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PDUFA V: MEDICAL INNOVATION, JOBS, AND PATIENTS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TWELFTH CONGRESS

FIRST SESSION

JULY 7, 2011

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PDUFA V: MEDICAL INNOVATION, JOBS, AND PATIENTS

THURSDAY, JULY 7, 2011

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

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Shimkus, Rogers, Myrick, Murphy, Blackburn, Gingrey, Latta, Lance, Cassidy, Guthrie, Upton (ex officio), Pallone, Dingell, Engel, Capps, Gonzalez, and Waxman (ex officio).

Also present: Representatives Bilbray and Christensen.

Staff present: Gary Andres, Staff Director; Clay Alspach, Counsel, Health; Howard Cohen, Chief Health Counsel; Ryan Long, Chief Counsel, Health; Alan Slobodin, Deputy Chief Counsel, Oversight; Jeff Mortier, Professional Staff Member; Andy Duberstein, Special Assistant to Chairman Upton; Debbee Keller, Press Secretary; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; Lyn Walker, Coordinator, Admin/Human Resources; Carly McWilliams, Legislative Clerk; Kirby Howard, Legislative Clerk; Rachel Sher, Minority Senior Counsel; Stephen Cha, Minority Senior Professional Staff Member; Alli Corr, Minority Policy Analyst; Karen Lightfoot, Minority Communications Director and Senior Policy Advisor; Eric Flamm, FDA Detailee; and Karen Nelson, Minority Deputy Committee Staff Director for Health.

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

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

The Prescription Drug User Fee Act, PDUFA, was first authorized by Congress in 1992 with the goal of expediting human drug applications through the Food and Drug Administration's approval process. Under the Act and in subsequent reauthorization, the drug industry pays user fees to FDA, and FDA commits to meet performance goals such as reviewing applications within a certain period of time. This construct was designed to give industry certainty and predictability, but also to speed new drugs and treatments to the public. Details of the agreement between FDA and industry

will be published on September 1st of this year, and by January 15, 2012, FDA will send its final recommendations to Congress.

The current PDUFA authorization expires September 30, 2012, and it is my intention to have the reauthorization legislation signed into law by June 30 of next year. PDUFA is too important to leave to the last minute. The drug industry employs thousands of people here in the United States, providing good jobs that we cannot afford to lose.

The forthcoming study from Patel Memorial Institute has found that every job in the biopharmaceutical sector supports nearly six additional jobs in the greater economy. If PDUFA is not reauthorized, this study estimates that 130,000 to 260,000 jobs would be lost. Americans are the most innovative people on Earth.

Given certainty, predictability and transparency in the approval process, venture capitalists will continue to fund new research and companies will continue to develop new and innovative drugs. What we have heard, however, is that certainty, predictability and transparency oftentimes do not characterize the FDA's approval process. Frustrating both the drug sponsors and the public who are waiting for treatments and cures to everyday maladies, chronic illnesses and terminal diseases.

The American people expect and have a right to expect that the Federal Government is doing everything possible to ensure that drugs on the market are safe and effective. They also have a right to expect that applications for life-enhancing and lifesaving drugs are not languishing on a reviewer's desk at the FDA. It is my hope that the new agreement balances both of these considerations, and I look forward to hearing from FDA, the drug industry, patient advocates and researchers today on our panels.

I yield the remainder of my time to Dr. Burgess.

[The prepared statement of Mr. Pitts follows:]

Opening Statement of Rep. Joseph R. Pitts
Energy and Commerce Subcommittee on Health
Hearing on "PDUFA V: Medical Innovation, Jobs and Patients"
July 7, 2011
(Remarks Prepared for Delivery)

The Prescription Drug User Fee Act (PDUFA) was first authorized by Congress in 1992, with the goal of expediting human drug applications through the Food and Drug Administration's (FDA) approval process.

Under the Act and its subsequent reauthorizations, the drug industry pays user fees to FDA, and FDA commits to meet performance goals, such as reviewing applications within a certain period of time.

This construct was designed to give industry certainty and predictability, but also to speed new drugs and treatments to the public.

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The American people expect – and have a right to expect – that the federal government is doing everything possible to ensure that drugs on the market are safe and effective.

They also have a right to expect that applications for life enhancing and life saving drugs are not languishing on a reviewer's desk at FDA.

It is my hope that the new agreement balances both of these considerations, and I look forward to hearing from FDA, the drug industry, patient advocates, and researchers today on our panels.

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

Mr. BURGESS. I thank the chairman for yielding.

I am mindful of the fact that the last reauthorization was June of 2007, so it is a little over 4 years ago. At that time, I was concerned about some of the restrictions that this committee placed on the advisory panels that advise the FDA about the approval or nonapproval of drugs and devices. One of my concerns was we didn't follow the Institute of Medicine guidelines that no more than 40 percent of the people who are on the advisory committees have an interest in the product under consideration, and it was the will of the committee over my objections that no one on these advisory panels should have any interest or perhaps even any knowledge of the drug or device being considered.

I thought that was a serious and glaring oversight on the part of this committee, and I discussed it with then-Chairman Dingell extensively and offered amendments that were repeatedly voted down on party lines. But that is an oversight that I hope that this committee can now correct in this reauthorization period.

It appears we saw it unfortunately on display with the Avastin advisory panel last week in that there, to the best of my reading of the makeup of that group, there was not a specialist who dealt with breast cancer patients on that advisory panel so that there was no one on that advisory panel who actually followed a patient who was on Avastin for their breast cancer. Now we are left to defend the decision from the advisory panel to the FDA about the removal of that drug. And we are in a difficult position with Avastin because some people are apparently dramatically helped. Other people, the help is not so great. But it is, I think, incumbent upon us to get that right.

Other things that I think we need to do, we need to discuss the possibility of surrogate endpoints for studies within the FDA. Certainly that was useful in the early days of the AIDS research back in the 1980s. And the fact that we base everything upon survival statistics now and we are not looking at things like tumor burden or some other surrogate endpoint I think is a mistake on the part of our advisory panels.

I thank the chairman for yielding the time and I yield back the balance of my time.

Mr. PITTS. I thank the gentleman and recognize the ranking member of the subcommittee, Mr. Pallone, for 5 minutes for an opening statement.

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 on this very important subject.

Five years ago, this committee led the way in making grade strides in FDA policy and safety measures. In fact, some have said it was the most extensive overhaul of FDA policy and procedure in decades. What is important to note, however, is that this committee worked through the issues in a bipartisan manner, and I am proud of the consensus that we reached.

That legislation was supported by members, consumer groups and industry stakeholders. Together we recognized the need for a strong and well-resourced FDA to complete its mission. In addition, we accepted the reality that FDA must have the ability to be well-versed on the best science in order to get the safest and most effective drugs to the marketplace.

Now, in doing so I recognize that FDA must minimize the inappropriate burden it placing on the drug companies so that they do not stifle innovation. America's competitiveness depends on our ability to innovate and keep America number one, and as such I continue to believe that the government must be responsible for facilitating an environment where Americans can continue to innovate. This is the key to creating new thriving industries that will produce millions of good jobs here at home and a better future for the next generation. That said, we must not sacrifice safety and efficacy in exchange for innovation. PDUFA has been a true success and we must build on that success. We can't move backwards under the auspices of economic benefits.

So, Mr. Chairman, I hope we can move in the same bipartisan spirit as we did in 2007. Even more so, I hope that we can produce consensus legislation free of conflict and contentious issues. I look forward to working with you and my colleagues on this committee as this process moves forward and I welcome today's hearing as a first step towards that goal.

I wanted to yield 2 minutes to my good friend from Michigan, Chairman Dingell, but I still have another minute left, so let me say that I would like to close by commenting on the importance of the Drug Safety Enhancement Act. That is a bill that I coauthored with Mr. Dingell and Representatives Waxman and DeGette.

High-profile risks associated with the globalized drug supply like the Heparin crisis of 2007 have put Americans' lives at risk and our bill would equip FDA with the authorities and resources this it needs to keep peace with an increasing international marketplace of products so that Americans can have confidence that drugs they rely on will help them get better and not make them more sick.

So as we move forward, I will continue, Mr. Chairman, to make reference to the Drug Safety Enforcement Act and that bill because I do think it is important and also has a place during this PDUFA debate.

I see the gentleman is here. I yield to Chairman Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, I thank the gentleman and I thank you for holding today's hearings. I ask unanimous consent to revise and extend my remarks because of the shortness of time here.

I commend you for the hearing today with regard to the FDA amendments that we are discussing with regard to PDUFA. This is important. If everyone will recall, it has been accepted, it has been a tremendous success because of the cooperation between government and industry.

However, we need to address more problems. Commonsense authorities, like mandatory recalls, subpoena power, ability to seize and destroy imported drugs and raw materials at the border, making delay or refusal for inspection a prohibited act, are now needed to ensure that Food and Drug has the capabilities to properly oversee safety of our drug supply.

These are authorities that would be given FDA under H.R. 1483, the drug safety bill I introduced with my colleagues Mr. Waxman, Mr. Pallone and Mrs. DeGette. These are authorities that are desperately needed in order to address the safety of our American public. I would note that without them, imports of dangerous components and raw materials of pharmaceuticals, as in the case of Heparin, continue to threaten the well-being of our people.

My colleagues will remember that in the last Congress, we passed a food safety bill, which gave many of these authorities to Food and Drug, and which was, in fact, supported by the industry. It passed out of this committee by a heavy majority. It also passed the House and the Senate by a very large majority, and it is now standing to help and protect the American people.

