provide a forum to discuss clinical trial designs, endpoints, and indications for drugs to treat obesity. Both the public advisory committee meeting and the GWU effort are important steps for FDA as we continue the process of developing guidance for obesity drugs.

5. **The draft menu labeling regulation issued by FDA require calorie labeling based on the total calorie count of the menu item, not the portion of the menu item that customers are accustomed to consuming. For example, it appears that FDA is insisting that pizza be labeled by the whole pie, not by calories per slice. Yet, most consumers eat a few pizza slices, not the entire pizza. Would it be better to give restaurants flexibility in posting calorie counts, especially for items like pizza?**

In the proposed rule, FDA tentatively concluded that a "standard menu item" means a restaurant or restaurant-type food that is routinely included on a menu or menu board or routinely offered as a self-service food or food on display, regardless of how many servings are included in the item. Consequently, under the proposed rule, if a multi-serving item such as a pizza is listed on the menu or menu board, then it is a standard menu item and calorie information would be disclosed for the entire pizza. In contrast, if the standard menu item is a slice of pizza, the calorie information would be presented for the slice. FDA requested comment on this tentative conclusion and proposed definition, and we are considering the comments we have received carefully before promulgating a final rule.

The Honorable Mike Rogers

1. **The Family Smoking Prevention and Tobacco Control Act called for user fees to fund the Center for Tobacco Products at FDA. What kind of information can you provide regarding the user fee funds spent at FDA on tobacco-related activities? For example, as part of PDUFA, the FDA puts out financial and performance reports that show how the FDA spends user fee money.**

   a. **Does the FDA put out a report on how it spends the tobacco user fee money?**
   b. **Is this a statutory requirement?**
   c. **Should the Agency put out such a report?**

The Tobacco Control Act required FDA to produce a quarterly report to the House and Senate Appropriations Committees through FY 2010. FDA submitted each of those quarterly reports to those Committees. There is no statutory requirement to issue a report on FDA use of tobacco user fees similar to requirements for reporting on PDUFA or any of FDA's other user fees. FDA intends to publish an annual tobacco user fees report with financial information related to its use of the tobacco user fees, including collection rates, arrears, and obligations beginning in the first quarter of fiscal year 2013.

2. **Under the Family Smoking Prevention and Tobacco Control Act, how many substantial equivalent applications have been filed since March 23, 2011?**

   a. **Has the Agency acted on any of these? If not, why?**
   b. **Has the Agency announced a time frame in which it will provide a final Agency response to a submitter?**

Between March 23, 2011, and July 1, 2012, FDA received 390 substantial equivalence reports.

As general background, on January 5, 2011, FDA published a final guidance on substantial equivalence entitled "Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products (*www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf*)." This guidance provides recommendations and information related to the submission and review of substantial equivalence reports. In addition, the Agency published a draft guidance entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions" in September 2011. This draft guidance, when finalized, will represent FDA's current thinking on this topic (*www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM271242.htm*). In these documents, FDA describes the information needed for the Agency to make a determination of substantial equivalence.

As of July 1, 2012, FDA has carried out a jurisdictional review on 338 of the 390 substantial equivalence reports received since March 23, 2011, and provided information to the manufacturers about whether their product falls under the current jurisdictional authority of the Center for Tobacco Products (CTP). As of July 1, 2012, FDA has performed an initial "Completeness Review" on 133 substantial equivalence reports received since March 23, 2011. As of July 1, 2012, FDA has sent "Advice and Information" letters to all 133 of those parties who have submitted reports, which have been reviewed for completeness. These letters ask that the parties either provide clarification about their report or submit the missing information to facilitate FDA's review of the substantial equivalence reports. As of July 1, 2012, FDA has received responses from 130 of the advice and information letters and is proceeding with its substantial equivalence evaluation on these reports.

FDA is developing final policies and procedures about the time frame for responding to substantial equivalence reports. Submission of substantial equivalence reports for tobacco products is new to both FDA and tobacco product manufacturers. The optimal time it might take for various tobacco manufacturers to develop substantial equivalence reports for tobacco products and respond to FDA requests for additional information is not yet known. Thus, FDA will base final policies on this experience.

3. **How many tobacco ingredient substantial equivalent exemption requests have been filed since July 5, 2011? How many has the Agency acted upon?**

FDA published a final rule entitled "Tobacco Products, Exemptions from Substantial Equivalence Requirements" on July 5, 2011. In this document the Agency describes the procedures for submitting a product for exemption from substantial equivalence requirements. As of July 2012, FDA has received 22 substantial equivalence exemption requests, and is in the process of reviewing all of the requests.

4. **Outside of FDA-initiated contacts, how many requests for meetings have been submitted by tobacco manufacturers to the Center for Tobacco Products and how many meetings has it granted?**

As of July 1, 2012, FDA has received 78 requests for meetings from tobacco manufacturers or related trade associations and CTP has granted 59 of the requests. One meeting request was cancelled by the manufacturer.

In addition, CTP has initiated meetings with the tobacco industry. Specifically, CTP has:

- Met seven times with either individual manufacturers or multiple manufacturers on the general science of smoked and smokeless tobacco products;
- Met three times with individual manufacturers on science related to dissolvable tobacco products;
- Met three times with individual manufacturers on science related to e-cigarettes;
- Conducted in December 2011, six manufacturing site visits at the invitation of

industry to learn more about the manufacturing, marketing, and distribution of tobacco products. Several more educational site visits are planned this year; and

- Sponsored two specific stakeholder discussion meetings for industry. The first was held with large and small tobacco manufacturers and growers in December 2010 and was attended by more than 30 industry leaders. The second was conducted in August 2011 with tobacco distributors, wholesalers, importers, and retailers.

Also, at the request of the Tobacco Manufacturers Association, CTP leadership has presented at the last three annual meetings in 2010, 2011, and 2012.

5. **How many meetings have been requested by third-party smoking cessation groups and how many of those requests for meetings have been granted by the Center for Tobacco Products?**

As of July 2012, FDA has received 31 requests from third-party smoking cessation or similar groups and granted 26 meetings. In addition, CTP sponsored a stakeholder discussion meeting for public health and medical associations in April 2011, which was attended by 13 organizations.

6. **With respect to the Tobacco Control Act, FDA is now starting to impose fines for retailers that fail inspections, but they are imposing multiple fines and alleging multiple violations for a single inspection. That seems to be contrary to the provisions of the law establishing the Center for Tobacco Products, which specifically states that retailers must be informed of all previous violations before being charged with another violation. Can you explain how FDA imposing multiple fines for a single inspection is consistent with the law?**

The Tobacco Control Act provides that a person "may not be charged with a violation at a particular retail outlet unless the Secretary has provided notice to the retailer of all previous violations at that outlet" (section 103(q)(1)(D)). The language in this provision refers to "violations," not to "inspections." FDA has interpreted this to mean that each violation is a separate finable offense, even if several violations are observed within one inspection. We do not interpret the requirement to provide notice of "previous" violations as implying a restriction on charging contemporaneous violations.

That being said, the Tobacco Control Act requires that FDA provide "timely and effective notice by certified or registered mail or personal delivery to the retailer of each alleged violation at a particular retail outlet *prior to conducting a follow-up compliance check...*" (section 103(q)(1)(B)). Following is a description of how FDA complies with this requirement. FDA has contracted with states and U.S. territories to conduct tobacco compliance check inspections of retailers that sell or advertise regulated tobacco products to determine whether those retailers are complying with the Tobacco Control Act and its implementing regulations. Inspectors working under these contracts are commissioned

by FDA to conduct such activities on the Agency's behalf. After each inspection is conducted, the commissioned inspector submits observations and inspection results to FDA. FDA then takes appropriate regulatory actions based on its review of the inspection data and evidence. Although FDA is not required to issue a Warning Letter before taking further regulatory action, the first time FDA identifies violation(s) at a retail outlet, we generally issue a Warning Letter that describes each violation. FDA then issues an assignment to a commissioned inspector to conduct follow-up inspections of this retail establishment. Subsequent violations may result in FDA issuing a complaint seeking civil money penalties. Thus, violations documented during initial inspections by FDA-commissioned inspectors are communicated to retailers via an FDA Warning Letter (not a fine). It is only violations documented during subsequent inspections that have precipitated complaints seeking civil money penalties.

The Honorable Marsha Blackburn

1. **How many substantial equivalent applications have been filed since March 23, 2011? Has the Agency acted on any of these? Why not?**

Between March 23, 2011, and July 1, 2012, FDA received 390 substantial equivalence reports.

As general background, on January 5, 2011, FDA published a final guidance on substantial equivalence entitled "Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products (*www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf*)." This guidance provides recommendations and information related to the submission and review of substantial equivalence reports. In addition, the Agency published a draft guidance entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions" in September 2011. This draft guidance, when finalized, will represent FDA's current thinking on this topic (*www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM271242.htm*). In these documents, FDA describes the information needed for the Agency to make a determination of substantial equivalence. In these documents, FDA describes the information needed for the Agency to make a determination of substantial equivalence.

As of July 1, 2012, FDA has carried out a jurisdictional review on 338 of the 390 substantial equivalence reports received since March 23, 2011, and provided information to the manufacturers about whether their product falls under the current jurisdictional authority of the Center for Tobacco Products (CTP). As of July 1, 2012, FDA has performed an initial "Completeness Review" on 133 substantial equivalence reports received since March 23, 2011. As of July 1, 2012, FDA has sent "Advice and Information" letters to all 133 of those parties who have submitted reports, which have been reviewed for completeness. These letters ask that the parties either provide clarification about their report or submit the missing information to facilitate FDA's review of the substantial equivalence reports. As of July 1, 2012, FDA has received

responses from 130 of the advice and information letters and is proceeding with its substantial equivalence evaluation on these reports.

2. Has the Agency announced a time frame in which it will provide a final Agency response to a submitter?

FDA is developing final policies and procedures about the time frame for responding to substantial equivalence reports. Submission of substantial equivalence reports is new to both FDA and tobacco product manufacturers. The optimal time it might take for various tobacco manufacturers to develop substantial equivalence reports for tobacco products and respond to FDA requests for additional information is not yet known. Thus, FDA will base final policies on this experience.

3. How many tobacco ingredient substantial equivalent exemption requests have been filed since July 5, 2011? How many has the agency acted upon?

FDA published a final rule entitled "Tobacco Products, Exemptions from Substantial Equivalence Requirements" on July 5, 2011. In this document the Agency describes the procedures for submitting a request for exemption from substantial equivalence requirements. As of July 2012, FDA has received 22 substantial equivalence exemption requests, and is in the process of reviewing all of the requests.

4. Outside of FDA-initiated contacts, how many requests for meetings have been submitted by tobacco manufacturers to the Center for Tobacco Products and how many meetings has it granted?

As of July 1, 2012, FDA has received 78 requests for meetings from tobacco manufacturers or related trade associations and CTP has granted 59 of the requests. One meeting request was cancelled by the manufacturer.

In addition, CTP has initiated meetings with the tobacco industry. Specifically, CTP has:

- Met seven times with either individual manufacturers or multiple manufacturers on the general science of smoked and smokeless tobacco products;
- Met three times with individual manufacturers on science related to dissolvable tobacco products;
- Met three times with individual manufacturers on science related to e-cigarettes;
- Conducted in December 2011, six manufacturing site visits at the invitation of industry to learn more about the manufacturing, marketing, and distribution of tobacco products. Several more educational site visits are planned this year; and
- Sponsored two specific stakeholder discussion meetings for industry. The first was held with large and small tobacco manufacturers and growers in December 2010 and was attended by more than 30 industry leaders. The second was conducted in August 2011 with tobacco distributors, wholesalers, importers, and retailers.