I would hope that we would follow the example that we set last Congress when we worked together in a remarkably bipartisan fashion to see to it that we went well beyond just scratching the surface with regard to food safety and do a similar thing with regard to prescription pharmaceuticals and so move to protect the health, safety, life expectancy and to ensure that pharmaceuticals will not cause harm or death, particularly where it is from imported raw materials for the manufacture of finished products.

I thank you, Mr. Chairman. I thank the gentleman from New Jersey. I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and recognizes the full committee chairman, Mr. Upton, for 5 minutes.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Thank you, Mr. Chairman.

This is the first hearing of the 112th Congress on the reauthorization of Prescription Drug User Fee Act in the current state of medical innovation in America. I look forward to discussing FDA regs and how they effect innovation, job creation and the American patient's accession to life-improving drugs.

Congress last reauthorized PDUFA in 2007 with the Food and Drug Administration Amendments Act. That law as we know expires in September of 12, 2012, which is why our work to reauthorize this law begins today.

One area that the committee will examine is the lack of predictability and certainty at the FDA. These problems at FDA appear to be stifling American innovation, costing Americans jobs and obviously hurting American patients. Another area we will examine is the risk-benefit analysis used by FDA when approving drugs and whether the agency is striking the right balance on delicate issues. These are concerns that the FDA is failing to consider the views of patients who need access to lifesaving drugs, including those drugs that carry some risk.

The committee will evaluate provisions of the Food and Drug Administration Act amendments, including those affecting advisory committees in the risk evaluation and mitigation strategies. The rigid unrealistic conflict of interest provision has prevented in my view the FDA and its advisory committees from utilizing some of science's best minds and left advisory committee slots unfilled. We have to look at the implementation of this provision as to whether it really has caused delays in the approval process.

Our goal has to ensure America remains the leader in medical innovation. When the law works properly, the field creates new jobs and ensures American patients do have access to the best therapies available.

I thank the chairman, and I yield the balance of my time to Dr. Gingrey.

[The prepared statement of Mr. Upton follows:]

Opening Statement of Chairman Fred Upton
Health Subcommittee Hearing on PDUFA V: Medical Innovation, Jobs, and Patients
Thursday, July 7, 2011

This is the first hearing of the 112th Congress on reauthorization of the Prescription Drug User Fee Act and the current state of medical innovation in America. I look forward to discussing FDA regulations and how they affect innovation, job creation, and American patients' access to life-improving drugs.

Congress last reauthorized PDUFA in 2007 with the Food and Drug Administration Amendments Act, which is known as FDAAA. That law expires in September 2012, which is why our work to reauthorize the law begins today.

One area this committee will examine is the lack of predictability and certainty at FDA. These problems at FDA appear to be stifling American innovation, costing American jobs, and hurting American patients.

Another area we will examine is the risk/benefit analysis used by FDA when approving drugs and whether the agency is striking the right balance on this delicate issue. There are concerns that FDA is failing to consider the views of patients who need access to life-saving drugs, including those drugs that carry some risk.

The committee will evaluate provisions of FDAAA, including those affecting advisory committees and Risk Evaluation and Mitigation Strategies (REMS). The rigid and unrealistic conflict of interest provision has prevented FDA and its advisory committees from utilizing some of science's best minds and left advisory committee slots unfilled. We must also look at implementation of FDAAA's REMS provision and whether it has caused delays in the approval process.

Our goal must be to ensure America remains the leader in medical innovation. When the law works properly, this field creates new jobs and ensures American patients have access to the best therapies available. I thank Chairman Pitts for holding this hearing so we can identify ways to do just that.

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

Mr. GINGREY. I thank the overall chairman for yielding to me.

I believe the Prescription Drug User Fee Act reauthorization gives an opportunity to review the ways in which we can help improve the FDA approval process. In an age where our economy is fighting an international battle to remain the leader in medical innovation and the jobs that goes with those industries and patients in other countries have access to medical treatments that American patients do not, we need all hands on deck. No longer can we afford to sideline experts simply because of their ties to industry.

One idea I believe that deserves consideration, Mr. Chairman, is drawing from the joint NIH–FDA Leadership Council. This council was created in 2010 to spearhead collaborative efforts to improve the FDA regulatory review process. This initiative is a good, proactive first step toward improving and modernizing the FDA.

However, I believe if we are going to be truly successful in improving both the efficiency of the FDA as well as our understanding of how emerging technology can be used to improve regulatory review, other parties need to be at the table. Agencies like the CDC and Homeland Security, experts from the drug industry and academia, as well as patient advocates all need to be involved. A stakeholder group made up of various agencies, scientific leaders and business and academia and patient advocates can help support the FDA in its mission to advance regulatory science as well as other meaningful reforms and emerging public health issues. I look forward to working with Dr. Hamburg, the chairman and this committee on the issue.

In addition, this committee has spent years studying the oncoming public health threat posed by antibiotic resistance. It is a threat to our patients, it is a threat to our troops, and in the hands of terrorists, our national security. My colleagues and I on this committee, four Republicans, three Democrats, have introduced H.R. 2182, the GAIN Act. If we are to have the drugs needed to fight the looming threat of drug resistant bacteria, our legislation is an important first step in that fight. I hope to see it considered by this committee, this Congress, the 112th.

With that, Mr. Chairman, I thank the overall chairman for yielding to me and I yield back the remaining time.

Mr. PITTS. The chair thanks the gentleman and at this time recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes for an opening statement.

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

Mr. WAXMAN. Thank you, Chairman Pitts, for holding this hearing today.

I think we can all agree that it is critically important that there be a vibrant and flourishing innovation in the pharmaceutical industry. The medicines this industry has brought us have saved countless lives and improved the quality of life for people the world over. Unfortunately, by most accounts we are in the midst of a dramatic slowdown in drug development in the U.S. The reasons for

the slowdown are complex and multifaceted. At a time when you would expect there to be a surge of innovation, for example, because there is an unprecedented number of drugs coming off patent, the opposite appears to be true. I hope our witnesses will help us understand what is causing this innovation deficit and what we can do to help our drug companies succeed.

A rising chorus of voices have begun to assert the view that it is the FDA that is responsible for this downward trend. These critics claim that the FDA takes far longer to approve drugs than its counterparts in Europe. Some claim it takes the U.S. twice as long as Europe. Others claim it takes three times as long. These claims may sound convincing, but we have yet to see the data to support them.

I am aware of only one peer review study comparing drug approval times in the United States and Europe, and it found the exact opposite. This study, which examined the approval of 35 new cancer drugs, was conducted by one of our witnesses today, the Friends of Cancer Research. It found that the FDA is actually approving these lifesaving therapies much faster than its European counterparts.

Some view every decision FDA makes through the prism of whether it is good for the pharmaceutical industry. But that is not the right perspective. The question we should be asking is, what is the right decision for patients? It is in no one's interests to have a weak FDA. American consumers depend on FDA to verify the drugs we are taking are truly safe and effective. If Americans lose confidence in the FDA, they will lose confidence in the pharmaceutical industry as well.

We should all be united in the goal of ensuring that we have a strong, well-resourced FDA that is armed with a full compliment of authorities to protect us from unsafe drugs and to assure that these drugs work. That is FDA's fundamental mission, and that is why I strongly oppose any legislative proposal that would prevent FDA from insisting on adequate data from clinical trials and force it to approve drugs on an incomplete record. These proposals would prove disastrous for the safety and efficacy of our drugs supplied.

The title of this hearing suggests that our colleagues across the aisle believe that FDA's mission should encompass job creation. Democrats have been leading the charge for legislation to promote jobs and we have been bitterly disappointed by the failure of the House to pass pro-jobs legislation. But we should not be misled. 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 the drugs we take are safe and effective. Whether jobs will be created is simply not a part of that scientific public health equation.

I do believe there are areas in which the agency's regulation of drugs could improve. For example, improvements in FDA's scientific capacities will enable FDA to identify early end-points that can predict whether a drug will be effective which can result in better design of clinical trials and faster approval of new drugs. Making these kinds of strides require we work from real data, not self-serving urban myths.

We should require a significant influx of resources. It is ironic that at the same time they are complaining that FDA should do a better job, the Republicans in the House passed a budget and an appropriations bill that would gut FDA funding by over $500 million.

I want to turn briefly to the fact that we have an increasing globalization of our drug supply. The world has changed from the time of the original Food, Drug and Cosmetic Act. Today, more than 80 percent of active pharmaceutical ingredients are manufactured abroad, with China and India comprising the largest sources. Just yesterday, The Wall Street Journal talked about poor regulatory oversight of Chinese pharmaceuticals. That is why it is important to look at the Drug Safety Enhancement Act, which will go a long way toward providing FDA with these much-needed resources.

Mr. Chairman, our staff has reached out to your staff and Mr. Upton's as well requesting we engage in a bipartisan process to look at this bill and work toward incorporating whatever we can ultimately agree upon into the PDUFA package next year. I hope we can count on this opportunity to work together because it is in the public interest.

Thank you very much, Mr. Chairman.

[The prepared statement of Mr. Waxman follows:]

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS

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Opening Statement of Rep. Henry A. Waxman
Ranking Member, Committee on Energy and Commerce
"PDUFA V: Medical Innovation, Jobs, and Patients"
Subcommittee on Health
July 7, 2011

Thank you, Chairman Pitts, for holding this hearing today.

I think we can all agree it is critically important that there be vibrant and flourishing innovation in the pharmaceutical industry. The medicines this industry has brought us have saved countless lives and improved the quality of life for people the world over.

Unfortunately, by most accounts, we are in the midst of a dramatic slowdown in drug development in the United States.

The reasons for this slowdown are complex and multi-faceted. At a time when you would expect there to be a surge of innovation—for example, because there is an unprecedented number of drugs coming off patent—the opposite appears to be true. I hope our witnesses will help us understand what is causing this innovation deficit and what we can do to help our drug companies succeed.

A rising chorus of voices has begun to assert the view that it is the FDA that is responsible for this downward trend. These critics claim that FDA takes far longer to approve drugs than does its counterpart in Europe. Some claim it takes the U.S. twice as long as Europe; others claim it takes three times as long. These claims may sound convincing, but we have yet to see the data to support them.

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It is in no one's interest to have a weak FDA. American consumers depend on FDA to verify that the drugs we take are truly safe and effective. If Americans lose confidence in the FDA, they will lose confidence in the pharmaceutical industry as well.

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 that is why I will be strongly opposed to any legislative proposals that would prevent FDA from insisting on adequate data from clinical trials and force it to approve drugs on an incomplete record. These proposals would prove disastrous for the safety and efficacy of our drug supply.

The title of this hearing suggests that our colleagues across the aisle believe that FDA's mission should encompass job creation. Democrats have been leading the charge for legislation to promote jobs and we have been bitterly disappointed by the failure of the House to pass pro-jobs legislation.

But we should not be misled into believing that today's hearing is a genuine look at how to resolve our job shortage. 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 the drugs we take are safe and effective. Whether jobs will be created is simply not a part of that scientific public health equation.

I do believe there are areas in which the agency's regulation of drugs could improve. For example, improvements in FDA's scientific capacities will enable FDA to identify early endpoints that can predict whether a drug will be effective, which can result in better design of clinical trials and faster approval of new drugs.

Making these kinds of strides requires that we work from real data, not self-serving urban myths. It will also require a significant influx of resources. It is ironic that at the same time they are complaining that FDA should do a better job, the Republicans in the House have just passed an appropriations bill that would gut FDA funding by over $500 million.

Let me turn briefly to another issue that will be explored today: the increasing globalization of our drug supply. The world has changed from the days of the original Food Drug and Cosmetic Act. Today, more than 80% of active pharmaceutical ingredients are manufactured abroad, with China and India comprising the largest sources. Just yesterday there was a report in *The Wall Street Journal* about the poor regulatory oversight of Chinese pharmaceutical manufacturers and the resulting compromised drug quality.

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.

Our staff has reached out to your staff, Chairman Pitts, and Chairman Upton's staff as well, requesting that we engage in a bipartisan process to look at this bill and work toward incorporating whatever we can ultimately agree upon into the PDUFA package next year. I hope, Mr. Chairman, that I can count on your commitment to work with us on this critically important legislation.

I look forward to hearing from our witnesses today and, I hope, to work with my colleagues on a bipartisan basis on these important matters.

Mr. PITTS. The chair thanks the gentleman. The chair thanks the members for their opening statements. Any other opening statements will be entered into the record.

The chair thanks the witnesses for agreeing to appear before the committee today. Your written testimony will be made a part of the official record. We ask you summarize your opening statements in 5 minutes.

We have two panels today. The first panel contains a single witness. Dr. Woodcock is the Director of the Center For Drug Evaluation and Research at the Food and Drug Administration.

Welcome, Doctor. You may begin your testimony.

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you, Mr. Chairman and members of the subcommittee. I am Janet Woodcock, Director of the Center For Drug Evaluation and Research at FDA, and I would like to thank you for this opportunity to testify about the prescription drug user fee program, or PDUFA, as I am going to refer to it.

Congress instituted this program because patients in the United States were not getting access to new medicines as quickly as people in other parts of the world. This problem is called the drug lag, and it became particularly severe in the 1980s.

The chart we have brought, which you can see over there, shows that PDUFA really had an impact on this drug lag. In the 1980s, as you see, fewer than 10 percent of new medicines reached American patients first. They were available first in other parts of the world. PDUFA was started in 1992 and, as the data show, it quickly improved the availability of new medicines to the point now where we lead the world in introduction of new medicines.

I am a rheumatologist. I am a doctor who treats autoimmune diseases and arthritis, and I can attest to the revolution of therapies that has occurred since the start of PDUFA. Diseases that were crippling now have effective treatments that allow patients to lead full lives.

Recently, my seat mate on a plane showed me pictures of her wonderful gardens that she cared for herself. She told me that 10 years ago she was confined to a nursing home and it was only when she was started on a treatment, a new treatment for her autoimmune disease, that she was able to improve and is now active and well. This is the kind of treatments that we have seen coming out during the PDUFA period.

So since the start of PDUFA, increasing numbers of new medicines were available first in the United States. Currently we lead all other countries in the introduction of new therapies. Every 5 years, PDUFA must be reauthorized, and each cycle of reauthorization has brought new enhancements to the program. Most recently, there has been a focus on improving drug safety monitoring and that was the focus of the last cycle. Successful innovations, such as our sentinel initiative, resulted from that safety focus.

For this cycle of PDUFA renegotiation, Congress directed FDA to conduct a very open and inclusive process with significant stakeholder participation. We have done so, as detailed in my written

testimony, and I believe the outcomes of the negotiation have really been improved as a result of this new process.

Now, the drug development enterprise is in a very different place than previous PDUFA negotiation cycles. Drug development faces many of the problems other industries do right now due to the economic turn-down. But more significantly, there is a severe productivity problem worldwide in drug development in which an ever-increasing R&D investment is producing ever-fewer new drugs. This isn't just true in the U.S. It is true everywhere. It is no exaggeration to say that the industry is in crisis.

At the same time, the scientific opportunities have never been greater. It is incredibly frustrating to see the explosion in biomedical knowledge and at the same time to watch the struggles and repeated failures of drug development programs that try to utilize this knowledge. Despite these serious problems, things may be looking up. This year to date, FDA has approved 20 new medicines, just one short of the total approved last year, and many of these medicines are game-changers for patients. We do see a rise in new development programs coming into the FDA as well.

We have been moving through the process set down by Congress for this cycle of PDUFA negotiations and we have developed a set of recommendations that are laid out in my written testimony. These include new steps to incorporate scientific advances into regulation so we can do what we can for the problems that industry is facing; also providing for meaningful patient input into the standards of benefit and risk that FDA applies to these new products; to provide a more transparent and predictability review process for sponsors, and there is quite a bit in there for that; and to further enhance drug safety.

In closing, I would say that in addition to these challenges, the pharmaceutical industry and FDA does face the challenges of globalization, which are ever-increasing and are well covered, and I am sure you are aware of, both in clinical trials being done all around the world and medicines being made all around the world. We still have to ensure the safety and effectiveness for our patients.

We look forward to working with Congress on all these challenges. We feel that the success that is demonstrated of PDUFA can be extended and we can do the right things, both for the patients in this country and for the industry that brings them new medicines.

[The prepared statement of Ms. Woodcock follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

JANET WOODCOCK, M.D.

DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PDUFA V: MEDICAL INNOVATION, JOBS, AND PATIENTS

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

JULY 7, 2011

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA), also referred to as "PDUFA V," and other efforts underway at the Agency to continue access to innovative new medicines and to address the continuing challenges of a global marketplace.

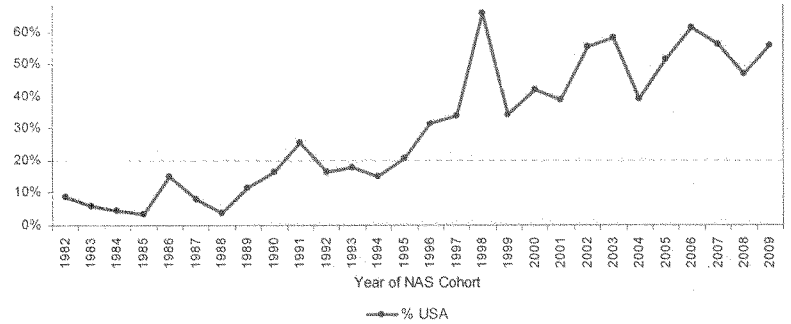
Background on PDUFA

FDA considers the timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) to be central to the Agency's mission to protect and promote the public health. Prior to enactment of PDUFA in 1992, FDA's drug review process was not very predictable and was relatively slow compared to 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 and biologics without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval.

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

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



diseases. As shown in Figure 1, the United States now leads the world in the first introduction of new active drug substances.[1] According to researchers at Tufts Center for the Study of Drug Development, the time required for the FDA approval phase of new drug development has been cut by 60 percent since the enactment of PDUFA,[2] from an average of 2.0 years for the approval phase at the start of PDUFA to an average of 1.1 years today.

FDA often hears claims that the United States approves new drugs less quickly than its foreign counterparts, particularly the European Medicines Agency (EMA). While we are not in competition with other countries, we recognize it is our public health duty to approve drugs

[1] Source: Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005), PharmaProjects R&D Annual Review (2006-2009).
[2] 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.

as quickly and safely as possible. A recent article in the journal *Health Affairs*[3] compared cancer drugs approved in the United States and Europe between 2003 and 2010. Of the 35 cancer drugs approved by FDA or the EMA from October 2003 to December 2010, FDA approved 32—in an average time of 261 days. EMA approved only 26 of these products, and its average time was 373 days. All 23 cancer drugs approved by both agencies during this period were marketed first in the United States.

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

Improvements in the efficiency of the drug review process and the quality of new drug applications is evident in the trends toward greater first-cycle approvals for novel drugs, known as "priority" new molecular entities (NMEs). A first-cycle approval means that the product application is approved after the initial, complete FDA review, rather than entering another cycle of FDA questions. Importantly, first-cycle approvals bring innovative drugs with new benefits to patients sooner. The average first-cycle approval rate for priority NMEs

[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.

has increased from 46 percent in PDUFA I to 68 percent to date in PDUFA IV. First-cycle approval rates have also increased for standard NMEs from an average of 30 percent in PDUFA I to 38 percent to date in PDUFA IV.