Also, at the request of the Tobacco Manufacturers Association, CTP leadership has presented at the last three annual meetings in 2010, 2011, and 2012.

5. **How many meetings have been requested by third-party smoking cessation groups and how many of those requests for meetings have been granted by the Center for Tobacco Products?**

As of July 2012, FDA has received 31 requests from third-party smoking cessation or similar groups and granted 26 meetings. In addition, CTP sponsored a stakeholder discussion meeting for public health and medical associations in April 2011, which was attended by 13 organizations.

6. **As I mentioned earlier, Section 919 of the Family Smoking Prevention and Tobacco Control Act requires manufacturers and importers of tobacco products to pay user fees. Are you aware of any companies that have registered as establishments with the FDA that have not paid user fees?**

The Tobacco Control Act did not give FDA authority to collect user fees for all types of tobacco products immediately upon enactment, so there are some registered establishments that have not paid user fees because the types of products they produce are not currently subject to assessment by FDA. However, as of August 9, 2012, there were 27 registered establishments that were in arrears to FDA for either all or part of the user fees that they owe. Overall, the collection rate of tobacco user fees has been 99.4 percent of fees billed.

7. **Are you aware of the current phenomena involving retail establishments selling consumers pipe tobacco that has been dried out for use by the consumer to convert this pipe tobacco into a cigarette through the use of a roll-your-own machine? Would you agree that tobacco sold by a retailer for the intended purpose of manufacturing a cigarette makes the tobacco cigarette tobacco the resulting product a cigarette? And if that is the case, doesn't that require the retail establishment to register the store as a manufacturer establishment under the Act?**

FDA is aware of retail establishments selling consumers pipe tobacco for use in roll-your-own cigarette machines and is gathering more information about this practice to determine the appropriate regulatory response.

8. **Community pharmacists have long felt that there exist certain prescription drugs that could be placed in a limited "class" and that could be dispensed to a patient pursuant to or following a one-on-one consultation with a pharmacist. What is the FDA's opinion on the feasibility or likelihood of the creation of this type of limited drug "class"?**

FDA is exploring a potential new paradigm under which the Agency would approve certain drugs that would otherwise require a prescription for nonprescription use (also

known as over-the-counter or OTC) under conditions of safe use specific to the drug product. These conditions of safe use would be specific to the drug product and might require sale in certain pre-defined health care settings, such as a pharmacy. FDA held a public hearing on March 22-23, 2012, "Utilizing Innovative Technologies and Other conditions of Safe Use to Expand Access to Nonprescription Drugs," to obtain information and comments from the public on the feasibility of this paradigm and its potential benefits and costs. For information regarding this meeting, including slide presentations and transcripts, please see: *www.fda.gov/Drugs/NewsEvents/ucm289290.htm.*

9. **Community pharmacists have a long history of advocating for the simplification of the written materials that currently are required to be distributed to the patient with each prescription. What is the current status of moving towards a "one-document solution" to address this issue?**

FDA welcomes community pharmacists' support of our efforts to simplify written materials given to patients with their prescription medications. We are developing a new framework, Patient Medication Information (PMI), to provide accurate and balanced medication information that is delivered in one consistent and easily understood format. Currently, patients may receive information about their prescriptions in a variety of formats, each with different content requirements or standards, including Patient Package Inserts (PPI) and Medication Guides (MG), which are required for certain products, and/or Consumer Medication Information (CMI), which pharmacies voluntarily dispense with prescriptions. FDA has determined that this current approach is not adequate to ensure that patients receive the essential information needed to use a drug safely. FDA is considering how to ensure that patients receive accurate and balanced PMI in a consistent and easily understood format. Among other things, FDA is considering developing content and format standards for PMI, a range of distribution and information accessibility mechanisms, and methods to ensure that PMI for each product is useful and comprehensible (e.g., consumer testing).

Currently, FDA is testing prototypes with consumers and is conducting ongoing stakeholder meetings to help FDA determine the appropriate regulatory path forward. FDA anticipates that two studies will be completed in late 2012 or 2013: an ongoing FDA study (75 FR 23775, May 4, 2010) and a study being performed under a cooperative agreement with the Engelberg Center for Health Care Reform at the Brookings Institution (currently in the design phase). Stakeholder discussions will also continue as FDA considers how best to accomplish its goal of ensuring that patients receive accurate and balanced information about their prescription medications, in an easily understood format.

The Honorable Brett Guthrie

1. **Why has FDA not approved a single tobacco product submission since the creation of the Center for Tobacco Products was created?**

As general background, on January 5, 2011, FDA published a final guidance on substantial equivalence entitled "Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products (*www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf*)." This guidance provides recommendations and information related to the submission and review of substantial equivalence reports. In addition, the Agency published a draft guidance entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions" in September 2011. This draft guidance, when finalized, will represent FDA's current thinking on this topic (*www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM271242.htm*). In these documents, FDA describes the information needed for the Agency to make a determination of substantial equivalence.

FDA received 3,126 provisional substantial equivalence reports before March 23, 2011. Products for which a substantial equivalence report was received before March 23, 2011, can remain on the market unless FDA finds that they are "*not* substantially equivalent." Additionally, between March 23, 2011 and July 1, 2012, FDA received 390 substantial equivalence reports. Those products cannot be marketed unless and until FDA issues a finding of substantial equivalence. The Agency has received seven modified-risk tobacco product applications.

See response to Question 2 below for discussion of the status of CTP's response to these submissions.

2. Please outline the specific backlog of submissions that have not been evaluated and how CTP is planning to address this backlog.

As you are aware, premarket review and marketing authorization of tobacco products is a new area for FDA. Given the enormous public health impact of tobacco products, there are critical scientific questions that must be answered and review decisions that must be made so that an effective, careful, and consistent review process is created and implemented. To date, FDA has taken a number of actions related to its review of substantial equivalence (SE) reports for tobacco products.

FDA has published several rules and guidance documents to assist industry and the public in understanding and responding to the requirements of the Tobacco Control Act. For example:

- In January 2011, FDA issued a final guidance on SE entitled "Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products". This guidance provided recommendations and information related to the submission and review of SE reports. The guidance is available at *http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm253273.htm.*

- In July 2011, FDA issued a final rule entitled "Tobacco Products, Exemptions from SE Requirements" (*http://www.gpo.gov/fdsys/pkg/FR-2011-07-05/pdf/2011-16766.pdf*). This rule described the procedures for submitting a request for exemption from SE requirements.

- In September 2011, FDA issued a draft guidance entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions" (*http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm271242.htm*).

FDA is working diligently to provide as much information and feedback as possible to affected parties because this is a new process and many of the companies are unfamiliar with FDA and product regulation. CTP is also interested in hearing and understanding industry concerns and has been very active in meeting with manufacturers to discuss a variety of issues. As of July 1, 2012, CTP has received 78 requests for meetings from tobacco manufacturers or related trade associations, and CTP has granted 59 of the requests. Additionally, we also have developed public webinars to explain our processes and describe the kind of information the Agency needs tobacco manufacturers to submit.

In response to industry feedback, where possible, FDA is trying to streamline the SE report review process:

- FDA has increased opportunities for communication with industry by encouraging teleconferences between the assigned regulatory project manager and the applicant. We have also taken steps to facilitate quicker responses to questions.

- FDA is taking industry concerns into account and has streamlined the SE report review process by modifying the preliminary review so that it focuses only on administrative issues (allowing submission deficiencies to get back to the applicant more quickly).

FDA has taken other actions based on industry feedback and questions including modifying the wording in our Advice and Information Request letters and informing submitters of potential contact by the Office of Compliance and Enforcement in our acknowledgement letters.

SE reports received before March 23, 2011, are considered "provisional," and the products covered by those reports can remain on the market unless FDA finds that they are "*not* substantially equivalent." FDA received 3,126 provisional SE reports before March 23, 2011. SE reports received on March 23, 2011, or after are "regular" reports, and products covered by those reports cannot be marketed unless FDA first issues a finding of SE. Between March 23, 2011, and July 1, 2012, FDA received 390 regular SE reports.

As of July 1, 2012, FDA has completed the following steps in its review of these SE reports:

- Completed jurisdictional reviews for 3,464 of the reports (including 338 of the 390 regular SE reports), with notifications made to the submitters about whether or not their product is currently being regulated by the Center for Tobacco Products (CTP);
- Performed an initial "Completeness Review" on 133 of the regular SE reports;
- Sent 133 "Advice and Information Request" administrative and/or scientific completeness review letters to submitters whose reports were missing information; and
- Received and processed 130 responses to the "Advice and Information Request" letters and is proceeding with the scientific evaluation of the supplemented SE reports.

3. **How many Full Time Equivalents (FTEs) are dedicated to product submissions at CTP?**

As of July 1, 2012, CTP has 98 staff members who had some specified duties that include the review of tobacco product submissions, development of review process, or support for the review process.

4. **HHS has hundreds of millions of dollars in the Prevention and Public Health Fund established in the Patient Protection and Affordable Care Act. A February 9, 2011, press release from HHS announced that a $750 million "investment in prevention," which includes $298 million for Community Prevention to, among other things, prevent and reduce tobacco use. How does FDA ensure that activities at CTP funded by user fees are not duplicating or at cross purposes with these efforts by HHS?**

The Tobacco Control Act authorizes FDA to collect quarterly fees from the tobacco industry. These fees are to be "*available only for the purposes of paying the costs of the activities of the Food and Drug Administration (FDA) related to the regulation of tobacco products....*" (section 919(c)(2)(A) of the Act)). Furthermore, the Act specifies that these tobacco user fees "*are the only funds authorized to be made available for tobacco regulation activities*" (section 919(c)(2)(B)(i)).

FDA has put a comprehensive financial stewardship and accounting plan in place to ensure that tobacco user fees are appropriately used. While many agencies and offices in the Department of Health and Human Services (HHS), including FDA, are working together to address the significant public health concerns created by the use of tobacco products, the Agency does not provide cessation services or engage in community-based

tobacco prevention activities that are funded by the Prevention and Wellness Fund section of the American Recovery and Reinvestment Act of 2009, or the Prevention and Public Health Fund authorized by the Affordable Care Act. FDA works closely with other HHS components to ensure that the various tobacco programs are coordinated and are not duplicative. For example, the Centers for Disease Control and Prevention's (CDC) Tobacco Information and Prevention Source (TIPS) communication campaign targets entrenched smokers (primary target is adult smokers 18-54) and focuses on the long-term chronic health effects to encourage cessation. Using its authorities under the Tobacco Control Act, FDA's public education efforts will educate teen and young adult consumers about the harms of tobacco products and the dangers of their use to decrease youth initiation.

The Honorable Brian P. Bilbray

1. **Dr. Hamburg, did you know that California is the only state in the United States that still requires both a state inspection as well as an FDA inspection for their life science facilities. What do you think of having FDA be the sole authority over facility inspections? Do you think this will save money and time?**

The California Department of Public Health Food and Drug Branch (CDPH FDB) conducts periodic licensing inspections of drug and device facilities, which are required by California state law. FDA conducts both pre-approval and post-approval inspections of drug and device establishments. The state of California pre-licensing inspection is not equivalent to FDA's pre-approval inspections. CDPH FDB and FDA meet on a semi-annual basis to share information about the drug and device manufacturing facilities that are subject to both CDPH FDB and FDA jurisdiction inventory. FDA and CDPH FDB also conduct joint inspections of drug and device firms. These joint inspections are a conscious effort to increase uniformity between federal and state agencies and provide training.

FDA collaborates with our counterpart authorities at the state level, as we do with other regulatory agencies, when doing so reduces unnecessary duplication of effort. There are some drug manufacturing facilities, like medical gas transfilling operations, that FDA is not able to inspect as frequently as other types of facilities. Relying on state inspection information has at times proven helpful to FDA in establishing our inspection priorities. FDA has also relied upon states to administratively embargo violative drugs while we pursued court action. If states cease to maintain the capacity to inspect and license facilities also under federal jurisdiction, FDA may not be able to collaborate, when efficient to do so.

2. **Are you aware/familiar with any areas where CA Food and Drug Branch (FDB) inspections look at issues that FDA does not? Are you aware of FDB identifying issues that FDA missed?**

The state of California inspects under its own authority to ensure compliance with its state laws. Also, the state of California performs food inspections under contract with FDA and is required to report violations encountered when performing work under this contract. The state of California does not perform human drug product inspections for FDA.

3. **With several products on the market and hundreds of clinical trials underway, many observers believe that regenerative medicine holds the promise of transforming treatment for diseases such as stroke, heart disease, diabetes, various cancers and spinal cord injury. Do you agree?**

Cell-based therapies show great promise for repairing, replacing, restoring, or regenerating damaged cells, tissues, and organs. The Agency recognizes that regenerative medicine products are novel and very complex and supports the development of these new innovative products. We encourage and work with sponsors to facilitate the development of safe and effective products.

Currently, FDA oversees over 500 investigational applications for regenerative medicine products that include clinical trials designed to treat serious diseases such as heart diseases, diabetes, cancer, and spinal cord injuries.

4. **In your view, what are the obstacles to faster commercialization of regenerative medicine and cell therapy products? What specific steps can the FDA take to facilitate commercialization of these products?**

Novel biological products containing living cells and tissues show great promise for use as therapies, but design, manufacture, and testing of these products have proven to be very challenging. FDA understands that the development of these novel and very complex products is an iterative process, and this is why FDA works closely with sponsors/innovators to close the science gaps and address any potential challenges.

One challenge to successfully developing cellular therapies has been the uncertainty about how to test these products to ensure that they are safe and effective. Testing will need to focus on safety to ensure the products are free from bacterial contamination and infectious agents, as well as on cellular characteristics, such as differentiation of immature cells (such as stem cells) to mature cell types, because both have the potential to affect the safety and effectiveness of these novel products.

Another challenge is ensuring that the cells manufactured outside of their natural environment in the human body do not become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue.

In response to these and many other challenges, FDA interacts with individual sponsors multiple times prior to, and following, submission of regulatory files, such as Investigational New Drug (IND) applications and Investigational Device Exemption

(IDE) applications, to discuss how to develop the data needed to support premarket notifications (510(k)s), premarket approval (PMA) applications, and biologics license applications (BLA) in order to market these products.

FDA also has active discussions with regenerative medicine stakeholder organizations to enable the Agency to recognize opportunities for the development of guidance, standards, or other tools needed to support product development in this area. FDA works with the clinical, research, academic, industry, and standards communities in various ways to ensure that there is useful and ongoing communications about issues related to the development of regenerative medicine products. When FDA has gained enough experience through their review process in a particular area, the Agency works in tandem with outside organizations to develop consensus standards. Additionally, FDA labs work on mission-related regulatory science research in cross-cutting areas. These research efforts support FDA's regulation of these novel products and can be useful to private and government entities as they develop their products. In this novel product area, the development of cross-cutting evaluation or development tools (for example, test methods that can be used for cell/scaffold characterization in many products) support product development. FDA's research is published in scientific and medical journals and presented at scientific meetings so that this information is available to all sponsors.

FDA has published several guidance documents to help sponsors develop their products. These guidances can be accessed through FDA's website at *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.*

5. **In 2006, the U.S. Department of Health and Human Services issued a report saying that it was essential to establish a cross-agency council to develop a set of coordinated federal research and regulatory policies on regenerative medicine products. Do you agree with this recommendation?**

As discussed below in response to Question 6, FDA participates in an established and effective cross-agency working group, the Multi-Agency Tissue Engineering Science (MATES). FDA's Center for Biologics Evaluation and Research (CBER) is the lead for coordination of FDA activities in this area, including providing leadership in review policy as well as in coordination with our international regulatory counterparts.

6. **How can key federal agencies such as FDA, NIH, DOD and others better collaborate to develop a coordinated national strategy to support regenerative medicine?**

The established and effective cross-agency working group, MATES, member agencies include the HHS agencies involved in the area: FDA; National Institutes of Health (NIH); Centers for Medicare & Medicaid Services (CMS); Department of Defense (DoD) agencies: Defense Advanced Research Projects Agency (DARPA), Army Medical Research and Material Command (MRMC), Navy/Navy Research Lab (NRL), Department of Veteran Affairs; Department of Commerce (National Institute of

Standards and Technology (NIST), Department of Energy; National Aeronautics and Space Administration (NASA); U.S. Environmental Protection Agency (EPA); and the National Science Foundation (NSF).

MATES facilitates communications, enhances cooperation among agencies, monitors technology in the field, fosters technology transfer and translation, and promotes formulation and use of standards. Current project highlights are an active interface with the National Nanotechnology Initiative, and a MATES Workshop, co-sponsored by NIH and NSF, on "Imaging in Tissue Engineering," held at NIST in May 2012. Agencies participate on specific cooperative MATES projects, according to their specific agency missions and capabilities, and also participate in additional cross-agency efforts as missions align. For example, FDA and NIH are in the midst of a series of workshops on "stem cells in translation" to advance translation of products from bench to bedside. Additionally, FDA and NIH participate, as their individual mandates allow, in the Armed Forces Institute of Regenerative Medicine efforts (which, as a DoD-led project, is a MATES member). MATES published a Multi-Agency Strategic Plan for advancing this field that incorporates overarching scientific goals and strategic priorities for federal agencies. The plan can be accessed at *http://www.tissueengineering.gov/*.

In addition to working with all of our partners noted above, such as NIH, the Health Resources and Services Administration (HRSA), DoD, and NIST, FDA also works with a number of other organizations that are not federal agencies, such as:

- ASTM International (formerly known as the American Society for Testing and Materials and the International Standards Organization (ISO));
- California Institute for Regenerative Medicine (CIRM);
- International Society of Cellular Therapies (ISCT);
- Alliance for Regenerative Medicine (ARM); and
- American Society of Gene & Cell Therapy (ASGCT).

Joint efforts by FDA and NIH on regenerative medicine have resulted in three recent workshops: the NIH/FDA Workshop, "Pluripotent stem cells in Translation: Early Decisions" (March 2011) and the Production Assistance for Cellular Therapies (PACT)/National Heart, Lung, and Blood Institute (NHLBI) Workshop, "Cell Therapy for Pediatric Diseases—A Growing Frontier" (September 2011), and a third workshop with NIH, "Pluripotent Stem cells in Translation: Preclinical Considerations."

FDA staff are members and co-chairs of a variety of NIH scientific interest groups that sponsor seminars on regenerative medicine topics, e.g., the FDA/NHLBI interagency group that meets to share information on cell, gene therapy, and regenerative medicine products relevant to studies funded by NHLBI. FDA is also a participant in the NHLBI Centers for Accelerated Innovation Program. The focus of this initiative is to establish centers that will address problems that hinder the critical steps necessary to translate novel scientific advances and discoveries, such as regenerative medicine, into commercially viable therapeutics. FDA representatives also participate on the NIH Center for Regenerative Medicine (CRM) Advisory Council. NIH serves as a resource

for the scientific community in translating advances in stem cell and progenitor cell-based technologies to the clinic. One function of the CRM will be to provide services as a repository for human stem cell line. CRM is within the NIH Intramural Research Program. FDA also serves as an Ex-officio member on the NIH Recombinant DNA Advisory Committee (RAC). The RAC discusses in a public forum gene therapy clinical protocols. FDA staff provides NIH/RAC with Agency perspective and clarifies FDA policy.

FDA/CBER also has strategic goals to improve global public health through international collaboration. The International Program at CBER uses a range of mechanisms to achieve its strategic goals: regulatory harmonization, information sharing, international standards development, regulatory capacity building, and regulatory science collaborations. CBER is focused on international activities and standards development as they relate to cellular therapy products, gene therapy products, and tissue engineering products.

7. **FDA recently issued a report on regulatory science research. Please describe specific regulatory science initiatives that would support development and approval of regenerative medicine products.**

FDA has published two reports to address how initiatives in regulatory science will support development and approval of new treatments and interventions, including regenerative medicine products. The 2010 report, "Advancing Regulatory Science for Public Health: A Framework for FDA's Regulatory Science Initiatives," explains how FDA's new Regulatory Science Initiative can speed progress in FDA's high-priority public health areas. The initiative will be characterized by a four-part framework:

- Leadership, coordination, strategic planning, and transparency to support science and innovation
- Support for mission-critical applied research, both at FDA and collaboratively
- Support for scientific excellence, professional development, and a learning organization
- Recruitment and retention of outstanding scientists

To that end, most of the FY 2011 resources were used to mobilize external collaborations and partnerships and support studies in four major regulatory science research areas:

1. Transforming Product Development for Patients: Bringing Progress to Patients (e.g., Methods for Modernizing Toxicology, Biomarkers for Personalized Medicine, the Stem Cell Initiative and Updating Drug Review Standards)
2. Science to Address Emerging Technologies in FDA-regulated Products (e.g., Nanotechnology and Expertise to Regulate New Animal Biotech Products)
3. Information Sciences for Health Outcomes (e.g., Medical Device Registry and Scientific Computing for Data Analyses)
4. Addressing Unmet Public Health Needs (e.g., Nutrition and Public Health)

In addition, the 2011 report, "Advancing Regulatory Science at FDA: A Strategic Plan," identifies eight priority areas of regulatory science to which FDA will apply resources to fulfill its public health and regulatory mission. The priority areas are:

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-focused Food Safety System to Protect Public Health
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

8. Are there regulatory science research initiatives that could address some of the scientific obstacles to product approval in regenerative medicine?

As noted in the response to Question 4, development and approval of regenerative medicine products is challenging in part due to the uncertainty about the safety and efficacy of regenerative medicine products and the unknown, potentially adverse effects of cells manufactured outside the human body. To expand its knowledge of these issues, FDA conducts a variety of research programs. For example, FDA is engaged in the following ongoing research efforts:

1. Ensuring safety and efficacy of stem-cell-based products
2. Developing ways to measure safety and efficacy of tissue-engineered products
3. Predicting the safety and efficacy of cell and tissue products used for repair of damaged tissue and structures through cell growth and maturation pathways
4. Developing predictive indicators of cell maturation as measures of cell therapy product safety and efficacy
5. Developing new methods to evaluate measurable stem cells using a variety of analytic methods that correlate measurable cell characteristics with a desired result (such as repair of blocked blood vessels) and undesirable (toxic) effects

The Honorable Bill Cassidy

1. Can inspectors as part of their union contracts refuse to inspect overseas?

The provisions in the Collective Bargaining Agreement related to foreign inspections are not a hindrance to our ability to conduct these inspections. We have procedures in place, agreed to by the union, for managing our foreign inspection program. For example, although the union agreement states that we must seek volunteers before directing

assignments, we may and have directed individuals when there are no volunteers for an assignment. Our procedures are working and we continue to increase the number of foreign inspections we conduct each year.