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. Under PDFUA IV, FDA agreed to aim to review priority NMEs more quickly—6 months vs. 10 months for standard drugs. Priority NMEs represent the truly innovative medicines 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.

Two recent examples of innovative products given priority review are Victrelis (boceprevir) and Incivek (telapravir), two new drugs for the treatment of hepatitis C. These drugs were approved this past May following the first FDA review cycle and are significant advances for patients suffering with hepatitis C. The Centers for Disease Control and Prevention estimate that about 3.2 million people in the United States have chronic hepatitis C. Most liver transplants performed in the United States are due to progressive liver disease caused by hepatitis C virus infection. Some with hepatitis C will develop cirrhosis of the liver over many years which can lead to liver damage with complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections, or liver cancer.

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. FDA followed this approach in its recent approval of Yervoy (ipilimumab) to treat patients with late-stage (metastatic) melanoma. Yervoy is the first therapy approved by FDA to clearly demonstrate that patients with metastatic melanoma live longer by taking this treatment.

Melanoma is the leading cause of death from skin disease. An estimated 68,130 new cases of melanoma were diagnosed in the United States during 2010, and about 8,700 people died from the disease last year, according to the National Cancer Institute. Late-stage melanoma is devastating, with very few treatment options for patients, none of which previously prolonged a patient's life. All patients in the study had stopped responding to other FDA-approved or commonly used treatments for melanoma. Patients who received Yervoy alone, or in combination with an experimental vaccine, lived an average of about 10 months, while those who received only the experimental vaccine lived an average of 6.5 months. However, Yervoy also poses a risk of serious side effects, including severe to fatal autoimmune reactions in 12.9 percent of patients treated with Yervoy. FDA decided that the benefits of Yervoy outweighed its risk, especially considering that no other melanoma treatment has been shown to prolong a patient's life.

PDUFA funds help support the use of existing mechanisms in place 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 the patients' safety.

One such program is accelerated approval. 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. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome, such as survival or symptom improvement. The use of a surrogate endpoint can considerably shorten the time to approval. Approval of a drug based on an unvalidated surrogate endpoint is given on the condition that post-marketing clinical trials verify the anticipated clinical benefit. Over 60 critical products have been approved under accelerated approval since the program was established.

While the best means of providing access to useful medical treatments for all Americans is to approve drugs proven to be safe and effective, 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 including clinical trials, single patient INDs and treatment protocols. 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 these cases, the patient may gain access to an investigational therapy through one of the alternative mechanisms.

Drug Safety Activities

In parallel with improvements in the drug review process, FDA has increased its focus on drug safety, including implementing the Food and Drug Administration Amendments Act of 2007 (FDAAA). In FDAAA, Congress authorized additional user fees totaling $225 million for the five years of PDUFA IV reauthorization to enhance drug safety activities. FDAAA also provided FDA with important post-market safety authorities. Under FDAAA, FDA was given the ability to require post-marketing studies and clinical trials to address important drug safety questions. Between the enactment of FDAAA on September 27, 2007, and June 1, 2011, FDA has required sponsors to conduct approximately 375 post-marketing studies or trials to address important drug safety questions that could not be addressed before the drug was approved. For example, FDA has required post-marketing clinical trials for Visicol and OsmoPrep (oral sodium phosphate bowel cleansing preparations) to assess the risk of developing acute kidney injury in patients undergoing bowel cleansing using these products. FDA is tracking the conduct of these studies and will take enforcement action if, without good cause, the studies are not conducted in a timely manner.

FDAAA also gave FDA the authority to require safety labeling changes based on new safety information identified after a drug is on the market. FDA has used its new authority to require sponsors to place important new safety information onto their drug labels quickly, in some cases using this authority to require changes to the labeling of all members of a class of drugs. For example, FDA required labeling changes for the Long Acting Beta Agonist

(LABA) products to include a new warning in the labels that these products should not be used alone in the treatment of asthma. Although these medicines play an important role in helping some patients control asthma symptoms, they also pose an increased risk of asthma exacerbations, hospitalizations and death. For this reason, their use should be limited whenever possible.

FDAAA also provided FDA with authority to manage risks associated with marketed drug products through required Risk Evaluation and Mitigation Strategies (REMS). FDA has been using this new authority judiciously. For example, FDA required a REMS for Caprelsa (vandetanib), the drug approved to treat medullary thyroid cancer. The approved REMS required a Medication Guide, a communication plan, and elements to assure safe use, including prescriber education and enrollment and pharmacy enrollment and training to mitigate certain cardiovascular risks and sudden death that can occur in some patients. Without this REMS, the benefits of Caprelsa would not have been considered to outweigh the risks, and the drug could not have been approved.

In addition, FDA has implemented other important drug safety initiatives under FDAAA, including, for example, initiating systematic reviews of the safety of marketed drugs 18 months after approval; conducting regular screening of the adverse event reporting system database and posting quarterly reports of new safety information or potential signals of serious risks identified from that screening; and developing an active post-market drug safety surveillance capability under the "Sentinel" initiative.

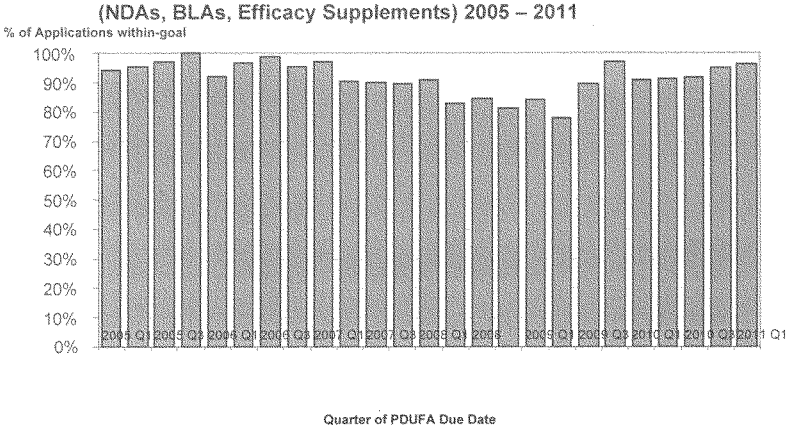
Challenges for the Current Program

Although we can report many important successes with the current PDUFA program, new challenges have also emerged that offer an opportunity for further enhancement. For example, while new FDAAA process requirements have strengthened drug safety, they have put strains on the review process time frames agreed to, as well as on post-market review activities, which compete for the same resources. 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 further to conduct preapproval 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 to ensure timely implementation of all the new FDAAA provisions that

affected activities in the new drug review process. This is shown in Figure 2. However, FDA

Figure 2. CDER PDUFA Application Review Performance (NDAs, BLAs, Efficacy Supplements) 2005 – 2011



wants to meet not only the letter (i.e., PDUFA goal dates), but also the spirit of the original PDUFA goal—speeding patient access to drugs shown to be safe and effective for the indicated uses. Therefore, the Agency is working towards getting more products approved in the first review cycle by trying to identify factors leading to first-cycle approval.

PDUFA Reauthorization

In PDUFA IV, Congress directed FDA to take additional steps to ensure that public stakeholders, including consumer and patient organizations, would have adequate opportunity to provide input to 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 regulated 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 were concluded in May 2011 and the enhancements are under internal review. We plan to hold a public meeting in the fall to solicit comments on proposed recommendations and then transmit the final recommendations to Congress in January 2012.

We are very pleased to report that the enhancements for PDUFA V under consideration 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 the enhancements under consideration.

A. *A Review Program for New Drug Applications (NDA,) New Molecular Entities (NME), and Original Biologics License Applications (BLA)*

FDA's existing review performance goals for priority and standard applications—6 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 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, an enhancement being considered in FDA's review program for NME NDAs and original BLAs in PDUFA V would include 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, FDA's review clock would begin after the 60-day administrative filing review period. The impact of these modifications on the efficiency of drug review for this subset of applications would 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. Regulatory science is the science of developing and applying new tools, standards and approaches to assess the safety, effectiveness, quality and performance of FDA-regulated products.

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 that will create uncertainty for patients and health professionals. 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 being considered 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 nearly a four-fold increase in this type of review work.

PDUFA V enhancements being considered include augmenting the Agency's clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmacogenomic 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 (PRO)

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 the 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 being considered 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 being considered 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 exploring an effort 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. 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 the drug review process. 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 being considered for PDUFA V include two post-market, safety-focused initiatives.

1. Standardizing REMS

FDAAA gave FDA authority to require 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 being considered would 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 would 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, and 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 would 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 would 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 nonclinical data submitted in marketing and investigational applications.

F. *User Fee Increase for PDUFA V*

Implementing the PDUFA enhancements being considered would add $40.4 million to the estimated PDUFA user fee revenue amount in FY 2012. This translates to a modest 6 percent increase, and a total estimated base of $712.8 million in FY 2013.[4]

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 being considered 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 would 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.

Additional Initiatives to Encourage Development of New Therapies

Both FDA and the pharmaceutical industry are facing economic and scientific challenges in drug development. Industry is facing a "patent-cliff," where many of the most profitable brand-name products will face generic competition for the first time. Although this

[4] The FY 2012 estimated user fee amount is $672.4 million. The exact amount will be determined when we have the final-year workload data for PDUFA IV. That number would be used to calculate the exact fee amounts for FY 2013, the first year of PDUFA V.

generic competition will benefit consumers by bringing down the cost of these medicines, their manufacturers will lose large sources of profit. Industry must also navigate changing reimbursement rules and increasing expenses from clinical trials. Only a profitable industry can continue to fund the research and development necessary to find new cures.