The Honorable Edolphus Towns

1. **Many tobacco retailers operate on Native American reservations. Can you tell me how many inspections of retail facilities have occurred on reservations?**

To date, there have been no inspections of retailers on "Indian country." FDA is working to develop a contracting mechanism for Indian tribes and/or tribal organizations to conduct inspections, similar to the state contract mechanisms that have been used to date for 37 states and the District of Columbia. CTP is currently reaching out to tribes and Native American organizations through meetings and discussions to learn about the tribes, their government, and laws in an effort to develop a working relationship with them to continue to expand our compliance program. The goal is to begin awarding contracts to tribes in FY 2013 to conduct inspections of retail establishments on tribal land.

FDA has met with various tribal representatives in a number of forums, including official Departmental Consultation, a public stakeholder discussion, and individually requested meetings, to discuss the broad range of implications the Tobacco Control Act has on tribally owned, operated, or located activities. These discussions are ongoing.

2. **Many tribes and tribal leaders are, in fact, the owners of smoke shops or other retail outlets that sell tobacco. Who is inspecting these outlets to ensure compliance with the law?**

As mentioned above, there have been no inspections of retailers on Indian country to date. FDA is working to develop a contracting mechanism for Indian tribes and/or tribal organizations to conduct inspections, similar to the state contract mechanisms that have been used to date for 37 states and the District of Columbia. In addition, CTP has begun to work with tribes and tribal organizations to educate tribal retailers about the Tobacco Control Act and its implementing regulations.

3. **Internet sellers of cigarettes do a brisk business-- and continue to evade taxes on many sales. Simply typing "tax free cigarettes" into a search engine produces pages of options. Are these Internet sellers being inspected to see whether people delivering their products actually verify the age of the person to whom cigarettes are delivered? If not, how do you plan to enforce the law?**

The (Prevent All Cigarette Trafficking) PACT Act of 2010, which was enacted after the Tobacco Control Act, imposes a number of restrictions related to the sale of

cigarettes and smokeless tobacco through the U.S. mail, including through Internet-based and other remote sellers. The purpose of the PACT Act, among others, is to create disincentives for the illegal smuggling of tobacco products and stem trafficking, and to prevent youth access through illegal Internet and contraband sales. The U.S. Attorney General is responsible for administering and enforcing the PACT Act.

The Honorable Frank Pallone, Jr.

1. **Under section 505-1 [of the FD&C Act, as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA)] FDA may require a REMS when necessary to ensure that the benefits of a drug outweigh its risks. Sponsors provide information on the safety of the product via REMS materials, but they also provide information on their labels. Both of these materials are updated periodically to reflect new safety information, but it is my understanding, that [under FDAAA] the process for review and approval of updated materials is not done simultaneously. Is that correct?**

We note that this question was posted in March 2012, and was based on the Risk Evaluation and Mitigation Strategies (REMS) provisions in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under FDAAA, when it has been determined that new safety information must be added to the labeling and corresponding modifications to the REMS are required to reflect the new safety information, the sponsor has been notified and directed to submit these changes in Prior Approval Supplements. Safety labeling changes are required to be submitted to FDA within 30 days of notification. However, under FDAAA, a supplement that included REMS modifications may not have had this same deadline. Sometimes, the corresponding modifications to the REMS to include the new safety information have involved the REMS document and multiple appended REMS materials, such as enrollment forms, prescriber training materials, and pharmacy training materials, and more time may have been allowed for the submission of these REMS modifications than the safety labeling changes. When possible, FDA has worked to promptly review and approve the safety labeling changes and the REMS modifications at the same time.

In addition, if the safety labeling changes and corresponding REMS modifications have involved a class of drugs, sponsors within the class may each submit different language for the REMS and REMS-appended materials. Additional time may be needed in this case to harmonize the language across the class so that the safety message is consistent with all of the products and then to incorporate it into the REMS. Given the differences in FDAAA's requirements for submission, review, and approval for safety labeling changes and modifications to a REMS, there have been times when the materials available to the public may have been inconsistent.

We also note that in July 2012, after this question was posed, the Food and Drug Administration Safety and Innovation Act, (FDADIA) (P.L. 112-144) was enacted.

Section 1132 of FDASIA includes a number of changes to the REMS provisions in FDAAA, including changes intended to help ensure that when a safety-related change is approved for a drug product's labeling, conforming changes to a REMS are made in a timely manner. More specifically, under FDASIA, FDA will review and act upon proposed modifications to conform the REMS to approved safety labeling changes within 60 days.

So it seems to me that [under FDAAA] the information contained in updated labeling and promotional materials may differ, for a significant period of time, from the safety information in the REMS materials.

a. **Does that potential, indeed exist?**

Yes, for the reasons described above, under FDAAA the safety changes to the labeling and corresponding modifications to the REMS document and REMS-appended materials have been submitted, reviewed, and approved on different time clocks.

However, also as noted above, FDASIA, which was enacted in July 2012 after this question was posed, includes changes to the REMS intended to help address this concern.

b. **So, recognizing that different entities within FDA review these materials, is there something that FDA can be doing [under FDAAA] to better coordinate the updating of REMS materials and product labeling and promotional materials to reflect new safety information so that the materials are not inconsistent?**

FDA is working on improving coordination between the various offices that review safety labeling changes and REMS modifications, which could improve the process of implementing the different FDAAA provisions.

In addition, as noted above, FDASIA, which was enacted in July 2012 after this question was posed, includes changes to the REMS provisions intended to help address this concern. For example, in accordance with FDASIA, FDA will review and act upon modifications to conform the REMS to approved safety labeling changes, and minor REMS modifications (as defined by FDA in guidance), within 60 days.

2. **As I understand it, [under FDAAA] the process for making changes to a REMS is pretty complex and time consuming. While FDA allows companies to make minor labeling changes without pre approval from FDA, the same is not true for minor changes to REMS. Currently, FDA requires pre approval for every change to a REMS, including minor changes, such as updating forms or adding a newly approved drug to a list of current medications and changes related to operational improvements, such as using a website or iPad, rather than a fax machine, to submit such data. Can you explain why a similar process that allows companies to make minor label changes without pre**

approval from FDA has not been implemented [under FDAAA] for minor changes to a REMS?

We note that this question was posed in March 2012, and was based on the REMS provisions in FDAAA. However FDASIA made a number of changes to the REMS provisions in FDAAA that may help to address this concern, by streamlining the process for certain REMS modifications. For example, in accordance with FDASIA, FDA will review and act upon minor modifications to REMS, as defined by FDA in guidance, within 60 days. In addition, under FDASIA, FDA will establish through guidance that certain REMS modifications may be implemented following notification to FDA.

We also note that FDA is working on improving coordination between the various offices that review safety labeling changes and REMS modifications, which could improve the process of implementing the different FDAAA provisions.

The Honorable Edward J. Markey

Deferral Requests [Under Section 402 of the Food and Drug Administration Act of 2007 (FDAAA)]

1. **What percentage of requests to defer postmarket pediatric requirements under PREA does FDA approve?**

Under FDAAA, FDA has not denied a company's petition for deferral. Part of the reason for this is that one of the legislative criteria for a deferral is that the product is ready for approval in adults. Most requests for deferrals are granted because pediatric studies are not completed but adult studies are complete and an application is ready for approval. This is the case regardless of the reason the pediatric studies are not complete.

Current Enforcement Authority [Under Section 402 of the Food and Drug Administration Act of 2007 (FDAAA)]

1. **If a company fails to submit its plan for pediatric studies at the time of submission, as required by PREA, what enforcement options does FDA currently have?**

Under FDAAA, if a company fails to submit its pediatric plan at the time of submission, FDA currently has three options: 1) refuse to file the application and inform the sponsor that they must submit a pediatric plan before we will file the application; 2) inform the sponsor in the filing communication that their application is deficient because they have not submitted a pediatric plan and they must do so prior to an action being taken; or 3) work with the sponsor to get a pediatric plan during the review period and if they still do not submit one, we could decide to not approve the application.

FDA has generally worked with the applicant, rather than refusing to file an application. It is often a challenge to consider not reviewing data that may prove beneficial for one segment of the population (adults) because the applicant has not addressed another population (pediatrics). If the indication in the application was largely a pediatric indication, it is likely that FDA would consider refusing to file the application. In addition, there are provisions in FDA regulations, in the event of a refuse-to-file action, for sponsors to require FDA to file the application "over protest."

2. **If FDA determines that a company isn't complying with its post-market pediatric requirements under PREA, is it true that the only enforcement tool FDA has at its disposal is misbranding of the product?**

Under FDAAA, the only enforcement mechanism provided under PREA is that FDA consider the product to be misbranded. Again, this enforcement mechanism places FDA in the position of potentially making a product unavailable, when that product is beneficial for one segment of the population (adults) because the applicant has not addressed another population (pediatrics).

3. **What are the implications for access to lifesaving treatments for adults if FDA were to deem a drug misbranded because the company failed to comply with its PREA requirements?**

Under FDAAA, the only enforcement mechanism provided under PREA is that FDA consider the product to be misbranded. FDA has not brought a misbranding case for failure to comply with PREA. If FDA were to exercise the misbranding provision under PREA, doing so would potentially prevent access to a safe and effective therapy for an adult population. This would have a negative impact on the public health.

4. **What are the implications for access to lifesaving treatments for children being prescribed a drug off-label if FDA were to deem the drug misbranded because the company failed to comply with its PREA requirements?**

Under FDAAA, if FDA were to deem a lifesaving treatment misbranded because the company failed to complete its pediatric requirements, children who were being prescribed the drug off-label would lose access to it. Adults would also lose access to the drug.

5. **How often has FDA used their misbranding authority in cases where companies failed to comply with its post-market pediatric requirements under PREA?**

Under FDAAA, FDA has never brought a misbranding case for failure to comply with PREA.

Current Levels of Company Compliance [Under Section 402 of the Food and Drug Administration Act of 2007 (FDAAA)]

1. **What percentage of drug and biologics applications and supplements that have NOT received a PREA waiver do not contain a plan for pediatric studies at the time of submission, as required by PREA?**

For the time period January 1, 2011, to May 2012, 94 percent of applications that were filed and triggered PREA appropriately addressed PREA in the submission, either by requesting a waiver, requesting a deferral and including a plan for the studies to be deferred, submitting pediatric studies or documentation that the product was already appropriately labeled for pediatrics, or some combination of the three. Of the applications that did not include a request for a full waiver, 88 percent contained a pediatric plan, pediatric studies, or documentation that the product was already appropriately labeled for pediatrics.

2. **FDA data shows that 78% of the PREA postmarket pediatric study requirements due since 2007 were not completed by their due dates. Does FDA track -either internally or publically- why the companies missed their postmarket pediatric requirements under PREA?**

The 78 percent figure is not accurate. It is based on a calculation that does not fairly represent the status of pediatric studies under PREA. That figure was derived using the number of deferrals granted since FDAAA was enacted and the number of studies that were completed by the due date. It does not take into account the fact that the due date for many of those studies may be several years in the future.