Although the NDA/BLA approval phase of drug development (the phase in which FDA plays the biggest role) is reported to have the highest success rate of any phase of drug development, 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 in the other phases of drug development. To promote the development of innovative new therapies, FDA is working on advancing our scientific base, even apart from the resources contained in the PDUFA V enhancements being considered. 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 and academic institutions to develop the science needed to maximize advances in biomedical research and bring the development and assessment of promising new therapies 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 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 recently approved Myozyme (alglucosidase alfa) for the treatment of Pompe Disease, which is a rare genetic disease resulting in progressive skeletal and respiratory muscle weakness caused by an accumulation of glycogen (a carbohydrate). About 1,000-2,000 patients in the United States suffer from Pompe Disease, of which only a few hundred are infants. In infants, the disease can be rapidly fatal due to respiratory failure. FDA approved this drug in April 2006, based on the results of a single, pivotal study in 18 patients.

In March 2010, FDA approved Carbaglu (carglumic acid) for the treatment of N-acetylglutamate synthase (NAGS) deficiency, the rarest of the Urea Cycle Disorders, which are diseases that lead to elevated ammonia levels in the blood and cause seizures, poor muscle tone, respiratory distress, coma, and even death. NAGS deficiency affects fewer than 10 patients in the United States at any given time. FDA approved this drug based on a case series in 23 patients.

The 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 up to 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. Last month, 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. 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 an international operating model that relies on improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources through partnerships.

We engage in international drug standards development and harmonization efforts, and last year we conducted more foreign inspections than ever before in our history. We also just established a new Office of Drug Integrity, Security, and Recalls, which specifically focuses on drug quality issues such as counterfeiting, economically motivated adulteration, cargo theft, and other supply chain threats and vulnerabilities.

New regulatory authorities may help ensure that we can hold industry accountable for the security and integrity of their supply chains and the quality control systems they use to produce drugs for the American people. In our increasingly complex and globalized world,

additional authorities could be important tools to help support FDA's efforts to protect the safety of imports and the health of our citizens.

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 accomplishment, 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. Thank you. I will now begin the questioning and recognize myself for 5 minutes.

Mr. GINGREY. Mr. Chairman, we cannot hear you. Your mic may not be working.

Mr. PITTS. All right. I will hold it closer.

According to reports from the California Health Care Institute, and Ernst & Young and testimony here today, FDA's regulatory uncertainty is stifling American job creation. To compound the problem, foreign countries like those of the EU, China and India, are proactively trying too take American jobs by making their regulatory systems more predictable and efficient and creating an ideal innovation climate for companies. Given the importance of these innovator companies to our country and our Nation's patients, these developments are disconcerting, to say the least.

While foreign regulatory bodies are becoming more efficient, FDA appears to be going in the opposite direction. Is FDA, first of all, aware that these foreign countries are proactively trying to take American jobs?

Ms. WOODCOCK. We are aware that both Europe, which has the Innovative Medicines Initiative, Singapore, China, many countries are looking to build a very strong R&D biomedical development industry in their countries. Absolutely.

Mr. PITTS. The second question: What is FDA's role in creating a hospitable climate for American innovator companies so that they can create jobs and create new lifesaving therapies for patients here?

Ms. WOODCOCK. Well, first of all, I would like to start with the facts, all right? That chart shows when the U.S. is the country that first launches a drug in our country, and you can see that is continuing to go up. So that is compared to all other countries worldwide.

You will also hear testimony about a comparison to Europe. And we are not in competition with Europe, but you can see in the U.S., the drug approval process is faster and drugs reach patients more quickly than in Europe. That is simply one comparison. However, we, since 2004 when we put out what was called the Critical Path Report, have been working with industry to try to solve a lot of both the scientific and regulatory problems that impede innovation and keep drug development from proceeding smoothly.

So we are very aware of this. It is a problem for us as well as for the industry. The people who work at the Center for Drugs and regulate new drugs are doctors, and they are rheumatologists and they are pulmonologists and they are cancer doctors and infectious disease doctors. They know their patients need additional therapies and they want to see them out there for the patients. So this drug development enterprise is important for everyone and it is important to get it right.

Mr. PITTS. And what has the FDA done to forestall the attempts by the EU, China and India to take our jobs?

Ms. WOODCOCK. FDA has a very predictable drug review process. In fact, our review process is the most predictable part of drug development. If you can get through all the clinical phases of drug development where you test it on people, the process that FDA

uses is extremely predictable. And that is a result of the user fee program.

Right now we have the highest rate ever of what we call first cycle approvals, which is if companies send in their application, they get it approved on the first try. And we have timelines for that and we meet our timelines of review. So we have a very predictable and open process, and companies usually come first to the United States with applications for their new drugs.

Mr. PITTS. OK, another question. I have heard from many patients that they believe their interests are not taken into account during the FDA approval process. Patients, including those with life-threatening diseases, are willing to tolerate additional risk in order to try these new drugs that will hopefully save their lives. How does FDA take patients into account when reviewing new drugs and how does it account for patients and their willingness to tolerate additional risk?

Ms. WOODCOCK. The patients are the most important part of this. It is really for patients that medicines are developed and that the FDA does the review process, and we fully understand that people facing more serious diseases are willing to take higher risks.

For example, we have a drug for multiple sclerosis that causes sometimes a rare, very serious and often fatal brain disease, and that drug was briefly withdrawn from the market because of doing this. When we talked to the patients, they said we are willing to take this risk, because this drug really helps prevent the progression of multiple sclerosis. That drug is available now to patients because we understand that when you face such terrible diseases, you are willing to take risks.

Mr. PITTS. My time has expired. I recognize the ranking member for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman. And Dr. Woodcock, some of my questions are along the same topic, if you will, as the chairman. I guess this really shows that we are being bipartisan today.

Most of my colleagues have been told that FDA is responsible for what is claimed to be a significant slowdown in development and marketing of new and innovative pharmaceuticals. Whether that is true or not, that is what we are told.

There is a statement in Mr. Leff's testimony, he is on the next panel, which sums up what I hear. He states, "While many factors have contributed to the escalating cost, time, and risk of new drug development, a changing regulatory environment at the FDA is the most significant."

He attributes this, in large part, to increasing public pressure on FDA to focus more on safety and lesson benefit in the wake of the emergence of safety problems associated with Vioxx in 2004. He further points to numbers showing that FDA approved an average of 36 new drugs and biologics per year from 1996 to 2004, but an average of only 21 per year from 2005 to 2010.

My question is, how do you respond to these claims? Is it really true that there was a sudden dropoff in approvals right after 2004 and that approvals in the years immediately preceding 2004 were well over one and a half times as frequent as in the years immediately after 2004, and has FDA really become too risk averse and

not focused enough on benefits such that maybe innovation is being blocked.

Ms. WOODCOCK. Well, I appreciate these questions. As a physician, I will tell you, I think it is important, though, to establish the diagnosis before we move to treatment. So it is really important to understand the facts.

The facts are, first of all, as we have already discussed, the FDA approves drugs and gets them on the market more regularly first than any other country in the world, all right? We are meeting all of our PDUFA goals for review times, so our review time is very prompt. We are approving more than two-thirds of critical new drugs, those important new drugs that will make a difference for patients, on the first round. After they are approved, we review them and then they get on to the market. And we have the highest rate historically in 20 years right now of these first round approvals.

So FDA is moving promptly and is approving a high percentage of the drugs that are submitted to us. However, we can't approve drugs that don't come in the door. And this slowdown is worldwide. This is not a FDA phenomenon. The pharmaceutical industry is suffering a crisis and we are not seeing as many submissions to us, nor is the EU, nor are the other regulatory authorities around the world, and this scientific challenge I think is the major problem that we face.

Mr. PALLONE. You have already, in response to the chairman's question, mentioned Europe. I read a study published in the July issue of Health Affairs by Friends of Cancer Research, which found that FDA actually approves cancer drugs significantly more quickly than its counterpart in Europe. Now, that was just for cancer drugs. But how does FDA compare with Europe in approval times of other classes of drugs besides cancer drugs?

Ms. WOODCOCK. This is true for all of the high priority drugs that are going to make a difference for patients. We don't have all the data in a tabular form that we can give you, but we have looked into this.

For example, we just approved two drugs for hepatitis C—treatment of hepatitis C. Hepatitis C has been poorly treated. The treatment has difficult side effects and it often leads to liver failure and need for liver transplant and even death. We have just approved two new drugs that have a high rate of what is called virological response or cure, so we expect that many more people will be able to be cured for hepatitis C. Those two drugs are not approved anywhere else in the world right now.

Mr. PALLONE. Let me just ask you, would you say FDA could make some improvements in terms of helping industry proceed through the regulator process, and more specifically, where do you think the major roadblocks are going from earliest research to drug approval? Where can more effective improvements be made to shorten the time between discovery and marketing?

Ms. WOODCOCK. The scientific breakthroughs we are currently experiencing with targeted therapy or personalized medicine or whatever, and I don't have time to go into it here, are giving us new opportunities to have new development pathways. We have been giving very significant thought to that, and I think we will be

coming forth with some new development pathways that can help speed these medicines along and get them to patients sooner.

This doesn't involve FDA review, because if we get a really good product into FDA, we can review it and get it on the market really quickly. What people are alluding to is the development time takes a long time. So we have some ideas about how to improve drug development for these highly effective therapies and we will be starting some efforts on that.

Mr. PALLONE. Mr. Chairman, could I just ask, I don't know if she does have something that she could follow up with on that, but if I could ask through you if there is more information, you could send us in writing about those new trends, I would appreciate it.

Ms. WOODCOCK. I would be happy to do so.

Mr. PITTS. If you would provide that to the committee.