FDA is currently working to revise the table from which this calculation was derived to more accurately reflect the status of PREA studies and plans to begin posting the new version of the table in the near future. The new table will show that the percentage of PREA post-market studies delayed or incomplete is much lower.

We do currently track the reasons why companies miss study due dates based on information the company provides in their NDA or BLA annual report. Once an annual report is reviewed by the FDA clinical review division and the information about the study status is verified, the information can be posted in the Explanation of Status in the Post-marketing Requirements (PMR) database on our website. Because FDA has no deadline for review of these annual reports, the timing of such posting about the pediatric PMR status is variable.

3. **If FDA does not currently request or track this information, does the agency intend to start? If so, when? Will this information be publicly available?**

All PMRs are tracked and are included in a PMR database that is available to the public using the following link: *http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.*

The Honorable Elliot L. Engel

1. **Commissioner Hamburg, I was the lead sponsor of the Paul D. Wellstone Muscular Dystrophy Act and the ALS Registry Act, both of which were signed into law by President George W. Bush. These laws promoted medical research and data collection with regard to these specific diseases, both of which have no cure and are always fatal. I am keenly aware of the challenges patients with these diseases face, as well as the incredible trials their families go through to care for their loved ones.**

   Therefore, I am pleased that the new PDUFA V agreement developed by industry and FDA includes some provisions for the advancement of drugs for rare diseases. Can you please elaborate on how the FDA plans to reduce barriers to getting safe and effective drugs to patients with rare diseases?

FDA has taken several steps to help facilitate the development and approval of safe and effective drugs for Americans with rare diseases. Because of the small numbers of patients who suffer from each disease, FDA often allows non-traditional approaches to establishing safety and effectiveness. We have also established the Rare Disease Program within the Center for Drug Evaluation and Research (CDER). This program coordinates the development of policy, procedures, scientific development, and training for review and approval of treatments for rare diseases.

The PDUFA V agreement includes enhancements to FDA's Rare Disease Program. As part of the agreement, FDA will develop relevant guidance, increase the Agency's outreach efforts to the rare disease patient community, and continue to provide specialized training in rare disease drug development for sponsors and FDA staff. PDUFA V will also add additional staff to CDER's Rare Disease Program and a Rare Disease Liaison in the Center for Biologics Evaluation and Research, which will enhance collaboration within the Agency as well as with external rare disease stakeholders.

Therapies for rare diseases—those affecting fewer than 200,000 people in the United States—represent the most rapidly expanding and innovative areas of drug development. Although each disease affects a relatively small population, collectively, rare diseases affect about 25 million Americans. Approximately one-third of the new molecular entities (NMEs) and new biological products (those products for which the active ingredient had not previously been approved by FDA) approved in the last five years have been drugs for rare diseases.

Also, Section 902 of FDASIA, establishes a new pathway for breakthrough therapies, which are defined as drugs that are intended to treat a serious or life-threatening disease or condition and for which preliminary clinical evidence demonstrates substantial

improvement over existing therapies. Drugs that receive this designation are eligible for additional consultation with the Agency to design an expedited drug development pathway.

2. **I was pleased to read in the PDUFA commitment letter that one of the FDA's goals includes, "... encouraging flexibility and scientific judgment, as appropriate, on the part of reviewers when evaluating investigational studies and marketing applications for drugs for rare diseases." Can you explain to me what this will look like in practice at the FDA under the terms of the PDUFA reauthorization?**

FDA's oversight of rare disease drug development is complex and resource-intensive. Rare diseases are a highly diverse collection of disorders, their natural histories are often not well-described, only small population sizes are often available for study, and they do not usually have well-defined outcome measures. Thus the design, execution, and interpretation of clinical trials for rare diseases require frequent interaction between FDA and drug sponsors. If recent trends in orphan designations are any indication, FDA can expect an increase in investigational activity and marketing applications for orphan products in the future.

But as stated above, FDA has taken several steps to help facilitate the development and approval of safe and effective drugs for Americans with rare diseases, and the PDUFA V agreement will build on these accomplishments. Existing regulations allow for the application of flexibility and scientific judgment in the development and approval of rare disease therapeutics. FDA's orphan drug approval history was recently analyzed in a study sponsored by the National Organization for Rare Disorders, which found that FDA exercised this flexibility in approximately two-thirds of orphan drug approvals.[1]

As a recent example, FDA approved Voraxaze (glucarpidase) in January 2012 to treat patients with toxic methotrexate levels in their blood due to kidney failure, which affects a small population of patients each year. Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. Patients receiving high doses of methotrexate may develop kidney failure. Voraxaze was approved based on data in 22 patients from a single clinical trial, which showed decreased levels of methotrexate in the blood. Prior to the approval of Voraxaze, there were no effective therapies for the treatment of toxic methotrexate levels in patients with renal failure.

3. **I have heard from advocates with rapidly progressing diseases that they have different levels of risk that they are willing to tolerate. Would the FDA consider more proactive efforts to better define New Drug Applications (NDAs) benefit-risk expectations for rare disorders, in order to expedite approvals for such unmet needs without compromising patient safety?**

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[1] Sasinowski FJ., Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs. Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders (2010), available at *http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf.*

FDA has been developing an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making. Part of FDA's decision-making lies in thinking about the context of the decision—an understanding of the condition treated and the unmet medical need. Patients who live with a disease have a direct stake in the outcome of drug review. The FDA drug review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and the potential gaps or limitations in available treatments in a therapeutic area.

PDUFA V enhancements include expanded implementation of FDA's benefit-risk framework in the drug review process, including holding public workshops to discuss the application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting. FDA would also conduct a series of public meetings between its review divisions and the relevant patient advocacy communities to review the medical products available for specific indications or disease states that will be chosen through a public process.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Michael C. Burgess, M.D.
House of Representatives
Washington, D.C. 20515-4326

FEB 09 2012

Dear Dr. Burgess:

This letter responds to questions you raised during the February 1, 2012, Committee on Energy and Commerce, Subcommittee on Health hearing entitled "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients," regarding the Food and Drug Administration's (FDA or the Agency) responsiveness to the Committee's letter of February 23, 2011, requesting information and documents related to the 2008 heparin contamination. Specifically, you expressed concern that the Committee had not received the requested documents.

FDA is committed to responding to all inquiries from Congress in a timely, responsive, and appropriate manner. The Department of Health and Human Services, of which FDA is a component, has a long-standing policy of complying with Congressional requests for information to the fullest extent consistent with our Constitutional and statutory responsibilities.

With regard to the February 23, 2011, letter you asked about during the hearing, the Agency has delivered 30 document productions to Chairman Upton, totaling nearly 50,000 pages of documents. The Agency delivered documents to the Chairman on the following dates: March 16, 2011; March 31, 2011; April 5, 2011; April 13, 2011; May 5, 2011; May 13, 2011; May 24, 2011; May 26, 2011; June 1, 2011; June 15, 2011; June 27, 2011; July 14, 2011; July 19, 2011; July 21, 2011; August 5, 2011; August 12, 2011; August 26, 2011; September 12, 2011; September 20, 2011; October 14, 2011; October 21, 2011; November 22, 2011; December 2, 2011; December 9, 2011; December 16, 2011; December 23, 2011; January 6, 2012; January 13, 2012; January 24, 2012; and February 1, 2012. Although the documents were delivered to the full Committee Chairman, the Agency provided written notification to you and to Chairman Stearns each time we delivered documents. As the Committee's request for records was broad in scope and is requiring significant personnel resources to search for responsive records, additional document deliveries will be forthcoming.

Generally, with regard to heparin-related inquiries from the Committee, the Agency has been actively cooperating with the Committee since 2008. Since 2008, the Committee has written to FDA regarding heparin a total of 14 times, including three letters during the current Congress:

- February 14, 2008, letter to then Commissioner Andrew von Eschenbach from then Chairman of the Committee on Energy & Commerce, John Dingell and then Chairman of the Committee's Subcommittee on Oversight and Investigations, Bart Stupak

- February 21, 2008, letter to then Commissioner Andrew von Eschenbach from then Chairman of the Committee on Energy & Commerce, John Dingell and then Chairman of the Committee's Subcommittee on Oversight and Investigations, Bart Stupak
- March 19, 2008, letter to then Commissioner Andrew von Eschenbach from then Chairman of the Committee on Energy & Commerce, John Dingell; then Ranking Member of the Committee on Energy & Commerce, Joe Barton; then Chairman of the Committee's Subcommittee on Oversight and Investigations, Bart Stupak; and then Ranking Member of the Committee's Subcommittee on Oversight and Investigations, John Shimkus
- March 28, 2008, letter to then Commissioner Andrew von Eschenbach from then Chairman of the Committee on Energy & Commerce, John Dingell and then Chairman of the Committee's Subcommittee on Oversight and Investigations, Bart Stupak
- April 24, 2008, letter to Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA from then Chairman of the Committee's Subcommittee on Oversight and Investigations, Bart Stupak
- December 10, 2008, letter to then Commissioner Andrew von Eschenbach from then Ranking Member of the Committee on Energy & Commerce, Joe Barton
- December 16, 2008, letter to then Commissioner Andrew von Eschenbach from then Ranking Member of the Committee on Energy & Commerce, Joe Barton
- May 6, 2009, letter to then Acting Commissioner Joshua Sharfstein from then Ranking Member of the Committee on Energy & Commerce, Joe Barton; and then Ranking Member of the Committee's Subcommittee on Oversight and Investigations, Greg Walden
- April 30, 2010, letter to Commissioner Margaret Hamburg from then Ranking Member of the Committee on Energy & Commerce, Joe Barton; and then Ranking Member of the Committee's Subcommittee on Oversight and Investigations, Michael Burgess
- July 22, 2010, letter to Commissioner Margaret Hamburg from then Ranking Member of the Committee on Energy & Commerce, Joe Barton; and then Ranking Member of the Committee's Subcommittee on Oversight and Investigations, Michael Burgess
- July 29, 2010, letter to Commissioner Margaret Hamburg from then Ranking Member of the Committee on Energy & Commerce, Joe Barton; and then Ranking Member of the Committee's Subcommittee on Oversight and Investigations, Michael Burgess
- February 23, 2011, letter to Commissioner Margaret Hamburg from Chairman of the Committee on Energy & Commerce, Fred Upton; and Chairman of the Committee's Subcommittee on Oversight and Investigations, Cliff Stearns; and Member of the Committee, Rep. Michael Burgess
- September 16, 2011, letter to Commissioner Margaret Hamburg from Chairman of the Committee on Energy & Commerce, Fred Upton; Chairman Emeritus of the Committee, Joe Barton; Chairman of the Committee's Subcommittee on Oversight and Investigations, Cliff Stearns; Chairman of the Subcommittee on Health, Joe Pitts; and Vice Chair of the Subcommittee on Health, Michael Burgess
- October 26, 2011, letter to Commissioner Margaret Hamburg from Chairman of the Committee on Energy & Commerce, Fred Upton; Chairman Emeritus of the

Committee, Joe Barton; Chairman of the Committee's Subcommittee on Oversight and Investigations, Cliff Stearns; Chairman of the Subcommittee on Health, Joe Pitts; and Vice Chair of the Subcommittee on Health, Michael Burgess

To date, FDA has responded to the Committee's inquiries in writing 46 times. Forty-two of those responses included document productions. In addition, since 2008, the Agency has responded to hundreds of telephone and e-mail inquiries from Committee staff. In just the last year, the Agency has also participated in four briefings for Committee staff with more than a dozen senior Agency officials regarding the 2008 heparin contamination. As documented above, the Agency has worked diligently to make documents, other information, and Agency personnel available to the Committee in a timely manner.