The chair recognizes the vice chairman, Dr. Burgess, for 5 minutes of questions.

Mr. BURGESS. I thank the chairman for the recognition. Dr. Woodcock, thank you for being here again.

Reference was made to the European Medicines Agency, that is, the FDA is actually more rapid. Now, would it be fair to say that the timeline is more predictable at the European medicines agency and the FDA?

Ms. WOODCOCK. Our timelines are very predictable.

Mr. BURGESS. Does that include a timeline start to finish, or a timeline where you reset the clock because you have asked for new information or a different study to be done? Because this is the question that people come in with. I see people in my office literally every week with a drug or device who say that the FDA changes the rules of the game when we are deep into the process. I can't get any of them to come here and testify before this committee because they are frightened, quite frankly, of you and your agency. They are scared to speak up because they know that that could reset the clock once again.

Is this a fair criticism that I am getting from people who have drugs and devices before your agency?

Ms. WOODCOCK. As I said, we ought to start with the facts. The facts show that we are approving a very high percentage of priority drugs, an extremely high percentage on the first cycle. So that is a 6-month review, all right, generally speaking. And so that is a very predictable review.

The second issue you are raising is do we change the standards? Sometimes as we learn about side effects of drugs as they are on the market and we gain more information, then we do need to ask companies that have additional drugs in that class or whatever to look for those side effects and study them before marketing. So that does happen sometimes.

Mr. BURGESS. It is not just sometimes. It seems like it happens all the time. Now, I have to be careful not to confuse drugs and devices, but let me talk about devices for just a moment.

I met a physician out in West Texas who developed a method for conscious sedation that was much more safe than anything that he had used in his practice as an anesthesiologist. It came to him while he was watching his newborn son being circumcised. And while it turns out that this device would not help in newborn cir-

cumcision, there are many other clinical applications where it would be very efficacious. As he told me this story, he said, just to put it in context for you, I developed this as a consequence of my son being a newborn and undergoing this procedure. And he is going to college this weekend, we are packing the car up to take him to wherever, and the device is no closer to being approved than it was 17 years before.

Now, this individual no longer had a financial interest. It was simply because it was his baby literally, his idea that he wanted to see come to fruition and help patients. He sold it to a large medical manufacturing entity. But this thing was still bogged down in the process, and it was months and years of FDA advisory panels and this sort of thing. Even when they got clean bills by the advisory panel, then for some reason, the FDA would overrule and send them back to the starting point.

He is not alone. There are other device manufacturers in my office, again, literally every week, and probably because this hearing is being televised, I will hear from a lot more of them now. But can you address that? We talked about the devices that are being offshored because the environment is more friendly in other locations. You admit that other countries are actively recruiting our innovators. Are you working on that?

Ms. WOODCOCK. Certainly. The reason that drug companies are going offshore has to do with the cost of either manufacturing or the cost of doing clinical trials. They are still submitting drugs to the U.S., because we are a large market. And as you see, we get drugs on the market before any other country in the world most frequently.

As far as——

Mr. BURGESS. I am going to run out of time, so let me go back to what you were talking about initially where you said your time line, that you are good, you are meeting your performance goals. There is a study from the California Health Care Institute where they talk about the FDA not meeting its goals and that your times have slipped since the last PDUFA reauthorization in 2007. Can you address that for us?

Ms. WOODCOCK. Certainly. In the year or so after the passage of the Amendments Act, we were given a very large assignment of work by Congress in the Amendments Act which had many, many activities that we had to do. We made that our priority and accomplished those activities that we were directed to do by Congress.

During that time, our goals did slip slightly and we failed to meet some of our goals, although we still had a very high performance. That situation has been rectified and we are now meeting and exceeding our user fee goals again.

Mr. BURGESS. According to this study, you have slipped 28 percent. It is fair to say the Democrats' last reauthorization slowed you down. Let's hope this reauthorization doesn't perform similarly.

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

Mr. PITTS. The chair thanks the question and recognizes the gentleman Mr. Gonzales for 5 minutes for questions.

Mr. GONZALEZ. Thank you very much, Mr. Chairman, and welcome, Doctor. Quickly following up on Dr. Burgess' question, it is very interesting, because I think there has been some comments

that we are losing jobs and such and investment in the United States because pharmaceutical companies want to do things outside of the United States, and the reason for that is the slow, cumbersome regulatory system that the FDA presents.

Your response was that is not necessarily true. If cost is cheaper in another country, whether it is manufacturing or research and development, that is where the investment may be made, and it is strictly more on finances than anything else, eventually that particular company, whatever it manufactures, whatever it presents for consideration, is still going to come through FDA, that is right, and the reason, and you cited it, is that this is an incredibly lucrative market for pharmaceuticals, the United States of America.

Would you say that in the United States of America, maybe there is a greater profit margin for pharmaceuticals than in other countries?

Ms. WOODCOCK. I am not really qualified to comment on that. I am a doctor, not an economist. Sorry.

Mr. GONZALEZ. Do you know of any literature that might support the proposition that because of the system that we have in the United States, we may well be paying more for a certain drug, the same drug that is available here in the United States as well as in other countries?

Ms. WOODCOCK. Yes, I am certainly aware of that.

Mr. GONZALEZ. How is FDA approval viewed? And I guess you can congratulate yourself because I assume it is very favorable, how is FDA approval viewed worldwide in other markets in other countries?

Ms. WOODCOCK. Well, FDA has generally been viewed as say one of the gold standards. We provide a scientific and technical and highly unbiased review, and we base it on the evidence. We are really the only place in the world that goes down to the patient level data, and we get that data in and review it. So we are confident when we make a decision that is based on the actual evidence that has been generated. Many countries in the world look to FDA, all of our standards, our standards for manufacturing, our standards for clinical trials and so forth. But we have made a lot of efforts to harmonize those internationally through various arrangements that have been made.

Mr. GONZALEZ. Let's just say that there was just total reciprocity and you could sell a drug that was manufactured and approved by another country, this is a make-believe world. In your position, of all the countries, which regulatory agency regarding drug approval would you depend on before you would prescribe that drug for a patient? I know you are from the FDA and this may be quite an obvious answer. But seriously, if you were a physician in another country, wouldn't it be FDA, the United States of America?

Ms. WOODCOCK. Well, I certainly have spoken to many physicians and many regulators around the world, and our process is viewed as a very robust and excellent process that people look up to as a gold standard.

Mr. GONZALEZ. We want you to do things timely, we want you to do it efficiently for all the right reasons, but not at the cost of quality and safety. That is the only point I think all of us would agree on.

How do other countries finance their regulatory—let's say their FDA, their equivalent of FDA?

Ms. WOODCOCK. In Europe, there are user fees. It is not the same arrangement because the countries give scientific experts to the process and there are multiple countries involved in the EU. There are different arrangements around the world. Many of them involve user fees of one type or another. Many countries do not have the personnel, scientific personnel and resources, to mount a kind of review that we do, so they rely upon conclusions from the World Health Organization, from the FDA, and from others.

Mr. GONZALEZ. I guess my final question, I have 30 seconds, and that is, we have been referencing what FDA means in the United States and such. We do not defer to other governmental regulatory agencies in other countries for the safety of our pharmaceuticals, is that correct?

Ms. WOODCOCK. That is correct.

Mr. GONZALEZ. Thank you. I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman Mr. Shimkus for 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Dr. Woodcock, thank you. You are not an economist, and although we have a lot of physicians on the committee, most of us are not, so you are in good company here.

From your opening testimony, the words I caught on to was the drug lag, R&D, investment, fewer drugs because of that. We are going to have a venture capitalist, I think, on the second panel, an investor, talking about, and that is where we are trying to marry how do we keep capital going into this.

I don't mind talking about the great job creating aspects of a thriving pharmaceutical industry that is putting safe and efficacious drugs out on the market. At a time when we are looking for job growth, that sector can do that, the telecommunications sector can do that, the energy sector can do that. But as my friend Charlie Gonzales was talking about, we still want it safe, and that is a big criteria. Globalization does play a big role, another word in your opening testimony.

So it is in these concerns that we—the issue of our European competitors, who have some quality standards, may be starting to close that gap, plus Asian producers who may be closing that gap. But we have had concerns about what we receive there. This committee has had numerous testimony on stuff, not just on pharmaceuticals, but also, just food products and stuff that has been of great concern.

Some of us have been focused on the antibiotics issue, which I would like to turn to a little bit, bacterial resistance to antibiotics, which I know is a concern to you all. Part of your guidance there was some concern that your agency was not giving adequate guidance for clinical trial design for new antibiotics, especially in the case where no treatment existed for a given infection.

Can you discuss what progress the FDA has made in this area since you last testified?

Ms. WOODCOCK. Certainly. We have been working with the foundation for NIH that convened a group that is working on endpoints for clinical trials for different classes of antibiotics. I think this is

very promising. We also have been having discussions about basically untreatable infectious diseases, multiple drug-resistant infections and how one would do trials, and we do hope to get out some guidance on that.

We don't know either, all right? This is unchartered territory. So we can put our best ideas forth, but we don't have all the answers about how to study these. I think we will show considerable flexibility in the standards that we apply when we are talking about diseases, infectious diseases that really lack any alternative treatment.

Mr. SHIMKUS. Can you give me any thoughts on the need for new antibiotics to treat resistant infections?

Ms. WOODCOCK. The bugs are always ahead of us, all right, and that is something we just have to live with, that the infectious organisms can mutate very rapidly. We give antibiotics out to a lot of people. We put the bugs under selective pressure, and bingo, we have resistant organisms that we can't treat very well.

So this is an ongoing problem where we need a robust pipeline of new antibiotics, and to some extent, we need some effective antibiotics that we don't use very much, all right, that we hold in reserve for those types of situations, because if we use them broadly, then the bacteria become resistant.