Lastly, in your letter dated October 26, 2011, you state that you have reason to believe that two Chinese firms that may have supplied Baxter and Scientific Protein Laboratories with contaminated heparin are still supplying crude heparin that is being imported into the United States. Although you have identified such a potentiality as a matter of significant public concern, Committee staff has declined FDA's request to identify these firms so that the Agency may investigate further. We would appreciate your assistance in obtaining this information.

Thank you for your continued interest in the strength and effectiveness of FDA. The Agency will continue to make every effort to respond to the Committee's inquiries in a timely manner, while at the same time remaining focused on the Agency's mission to protect and promote the public health.

Sincerely,

Jeanne Ireland
Assistant Commissioner
for Legislation

cc:

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce

The Honorable Joe Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce

The Honorable Cliff Stearns
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce

The Honorable Henry A. Waxman
Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigation
Committee on Energy and Commerce

Mr. Alan Slobodin
Ms. Stacia Cardille

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April 15, 2012

The Honorable Fred Upton
Chairman
Committee on Energy & Commerce
U.S. House of Representatives
2125Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

Attached, please find the answers in response to questions by Representative Eliot Engel related to my testimony at the February 1st hearing on the Prescription Drug User Fee Act. Should you have any question, please contact John Halliwell in our Federal Government Relations office at 202-783-7070 or John.P.Halliwell@pfizer.com

Sincerely,

Questions from Representative Eliot Engel

1. Several of you mentioned in your written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated fund for the FDA. I was pleased to see that for Fiscal Year 2012, the FDA received a $50 million increase in funding over Fiscal year 2011 funding level. But this was a hart fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for Fiscal Year 2012. Please elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patients your associations serve?

A. Pfizer believes it is critical for the Administration and Congress to adequately fund the FDA to ensure the Agency is able to carry out one of its core missions which is the timely review of new products to treat the myriad diseases afflicting Americans. We remain concerned that our user fees account for an ever increasing share of the FDA review budget which is approaching 70% under PDUFA V.

2. In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare and orphan disease caucus, which is why I am particularly interested in the provisions of the PDUFA V agreement related to the development and approval of drugs for rare disease.

- What barriers do you perceive in moving new candidate therapies through the development process?
- Do you feel that PDUFA V adequately addresses these barriers or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?

A: Specific rare diseases impact only a small number of patients. However, as a group, they affect millions of people around the world, including more than 25 million patients here in the U.S. Pfizer understands the impact of rare diseases on individual patients and their caregivers. We are dedicated to addressing these serious unmet needs through our focus on research, development and commercialization of orphan medicines.

The development of therapies for rare diseases poses many unique challenges; designing and conducting clinical trials is constrained as there is usually little information about the natural progression of the disease to inform endpoint selection. In addition, investigators often have difficulty identifying and enrolling a large number of patients due to the small number of patients with the disease. Even the most basic tools for product development, such as validated animal

models may not exist for specific rare disorders. Finally, the limited number of available patients dictates small sample sizes, which pose significant statistical hurdles under the current FDA regulations.

PDUFA V offers the potential for guidance and policy development on understanding approaches to studying rare diseases, non-traditional clinical development programs, study design, endpoints and statistical analysis. Public meetings with FDA, industry, academia and the patient community will improve the communication between all parties involved in developing new products and help inform the evolving Regulatory policy in this important area.

Pfizer believes PDUFA V has the potential to enhance development of new drugs for rare diseases through FDA policy development and training of review staff on scientific issues unique to rare diseases, as well as support outreach to industry, patients, and the scientific community.

C·H·I
CALIFORNIA HEALTHCARE INSTITUTE

The Honorable Joseph Pitts
Chairman, Subcommittee on Health
House Energy & Commerce Committee
2125 Rayburn House Building
Washington, DC 20515

March 28, 2012

Dear Chairman Pitts:

Thank you for the opportunity to appear before the Subcommittee during its hearing on "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients" on February 1, 2012. Below, please find responses to the additional questions provided by Congressmen Brian Bilbray and Eliot Engel.

The Honorable Brian Bilbray

What impact has duplicative inspections had on the industry in my state of California?

New medicines and medical technologies submitted for U.S. Food and Drug Administration (FDA) approval include not only information, such as clinical trial data, demonstrating products' safety and effectiveness, but information regarding how they will be manufactured. And prior to the manufacture and sale of a drug, biologic or medical device for human use, companies must have each facility that is engaged in the product's manufacturing inspected by the FDA. Indeed, manufacturing issues are among the reasons that product approval may be delayed or denied by the Agency. Following approval, manufacturers are also required to have each facility inspected every two years by the FDA to ensure compliance with standards for current Good Manufacturing Practices (GMP). The penalties for failing to comply with these standards are significant -- FDA may bring a seizure and injunction case before a federal court that would allow the federal government to seize all drugs still on the market and ban the manufacturer from further production of the drug until all the outstanding GMP noncompliance issues and deficiencies have been addressed.

These requirements are important to ensure patient and public safety and health. However, some states, such as California, require their own inspections. Unfortunately, these state inspections are normally duplicative of federal FDA inspections. Indeed, California's state Food and Drug Branch (FDB) inspections, also carried out every two years, use the same GMP compliance standards as the FDA. And according to CHI member companies, there is little differentiation in what is inspected and frequent lack of coordination in the state and federal inspection timelines. In sum, these waste state resources and cause companies to divert time and money from research and development, while contributing nothing to public health and safety.

Can you tell me what kind of impact the duplicative inspection issue has for California life sciences companies? What are your thoughts ou having FDA as the sole authority for inspection with caveats for state emergencies?

As mentioned above, California's state Food and Drug Branch (FDB) inspections use the same GMP compliance standards as the FDA. And according to CHI member companies, there is little differentiation in what is

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inspected and frequent lack of coordination in the state and federal inspection timelines. In sum, these waste state resources and cause companies to divert time and money from research and development, while contributing nothing to public health and safety.

Ending these unnecessary and duplicative state inspections would save time, money and resources of both companies and our cash-strapped states while maintaining protections for patient and public safety and health. We support making the FDA the sole authority for such inspections, while maintaining inspection authority for states and state agencies when determinations are made that a drug or device manufactured there presents threat of serious adverse health consequences or death, when the federal government orders a recall of a product manufactured or processed at a facility in the state, or upon the request of or authorization by the federal government.

The Honorable Eliot Engel

Several of you mentioned in yonr written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated funds for the FDA. I was pleased to see that for Fiscal Year 2012, the FDA received a $50 million increase in funding over Fiscal Year 2011 funding levels. But this was a hard fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for Fiscal Year 2012.
Please elahorate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patients your associations serve?

CHI strongly supports bolstering congressionally appropriated resources for the Food and Drug Administration (FDA), providing the agency the tools it needs to ensure that innovative products continue to reach patients in a timely fashion. Currently, industry user fees constitute a large percentage FDA funding. CHI believes that the FDA should he funded primarily through congressional appropriations, a step that will help in restoring the public's trust and faith in the agency.

In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare and orphan disease caucus, which is why I am particularly interested in the provisions of the PDUFA V agreement related to the development and approval of drugs for rare diseases.

a. **What harriers do you perceive in moving new candidate therapies through the development process?**

One barrier to moving new candidate therapies through the development and review process entails the quality and quantity, or lack thereof, of communications between sponsor companies and the FDA. Communication between the FDA and drug and device developers is critical. The earlier questions can be raised, and answers provided, the more likely that the review process won't be affected by late-breaking or unexpected complications. One of the primary FDA-related issues CHI hears from its membership, and especially from our smaller, emerging company members, regards concerns with these development stage communications and discussions.

A second barrier entails the quality of expert advice and counsel to the FDA from its Advisory Councils. This is especially the case for therapies to treat rare diseases and conditions and other unmet medical needs. Unfortunately, intensified Advisory Committee conflict of interest rules enacted as part of the FDA Amendments Act of 2007 (FDAAA), have made it increasingly difficult for experienced medical experts to

serve on Agency Advisory Committees. Members of the Subcommittee and the FDA itself have spoken to the importance of addressing this issue. CHI supports a solution that acknowledges the need for conflict of interest rules but better rationalizes the approach (through improved transparency processes, for example) to ensure that advisory committees are comprised of the most qualified, objective and experienced experts in the relevant field.

A third barrier entails how the Agency, as well as policymakers and the public, addresses the benefit-risk equation. Virtually all medicines bear some capacity for harm. A zero-risk approach would shut down the development of beneficial drugs. In this regard, however, the Agency focuses almost exclusively on the *direct* risks of drugs: side effects, adverse events and so forth. These are comparatively discrete and measurable. But *indirect* risks are both difficult to observe and subject to a much longer time horizon. Where are data that allow one to calculate the harm to public health if investors avoid an important disease because the FDA's demands for data are so extensive and its standards for drug approval so uncertain?

b. Do you feel that PDUFA V adequately addresses these barriers or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?

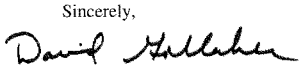
CHI lauds provisions in the PDUFA V agreement to advance the development of new medicines for rare diseases, such as through provisions to bolster the CDER Rare Disease Program and through the establishment of a Rare Disease liaison with the office of the CDER Director.

We also laud provisions in the PDUFA V agreement to improve and enhance Agency-sponsor communications, such as through the new review program for New Molecular Entities (NMEs) and measures to both enhance communications between FDA and sponsors during drug development and meet the challenges of emerging science in the areas of clinical trial endpoint assessment tools, biomarkers and pharmacogenomics, meta-analysis, and development of drugs for rare diseases.

CHI similarly acknowledges and lauds PDUFA V provisions to enhance Agency benefit-risk assessment as well as a concentration on patient-focused drug development.
Finally, while the PDUFA V agreement did not address the Advisory Committee conflict of interest rules issue, CHI is strongly supportive of efforts to address this problem during the reauthorization process.

Thank you for the opportunity to provide CHI's responses to these questions. And please do not hesitate to contact me or Todd Gillenwater, CHI's Senior Vice President for Public Policy, if we may be of any further assistance.

Sincerely,



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March 23, 2012

The Honorable Joseph R. Pitts
Chairman, House Energy and Commerce Committee
Subcommittee on Health
2125 Rayburn House Office Building
Washington, D.C. 20515-665

Dear Chairman Pitts:

Thank you for the opportunity to present my views on the reauthorization of the Prescription Drug User Fee Act (PDUFA V) at the February 1st subcommittee hearing on "PDUFA V: What it Means for Jobs, Innovation, and Patients."

On behalf of the Biotechnology Industry Organization (BIO), I am pleased to provide the following responses to subcommittee member questions for the hearing record.

If you have any additional questions or need of clarification, please feel free to contact me or Brent Del Monte, BIO's Vice President for Federal Government Relations at bdelmonte@bio.org or (202) 962-9200.