Mr. SHIMKUS. On a separate issue now, talking about the FDA advisory committee and situations in which an individual may be disqualified because they have worked on a clinical trial for an unrelated product, not a related product, and that is, I think, an issue—is that true? Do you know of cases where someone has been disqualified because they worked in a clinical trial for an unrelated product, and does that hurt in this clinical time lag that we are kind of debating today?

Ms. WOODCOCK. Yes, it is true. It is also true we have difficulty recruiting qualified people and having highly qualified panels. In some cases, we have had to delay advisory committees because of the difficulty, because once we go through in great detail, all the financials of the individuals we have nominated, we find that they have to be excused from participating.

Mr. SHIMKUS. Thank you, Mr. Chairman. Thank you, Dr. Woodcock.

Mr. PITTS. I thank the gentleman and recognize the gentlelady from California, Ms. Capps, for 5 minutes for questions.

Mrs. CAPPS. Thank you, Mr. Chairman.

And thank you for your testimony, Dr. Woodcock.

I would like to reiterate for a minute what others on the panel have been saying.

The PDUFA program has largely been a successful and creative partnership, in my opinion. And I look forward to working with my colleagues on both sides of the aisle to strengthen the program during this reauthorization process. Moreover, I think a lot of what we have heard today reinforces the importance of giving the FDA the resources it needs to ensure that the agency can do its work independently and in a timely manner while ensuring patient safety.

While the FDA's drug review process has a great number of strengths, I am concerned about reports that clinical trials data submitted to the FDA do not routinely include reporting based on

sex or other important demographics. For example, one study found that, despite FDA regulatory requirements that require the reporting of a broad range of demographic data, more than one-third of the time this information is not being provided. In addition, a 2007 study specifically looking at heart disease clinical trials—and, of course, heart disease being the number-one killer of women—found that only 25 percent of trials report sex-specific results in scientific journals.

These issues were highlighted in a 2010 Institute of Medicine report entitled, "Women's Health Research: Progress, Pitfalls, and Promise," which found that—and this is a quote from the report—"inadequate enforcement of recruitment of women and of reporting data by sex has fostered suboptimal analysis and reporting of data on women from clinical trials and other research."

Its recommendations included specific strategies for the agency. And another quote from them, which I am sure you know about: "For medical products, drugs, devices, and biologics that are coming to the market, the FDA should enforce compliance with the requirement for sex-stratified analysis of the efficacy and safety and should take those analyses into account in regulatory decisions."

Unfortunately, as you know, there is a limited transparency with these applications, making it difficult for the public or prescribing physicians to know if any improvements on this data collection are being made. So my question is, can you discuss this work with us, please? What has FDA done to address the gaps in these data?

Ms. WOODCOCK. Well, interestingly, when I started at the Center for Drugs in 1994 for the first time, I was instrumental in getting this regulation done that required reporting by sex, of how many women were in trials, you know, what the results were by sex and so forth.

I don't know the answer to your question. I am going to have to get back to you. My impression was that we have standard tables on reporting by sex, both for outcomes as well as how many people were recruited in the trial and all the other variables. So I am very surprised to hear what you have to say, and we can get back to you on this.

Mrs. CAPPS. Well, I do—I think this is really important. I want to make sure that—there are a number of diseases, not just heart disease, that have different symptoms for the different genders. And I am under the impression and this article would give—the Institute of Medicine report in 2010 would indicate that there is limited transparency within that application process. So that it would be very difficult for the public, it would be difficult for FDA, and it would certainly be difficult and challenging for the medical provider to know if any improvements on the data collection are being made.

And I look at the legislation I have introduced in this—that passed out of the House in the past, the HEART for Women bill, which specifically addresses this issue to ensure that these important data are being used to keep all Americans healthy.

So if you have any final thoughts—this is a topic I want to see thoroughly explored by the Food and Drug Administration and a report submitted back to us on whatever findings that you have.

Ms. WOODCOCK. I think part of the problem that we have in getting timely data on this and providing it is that we don't get all the information in a standardized electronic format. If we did that, we could easily run reports on these standard tables and we could tell everything there is to know about reporting by sex.

In the new PDUFA recommendations that we are putting forth, there is a requirement that we get standardized all-electronic data. And this would extremely help transparency of this issue and many others.

Mrs. CAPPS. Mr. Chairman, I think this is a really important topic.

And I would like to request that we have follow-up data that you provide, FDA provides, to us on the progress that has been made and/or any other changes that should occur so that we can get this information.

Ms. WOODCOCK. I would be happy to do so.

Mrs. CAPPS. Thank you very much.

And I yield back.

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

Mrs. MYRICK. Thank you, Mr. Chairman.

And thanks for being here and for your thoughtful comments today.

My concern is about the FDA's ability to approve potential drugs to treat deadly diseases. For example, we know a drug like Avastin has toxicities that aren't well-tolerated by some patients, but for some patients, especially metastatic breast cancer patients, it does not extend their survival, but for others it does extend their survival. And metastatic breast cancer patients are facing a deadly disease, as we all know, and many are willing to take that toxicity risk if the drug helps keep them alive. I believe you said that in your testimony today.

And so I applaud your efforts, you know, to promote the need for biomarkers and screening tests so that scientists and physicians have more certainty about which patients respond to certain particular treatments. But if we don't have the screening tests now, I don't think we should restrict access or pull approval for a drug simply because we are not sure how to define the category of patients who will respond.

So why can't the FDA approve the drug with appropriate warnings for doctors and patients by informing the doctors that many of their patients might not respond and that there are risks involved, I mean, as an example?

Ms. WOODCOCK. Well, I cannot comment on the Avastin situation very specifically. The Center for Drugs has made a recommendation, and now it is before the FDA commissioner. And we have had a hearing and so forth.

Generally speaking, if we have found that a drug saves lives, then we will approve it, regardless of many serious side effects, as long as the survival advantage is not outweighed by mortality caused by drug side effects, OK?

Mrs. MYRICK. Yes.

Ms. WOODCOCK. So we have many, many drugs—we have recently approved several cancer drugs——

Mrs. MYRICK. Right.

Ms. WOODCOCK [continuing]. That are very toxic——

Mrs. MYRICK. Right.

Ms. WOODCOCK [continuing]. All right? And people know, if they are going to take those drugs, they may be facing—they may die from the side effects. That is true of cancer treatment. But they are trying to extend their lives.

Mrs. MYRICK. Well, I know there are women who have taken this particular drug, Avastin, you know, for 3 or more years, and they are still doing well, so. I understand, it is just a little frustrating, because I know if you are in a position where you really have this disease and you want to do everything you can to extend your life.

One more question on this same line. The FDA and the European Union's drug-approval body reviewed the same data on Avastin as a metastatic breast cancer treatment. And I understand it is approved there for HER2-negative metastatic breast cancer, and it is widely used in Europe for those patients.

So what is the difference? How do you explain the difference between what they are doing and what we do? Because I know it is all global, and we look at all of it together.

Ms. WOODCOCK. We do look at all the same data. We have certainly talked to the EU about their decisions. Sometimes we reach different decisions. We approved Avastin for a deadly brain cancer——

Mrs. MYRICK. Right.

Ms. WOODCOCK [continuing]. Called "glioblastoma" that they did not approve Avastin for. So sometimes various experts come to different opinions.

But I can assure you that we have—our breast cancer oncologists at FDA are dedicated to the treatment and, hopefully, eventual cure of breast cancer and getting the best possible agents out there for women.

Mrs. MYRICK. Oh, no, I don't have any question about that. I guess my question is more about the fact of how we restrict some of these when they do work for a large share of women, even though there is a mortality rate in allowing the usage for those women for those drugs.

Ms. WOODCOCK. The trials that we looked at—and this is from the Center for Drugs, again, because it is up on appeal right now—but in the trials that were done of Avastin in breast cancer, there was no survival advantage at all. And there was also no——

Mrs. MYRICK. But—and I understand. But the point is, if it is helping some people and they are willing to take the risk, I guess I go back to the same thing, should we not allow them to have that opportunity? And that is really where I am coming from.

Ms. WOODCOCK. I understand.

Mrs. MYRICK. I yield back, Mr. Chairman.

Mr. BURGESS. Would the gentlelady yield to me for a moment?

Mrs. MYRICK. Yes.

Mr. BURGESS. Just on that question on Avastin, just looking at the list of people who were on the advisory panel last week who rendered this opinion, I don't see anyone—maybe you can educate me differently—I don't see anyone that would have had the ongoing daily treatment of breast cancer patients under his or her control.

You had a lot of experts and a lot of oncologists, but I didn't see a specific specialist in the specialty of metastatic breast cancer.

Wouldn't you want someone like that on a panel rendering that type of opinion?

Ms. WOODCOCK. Well, this was not run by the Center for Drugs, and so I can't comment. I agree, there was no breast cancer expert, to my knowledge, on that panel.

Mr. BURGESS. Thanks, Mr. Chairman.

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

Mr. WAXMAN. Thank you very much, Mr. Chairman.

Ms. Woodcock, good to see you again.

I mentioned in my opening statement that we want to ensure that innovation in the pharmaceutical industry is vibrant. This is an important national priority. I also think it is important to assure that the drugs that reach patients are both safe and effective. That is the mandate to FDA.

When critics assert that FDA is somehow stifling innovation, we need to look very carefully behind those claims and insist that we have reliable and accurate data to substantiate them. Without this kind of data, we can very quickly get to a place where the so-called solutions are being proposed to a problem that may or may not exist in the first place.