Sincerely,

Richard Pops
Chairman and CEO
Alkermes

cc: The Honorable Frank Pallone, Jr., Ranking Members, Subcommittee on Health
The Honorable Eliot Engel

Responses to Questions from the Honorable Eliot Engel:

1. **Several of you mentioned in your written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated funds for the FDA. I was pleased to see that for Fiscal Year 2012, the FDA received a $50 million increase in funding over Fiscal Year 2011 funding levels. But this was a hard fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for Fiscal Year 2012. Please elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patients your associations serve?**

   While industry user fees play an important role in supporting FDA's medical product review program, user fees should be complementary and additive to a sound base of appropriated resources for the Agency. BIO appreciates Congress' recognition of the importance of FDA's role in promoting biomedical innovation and protecting the public health, and we applaud the Congress for enacting increases to FDA's base budget in recent years. We encourage ongoing support for the Agency.

   BIO supports a strong, fully-funded FDA with the resources necessary to keep pace with rapidly-evolving biomedical science and to make sound regulatory decisions in a timely and efficient manner. For FY2013, BIO recommends $506 million for the Human Drugs program and $224 million for the Biologics program. For people with devastating diseases and disabilities, roadblocks to getting new cures developed and approved can be a matter of life or death. For patients who are still waiting for treatment options – such as a first-ever broadly-effective treatment for amyotrophic lateral sclerosis, a next generation treatment for multiple sclerosis, or the next miracle therapy for cancer – nothing is more important than seeing safe and efficacious products developed and approved as efficiently as possible without unnecessary impediments.

   Adequate FDA funding is an economic imperative as well as a public health priority. FDA regulates approximately $1 trillion in consumer products, or 25 cents of every U.S. consumer dollar spent, and it is critical to American economic health and competitiveness that FDA has the tools and resources necessary to effectively and efficiently ensure medical product quality. FDA support for medical innovation is also critical to tackling the nation's long-term fiscal health. Unmet medical needs for diseases such as Alzheimer's, cancers, diabetes, and Parkinson's will be significant drivers of our nation's entitlement spending as the Baby Boomer Generation continues reaching retirement age. Modern FDA regulatory approaches that promote the development of treatments that slow the advancement of Alzheimer's and other devastating diseases will have a profound impact on the nation's fiscal health, as well as public health. BIO also supports adequate resources to advance regulatory science at FDA and for the Agency's Medical Countermeasures Initiative (MCMi).

2. **In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare an orphan disease caucus, which is why I am particularly interested in the provisions of the PDUFA V agreement related to the development and approval of drugs for rare diseases.**
    a. **What barriers do you perceive in moving new candidate therapies through the development process?**

Over the last thirty years, initiatives and market-based incentives to support the drug development for rare disease, such as the Orphan Drug Act (ODA) of 1983, have brought success. To date, in excess of 1,000 orphan product designations have been granted by the FDA's Office of Orphan Product Development and more than 250 drugs and biologics have received approval by the FDA with Orphan designation, collectively helping millions of adults and children with rare diseases worldwide. We have come a long way, indeed. In the decade prior to enactment of the ODA, fewer than ten products for rare diseases came to market. Today, there are an estimated 7,000 rare diseases, each one affecting 200,000 or fewer individuals, but collectively affecting nearly 30 million Americans.

However, treatments exist for only a fraction of these devastating, life-threatening diseases leaving so many people of all ages with significant unmet medical needs. And of those treatments, the majority of approved orphan drugs are for those rare diseases with higher prevalence. Most of these diseases are associated with significantly shortened life span, poor quality of life, severe and many times painful co-morbidities, and major costs to the U.S. healthcare system.

Basic scientific, biomedical and preclinical research is taking place with groundbreaking technology in laboratories at colleges and universities, independent academic medical centers, at the National Institutes of Health, and in the biotechnology industry. The biotechnology industry has made a significant contribution to this field over the years. Indeed, the mission of many biotech companies is to bring hope to the patients who suffer from rare diseases, and relief to their families.

As a key entity in our nation's biomedical innovation ecosystem, the FDA must also continue to evaluate the current regulatory environment and the FDA's review process for orphan products. For instance, the sheer size of patient populations is an important factor for consideration in clinical study design. Affected individuals are part of such small individual patient populations; they may represent disease prevalence of as many as 67:100,000 to as few as 2:100,000. No one rare disease exceeds an incidence of 200,000 in the United States. Limited individual disease experience makes it unlikely that there are organized registries from which to draw information for the majority of these diseases, and unrealistic to consider conducting natural history studies as prelude to or in parallel with clinical trials. Numbers of subjects for any orphan product study should be carefully considered based on current disease situations. Given the significant morbidity and mortality often associated with rare and orphan diseases, the unmet medical need, the societal costs, and the challenges of conducting trials in these patient populations, the regulatory approval pathway needs to accommodate non-traditional approaches to drug development and be predictable, faster, and one that more clearly balances risk/benefit for these orphan disease patients and their families.

b. Do you feel that PDUFA V adequately addresses these barriers or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?

The PDUFA V rare disease proposal helps to address many of the challenges associated with rare disease drug development. This provision would support rare disease drug development through FDA focus on policy development, training of FDA review staff on unique scientific issues related to rare diseases, and education/outreach to industry, patient, and investigator communities. Engaging experts and developing FDA policy and guidance on key issues such as endpoint selection, clinical trials design, dose selection, statistical analysis, and the utilization of other drug development tools will help to ensure transparency and consistency in the use of these approaches in non-traditional drug development programs for rare diseases. The program also ensures that FDA medical reviewers are trained on novel approaches to rare disease drug development so that these approaches are integrated into regulatory practice at all levels of FDA.

The PDUFA V enhanced communication proposal will also facilitate the development of treatments for rare diseases by reducing the impact of regulatory barriers and scientific obstacles experienced by Sponsors during drug development.

Additionally, modernizations to FDA's Accelerated Approval pathway made by the *Faster Access to Specialized Treatments (FAST) Act of 2012*, sponsored by Reps. Stearns (R-FL) and Towns (D-NY), will help to expand the application of FDA's Accelerated Approval pathway to more rare diseases and expedite the development of therapies for these serious and life-threatening conditions. This bill will broaden the use of surrogate and clinical endpoints under Accelerated Approval, leverage modern drug development tools to provide additional supporting evidence, and take into account the severity, rarity, and availability of alternate treatments in FDA's approval determination. Importantly, this legislation in no way reduces the FDA's current standard for approval, nor does it remove the requirement that clinical work be conducted prior to approval. BIO strongly supports the enactment of the provisions of the FAST Act when the Congress considers reauthorizing PDUFA.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225-2927
Minority (202) 225-3641

March 9, 2012

Dr. David E. Wheadon
Senior Vice President
Scientific and Regulatory Affairs
Pharmaceutical Research and Manufacturers of America
950 F Street, N.W., Suite 300
Washington, D.C. 20004

Dear Dr. Wheadon:

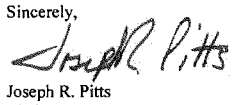
Thank you for appearing before the Subcommittee on Health hearing entitled "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients" on February 1, 2012.

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for 10 business days to permit Members to submit additional questions to witnesses, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please e-mail your responses, in Word or PDF format, to carly.mcwilliams@mail.house.gov by the close of business on Friday, March 23, 2012.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

The Honorable Eliot Engel:

1. Several of you mentioned in your written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated funds for FDA. I was pleased to see that for fiscal year 2012, the FDA received a $50 million increase in funding over fiscal year 2011 funding levels. But this was a hard fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for Fiscal Year 2012. Please elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA can impact your industry or the patients your association serve.

Congressman Engel, thank you for asking this very important question. The FDA has as its core mission to promote and protect the public health of American citizens. In carrying out that mission, the FDA has regulatory responsibility for roughly 25% of the United States' Gross Domestic Product (GDP). Given this weighty responsibility, it is imperative that FDA:

1. Have the necessary resources to insure that US citizens have access to safe, unadulterated food, as well as safe and efficacious drugs, biological products, and medical devices. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health. At the same time, FDA must be given adequate resources to employ state of the art science to promote innovative approaches to the development of new products in these domains of responsibility. Due to these critical public health goals, it is important that FDA be adequately funded. Failure to fund FDA adequately will needlessly delay the availability of new medical treatments to patients and healthcare professionals.

2. Avoid disastrous cuts in resources allocated to FDA such that its ability to carry out its important public health mission would be severely curtailed.

For the biopharmaceutical industry, cuts to the FDA's drug and medical device review budget would have a significant impact on the ability of this industry to invest in discovering and developing new medical products focused on addressing such unmet medical needs as Alzheimer's Disease, multi-drug resistant bacterial infections, Cancer, Diabetes, cardiovascular diseases and HIV prevention among many others. The biopharmaceutical industry depends upon an adequately funded FDA, resourced to attract up-to-date scientific and medical expertise to serve as a partner in the industry's developmental efforts and, ultimately, to make sound scientific regulatory decisions in a timely, efficient and thorough manner. Appropriate FDA funding will help speed the availability of needed medical advances to help patients who are suffering from these many diseases. Without a well-funded and resourced FDA, patients will ultimately be the ones who suffer the most.

2. In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare and orphan disease caucus which is why I am particularly interested in the provision in the PDUFA V agreement related to the development and approval of drugs for rare diseases.

a. What barriers do you perceive in moving new candidate therapies through the development process?

b. Do you feel PDUFA V adequately addresses these barriers or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?

The development process can be challenging for any therapeutic entity, given the basic nature of the science underlying drug discovery and development. This process is even more challenging when the therapeutic entity is targeted towards a particularly small patient population- as is the case for rare and orphan diseases. The barriers for developing drugs and biologics for rare and orphan diseases grow exponentially in the clinical trial process. First, researchers need to establish the molecular or genetic targets the drug or biological product is intended to impact. This entails having a reasonably sizable database of patients to confirm that these targets are indeed pathognomonic for the disease under study. Researchers then need to validate tests of efficacy to illustrate that the product under development indeed has the intended effect. Lastly pivotal proof of safety and efficacy must be carried out in clinical trials, utilizing these validated tests of efficacy. As you know, such clinical testing can require a fairly large set of patients and for many rare and orphan diseases this may not be tenable given the small numbers of affected patients. Such a reality requires that companies developing products targeted towards rare diseases utilize novel approaches for establishing that a product is safe and effective for the target population. FDA must be able and willing to work with these companies in developing and accepting these alternative approaches.

PDUFA V recognizes this need and specifically calls for increasing the number of FDA resources focused on the very unique needs of developing and, ultimately, approving a product for a rare or orphan disease. These resources will be imbedded in the various divisions of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), thus insuring that the specific considerations that must be employed for rare disease research will be institutionalized throughout the FDA review divisions. Additionally, FDA will engage public stakeholders, including patients and clinicians, in an open and transparent process to discuss complex issues in clinical trials for studying drugs for rare diseases, including such questions as endpoint selection and the use of surrogate endpoints/Accelerated Approval, reasonable safety exposures, and the development of patient-reported outcome instruments for rare diseases in order to

develop and implement specialized staff training and to facilitate the formulation of Guidance for developing drugs for rare diseases.

It is our opinion that these provisions in PDUFA V will be a significant asset in improving the industry's and FDA's ability to enhance development and approval of drug and biological products targeted towards rare and orphan diseases.

March 20, 2012

The Honorable Joseph R. Pitts, Chairman
Energy and Commerce Subcommittee on Health
US House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

This letter is in response to your March 9, 2012, request to respond to two questions posed by Congressman Eliot Engel following the February 1 hearing, "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients."

Questions 1

Several of you mentioned in your written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated funds for the FDA. I was pleased to see that for Fiscal Year 2012, the FDA received a $50 million increase in funding over Fiscal Year 2011 funding levels. But this was a hard fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for FY 2012. Please elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patients your associations serve?

NORD Response

The Food and Drug Administration (FDA) is unique—in that it is the only federal agency that touches every American multiple times each day. NORD and the entire rare disease community rely on FDA for the safety of the foods we eat and the safety and effectiveness of the drugs and devices we use. Rare disease patients are totally reliant on FDA for the review and approval of the orphan drugs that alleviate symptoms, improve quality of life and are often, life-saving. The bulk of this work is done using appropriated funds. The provisions in the new PDUFA legislation are welcome and truly needed, but additive to the review and approval process we depend upon.

FDA's mission and responsibilities continue to grow and additional funding is required to handle them. An obvious source of agency growth is new legislation—from which the rare disease community expects to benefit with the enactment of a new biosimilars drug approval pathway as well as elimination of the barriers to the development of humanitarian use devices. In FY 13, FDA will need a minimum of $20 million in appropriated funding to match the funds that will become available upon passage of the biosimilars user fee.

Additionally, most new demands on the agency do not come through legislation. The agency's efforts to address problems of drug shortages is of great interest to the rare disease community because the shortages are heavily centered in biologic products, particularly generics that are cost-effective alternatives for our patients and often the only source for a particular therapeutic.

There is also a resource-intensive demand on the agency created by the growing complexity of science. The rare disease community is experiencing major advances in new scientific knowledge—but this also means that FDA needs the funds to hire more and better-trained scientists. Because of the growing complexity of science, we all must recognize that reviewing a new drug application or evaluating a clinical trial take longer now than five years ago.

Finally, consumers, patients, industry, NIH, Congress and international regulatory bodies are asking FDA at all levels for greater interactions, improved clarity, and clearer proactive guidance. In the specific case of the rare disease community, we have benefited greatly from the many meetings and conferences that FDA participates in to discuss new scientific findings and medical products that will help our community.

Question 2

In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare and orphan disease caucus, which is why I am particularly interested in the provisions of the PDUFA V agreement related to the development and approval of drugs for rare diseases.

a. What barriers do you perceive in moving new candidate therapies through the development process?

b. Do you feel that PDUFA V adequately addresses these barriers, or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?

NORD Response

The agreement between the FDA and industry representatives contains a number of provisions NORD believes will provide the agency the flexibility and resources needed by both the Agency and industry to move orphan drugs and biologics through the development and approval process. Specifically:

Enhancing Benefit-Risk Assessment in Regulatory Decision-making

"FDA will develop a five-year plan to further develop and implement a structured benefit/risk assessment in the new drug approval process. FDA will publish its draft plan for public comment by the end of the first quarter of FY 2013. FDA will begin execution of the plan to implement the benefit-risk framework across review divisions in the pre- and post-

> market human drug review process by the end of the fourth quarter of FY 2013, and the Agency will update the plan as needed and post all updates on the FDA website."

As the FDA commits to a more patient-centric posture, and as patients themselves become more knowledgeable and sophisticated about diseases and their treatment options, we hope that more systematic processes will enable contributions from the patient community at the time that critical decisions on risk tolerance are being made, and from a representative sample of patient views. We believe the process should be well-defined and well-understood within the review divisions, and provide a universally applied opportunity for patients to make such input. We are conscious that FDA reviewers and other relevant FDA staff have many demands on their time, but strongly believe that this suggested new process for input will improve product analysis and approval and access to necessary treatments.

Advancing Development of Drugs for Rare Diseases

Please note that NORD believes the public meetings and other initiatives scheduled to begin in 2014 should be moved up by one year. For example, the public meeting scheduled by mid-FY 2014, should be conducted by no later than mid-FY 2013.

"By the end of FY 2013, FDA will complete a staffing and implementation plan for the CDER Rare Disease Program within the Office of New Drugs and a CBER Rare Disease liaison within the Office of Center Director.

> FDA will increase by five the staff of the CDER Rare Disease Program and establish and fill the CBER Rare Disease liaison position.
>
> On an ongoing basis, the staff in the Rare Disease Programs of the two Centers will develop and disseminate guidance and policy related to advancing and facilitating the development of drugs and biologics for rare diseases, including improving understanding among FDA reviewers of approaches to studying such drugs; considering non-traditional clinical development programs, study design, endpoints, and statistical analysis; recognizing particular challenges with post-market studies; and encouraging flexibility and scientific judgment, as appropriate, on the part of reviewers when evaluating investigational studies and marketing applications for drugs for rare diseases. Rare Disease Program staff will also engage in increased outreach to industry regarding development of such drugs and to patient representatives and organizations.
>
> By mid-FY 2014, FDA, through the Rare Disease Program, will conduct a public meeting to discuss complex issues in clinical trials for studying drugs for rare diseases, including such questions as endpoint selection, use of surrogate endpoints/Accelerated Approval, and clinical significance of primary endpoints; reasonable safety exposures; assessment of dose selection; and development of patient-reported outcome instruments. Participants in the discussion will include FDA staff, academic and clinical experts, and industry experts. A summary from the meeting will be made available publicly through the FDA website.
>
> By the end of FY 2015, FDA will develop and implement staff training related to development, review, and approval of drugs for rare diseases. The training will be provided to all CDER and CBER review staff, and will be part of the reviewer training core

curriculum. Among the key purposes of this training are to familiarize review staff with the challenges associated with rare disease applications and strategies to address these challenges; to promote best practices for review and regulation of rare disease applications; and to encourage flexibility and scientific judgment among reviewers in the review and regulation of rare disease applications. The training will also emphasize the role of the Rare Disease Program staff as members of the review team to help ensure consistency of scientific and regulatory approaches across applications and review teams.

By the end of FY 2016, FDA, through the Rare Disease Program, will develop an evaluation tool to evaluate the success of the activities of the Rare Disease Program, including the reviewer training. Among potential measures of success are the development of a system to track rare disease applications from IND submission through the post-marketing period, increased number of reviewers receiving rare disease-specific training, increased number of activities contributing to regulatory and biomedical science for rare disease drug development, and meeting of PDUFA goals for rare disease applications."

Respectfully Submitted,

Diane Edquist Dorman
Vice President, Public Policy

National Organization for Rare Disorders (NORD)
1779 Massachusetts Avenue, NW, Suite 500
Washington, DC 20036
(202) 588-5700
ddorman@rarediseases.org

Cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health
The Honorable Eliot Engel

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

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March 23, 2012

The Honorable Joseph R. Pitts
Chairman
Energy and Commerce Committee
Subcommittee on Health
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Frank Pallone, Jr
Ranking Member
Energy and Commerce Committ
Subcommittee on Health
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Pitts and Ranking Member Pallone:

On behalf of the 62,000 primary care pediatricians, pediatric medical subspecialists, and surgical specialists of the American Academy of Pediatrics (AAP) who are committed to the attainment of optimal physical, mental and social health and well-being for all infants, children, adolescents, and young adults, I thank you for inviting me to testify before the Subcommittee on Health on February 1, 2012, and welcome this opportunity to respond to questions for the record for the hearing entitled "Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients."

The Honorable Eliot Engel

Several of you mentioned in your written testimony that the user fees included in PDUFA V are meant to be in addition to a solid base of annually appropriated funds for the FDA. I was pleased to see that for Fiscal Year 2012, the FDA received a $50 million increase in funding over Fiscal Year 2011 funding levels. But this was a hard fought victory, given that House Republicans first proposed a $285 million cut in FDA funding for Fiscal Year 2012. Please elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patents your associations serve?

Adequate funding for the FDA is critical in order for the agency to fulfill its mission. The FDA regulates roughly twenty-five percent of all products consumed by Americans and, as such, it is critical that Congress provide the agency adequate funding to ensure that these products are safe, effective, and of high quality. The FDA relies on discretionary, appropriated funding in order to carry out many of the responsibilities in the Best Pharmaceuticals for Children Act (BPCA), the Pediatric Research Equity Act (PREA), the Pediatric Medical Device Consortia program and other successful pediatric medical product initiatives. The AAP urges Congress to provide $6 million in funding for the Pediatric Device Consortia program in the Office of Orphan Products Development at the FDA in Fiscal Year 2013. The Pediatric Device Consortia program at FDA has helped to foster job growth and increased the commercial availability of pediatric medical devices in the United States. According to the FDA, the five FDA-funded Pediatric Device Consortia have assisted in advancing the development of 135 proposed pediatric medical devices.

In addition to my legislative work on ALS and muscular dystrophy, I serve on the rare and orphan disease caucus, which is why I am particularly interested in the provisions of the PDUFA V agreement related to the development and approval of drugs for rare diseases.

a. **What barriers do you perceive in moving new candidate therapies through the development process?**

Drug development for children and other smaller market populations such as individuals with rare diseases has traditionally faced economic and scientific barriers. Congress has shown great leadership in helping to address these challenges through market incentives and requirements. The AAP applauds this Subcommittee for its longstanding support of BPCA and PREA. Through BPCA and PREA we have gained more useful information on drugs and biologics used in children than we had in the seventy years prior to their enactment. Since BPCA was first enacted in 1997, more than 426 drug labels have been updated with important pediatric information.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. BPCA provides a voluntary incentive to drug manufacturers of an additional six months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children. PREA provides FDA the authority to require pediatric studies of drugs when their use in children is for the same indication as for adults.

BPCA and PREA have advanced medical therapies for infants, children, and adolescents by generating substantial new information on the safety and efficacy of pediatric pharmaceuticals where previously there was little. It is vitally important for these pediatric subpopulations that these laws be reauthorized and strengthened.

The AAP also underscores the importance of the Orphan Drug Act in stimulating drug development for populations with rare diseases, half of whom are children. Families with children facing these devastating diseases require the special consideration the Orphan Drug Act, BPCA and PREA provide.

b. **Do you feel that PDUFA V adequately addresses these barriers or what additional provisions are necessary to ensure that patients with rare diseases have access to promising drug treatments?**

Although the AAP does not have an official position on PDUFA V, about half of all rare diseases affect children. The AAP supports efforts to increase the availability of treatment options for children, including children with rare diseases. As previously discussed, the Orphan Drug Act, BPCA and PREA have all helped to stimulate drug development in rare disease populations but the lack of insurance coverage or inadequate insurance coverage for many of these treatments denies access and can harm patients.

Despite the success of these programs, many children and families find that insurance companies treat FDA-approved treatments or off-label uses of treatments for children as experimental and routinely deny coverage. This must change.

Since half of drugs used in children still lack pediatric labeling, off-label use remains an unfortunate but necessary practice. In pediatrics, off-label use falls within the standard of care for our patient population and insurance companies must account for this reality so that our patients have coverage of needed treatments.

The AAP appreciates this opportunity to provide additional information to the Subcommittee. If you have further questions, please contact Tamar Magarik Haro in AAP's Washington Office at 202/347-8600.

Sincerely,

Daniel A.C. Frattarelli, MD, FAAP

DF/tmh