The same critics allege FDA's slowness is because of regulatory changes that I fear could prove—they are suggesting some of these regulatory changes—for instance, some have suggested that Congress pass legislation preventing FDA from having the ability to insist on critical trial data that FDA feels is necessary and force it to approve drugs on the basis of less information.

Specifically, some have also suggested that the FDA be required to approve drugs for certain conditions on the basis of a single study instead of two randomized, placebo-controlled trials. In 1997, we did adopt a law that gave the FDA discretion to do less than two randomized trials, and then we hear critics claiming that FDA has not used this discretion, always insisting on two trials.

Now, we are not scientists; we rely on you to make scientific decisions at the FDA. But we hear all the time about how FDA is taking too long and asking for information that is not necessary.

Can you comment on this? Is it true that FDA has failed to use the discretion we gave you in PDMA and that the agency always insists on two trials? Would FDA be concerned about legislation that spelled out the number or type of clinical trials that the agency could look at in assessing a drug application?

Ms. WOODCOCK. Well, first, let me say, I would be concerned about trying to legislate at a more detailed level what type of evidence is required. We try to match the evidence to the situation, the requirement of evidence to the situation. So for rare diseases or mortal diseases, less evidence usually is required.

For example, we did a study of orphan data, and half of orphan approvals were based on a single trial, one trial. Recently, this year, we have approved seven orphan or rare disease indication, all right? Some new products, some efficacy supplements. For one of those, there was no human trial—it was done on animal data—to

show efficacy, right? In one of them, there were 17 patients. And this was a rare disease. But there wasn't a randomized trial. We compared how the patients were doing before they took the drug compared to how they did after they took the drug.

Mr. WAXMAN. So you use that discretion like you have under the law to set up priorities, how serious the disease is, how small the population may be that is being affected by a particular disease or would be helped by a particular drug. And you feel that if we micromanaged your activities by specifying that this trial is all that is needed or that trial is sufficient, that we would end up with, what, stultifying FDA or not letting you do your job?

Ms. WOODCOCK. We might slow things down.

Mr. WAXMAN. Slow them down even further?

Ms. WOODCOCK. That is what I think, because we would be involving a lot of lawyers and whether we were obeying the law in medical decisions that we were making. Nothing against you lawyers, but sometimes that slows things down a little bit.

I would say that we have considerable flexibility. And, say, a drug for headache pain that is going to be used by millions of people, all right, you want to know more about that—you want to know it is not going to cause a stroke, for example—than a drug here for the orphan indication or for a disease where people are dying and they don't have any other alternatives. We have great flexibility in the standards that we apply.

Mr. WAXMAN. Has there been a change in FDA's protocols for reviewing drugs? In other words, has there been something where, according to Mr. Leff, who is going to testify in a while, that FDA has shifted to a more cautious decision-making posture, begun to require more and more data to provide a higher degree of statistical proof of both efficacy and safety? And it sounds like FDA has somehow formally changed the drug review process. Is that an accurate statement? How do you respond to that?

Ms. WOODCOCK. No. I believe that we still have the standards of safety and effectiveness that we have always had, and we continue to apply them.

We have learned, though—we have learned some things. For example, we have learned that drugs that raise blood pressure will cause a certain incidence of strokes. And so, for example, in obesity, if you are going to have a drug to treat obesity, maybe it causes weight loss, but if it raises the blood pressure—I mean, you are treating the obesity, in part, to decrease cardiovascular complications, OK?

Mr. WAXMAN. Right.

Ms. WOODCOCK. What if, in fact, you are actually going to increase them?

So we have to know, because the standard is that it works, right? And patients take these drugs because they believe they are going to better their lives and better their health. And so, when we learn new medical facts, new scientific facts, we have to make sure that they are taken into account in the drug development program. But that is part of the standard of safety and effectiveness.

Mr. WAXMAN. Thank you, Mr. Chairman.

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

Mrs. BLACKBURN. Thank you so much, Mr. Chairman.

And we appreciate that you are here, Dr. Woodcock.

I want to stay with the line of questioning that Ms. Myrick had started with you, looking at this approval process. I had gone through the forensic cancer research report on FDA and the EMA, European Medicines Agency, looking at those approvals from 2003 to 2010. And, you know, that said, well, FDA was faster than EMA. But when you look at the year by year on that—and I am sure you have done that—and you go back to 2007 or 2008, there is a significant narrowing of the lag in cancer medicine approval times between the FDA and the EMA. And that was repeated—the noting of that lag was repeated in the California Healthcare Institute—and I know you are familiar with that report—and also the Boston Consulting Group report.

So I want to ask you four questions relative to that, because I think this should be of great concern with us. And it ties into what we hear from our constituents, who are concerned about the process that you are having individuals go through, as they try to file and go through the approval process.

So here are the four questions for you on that: Number one, what accounts for these trends? Number two, is the FDA getting slower and more inefficient? Number three, is the EMA getting better and more efficient? And, number four, is it a combination of things?

Because if we are getting slower, we need to nip this in the bud and we need to know what the precise problem is. Can you define that?

Ms. WOODCOCK. Well, I can't remember each one of your four questions——

Mrs. BLACKBURN. I will be happy to submit for writing.

Ms. WOODCOCK. Right.

The FDA most recently—our most recent data for 2011 show that we have the highest first-action approval rate we have ever had, which means the applications are coming in and they are getting out the door on the first cycle. And that, for priority applications, is 6 months usually. All right? So you can't get too much faster than that, all right?

The Europeans may be getting faster. Another hypothesis or thought is that the applications are getting better, all right? If the industry fully understands what the regulators want and they have a very important drug that is needed by the population, then it usually will move through the regulatory process in any country very rapidly.

So we don't feel we are in competition with the European Union or whatever. We were simply responding to criticism that it was taking us twice as long or three times as long as they. If the drug were approved simultaneously around the world and available to all patients with whatever disease, say, hepatitis C, that would probably be the best outcome.

Mrs. BLACKBURN. Well, and I agree with you on that. And I think that the two things that we hear you could kind of distill down to companies that are spending billions of dollars, want to make certain that they are provided with both transparency and consistency in that FDA review process. And they want to make

certain that you all are conducting these with certainty and predictability. And as you well know, that has been a problem.

One other question I wanted to ask you about, because I have written you about the PGAs and the issue that is there. And I was due a response—I am trying to find it—by the end of June, and I still have not had a response from you all about the products that are there, with the PGAs and what you are doing with those over-the-counter, unapproved, PGA-containing eyelash growth products.

What are you doing to investigate the marketing of those products and to restrict those in the marketplace? And do you plan to take enforcement action against all companies marketing these companies without FDA approval?

I think that all of us who look at the market for young women, we are very concerned about these products in the marketplace.

Ms. WOODCOCK. Yes, we are looking into this issue. As you know, there are numerous products in the marketplace, dietary supplements, that have been contaminated with many dangerous drugs. And so we have been taking action on products that are contaminated with these drugs. And we are looking into this issue, and we will be happy to get back to you on our progress.

Mrs. BLACKBURN. OK. I am speaking specifically of the eyelash——

Ms. WOODCOCK. I know.

Mrs. BLACKBURN [continuing]. Growth.

Ms. WOODCOCK. I know.

Mrs. BLACKBURN. OK. Well, we were due a response by the end of June.

Ms. WOODCOCK. Yes, I am sorry that you have not received that in a timely manner.

Mrs. BLACKBURN. OK. And I think that we want to know that there is action taken against these unapproved——

Ms. WOODCOCK. Yes.

Mrs. BLACKBURN [continuing]. Products. Thank you.

I yield back.

Mr. PITTS. The chair thanks the gentlelady, recognizes the gentleman, Mr. Engel, for 5 minutes for questions.

Mr. ENGEL. Thank you, Mr. Chairman. I want to thank you for holding this important hearing today. As we all know, the reauthorization of PDUFA is vitally important to both patients and industry alike.

As many of us remember, PDUFA was originally enacted in 1992 to address the unusually long and unpredictable wait period that it used to take for new drugs to be approved for market consumption. At that time, it would take an average of more than 2 years for a new drug to be approved, which meant that patients would not have access to new medicines when they needed them, and innovation suffered.

I am proud to say that, since then, we have come a long way in making more drugs available to patients while maintaining safety. I recognize that the system is not perfect, but we have come a long way.

Mr. Chairman, as we move along in the reauthorization process, I look forward to working with the various stakeholders and my colleagues on the other side of the aisle to address ways in which

Congress can strengthen the FDA and achieve our common goals. I mention working with my colleagues on the other side of the aisle because I think it is very important that we remember that this is not a partisan issue.

However, the appropriations bill that was passed last month cut the FDA's funding drastically, and I think that was a mistake. How can we expect the FDA to do their job effectively and efficiently while at the same time take away the valuable resources they need to do it? This only hurts patient safety, and it also hurts one of our strongest and most innovative industries.

So, Dr. Woodcock, let me ask you this. Today we are discussing legislation that authorizes prescription-drug user fees, which are critical to the FDA's ability to approve drugs more quickly while at the same time the House is cutting the funding. Can you tell me how you plan to reconcile these cuts and see that new, innovative drugs continue to come into the market in a timely manner?

Ms. WOODCOCK. Well, I mean, any cuts would make various programs at FDA more difficult. We also approve generic drugs, and the flow of those is important to keeping health-care costs under control in the United States. And we would become more challenged, I think, in our review of generic drugs if we had substantial cuts. We also manage post-market drug safety problems, and that requires a considerable amount of resources and effort.

We also keep guard over quality of all the drugs in the United States. And, as has already been mentioned, the import of drugs from all around the world and manufacture around the world have challenged us to make sure that we are able to ensure high quality of the U.S. drug supply. So that would be a challenge. Also, clinical trials are conducted all around the world, and so we are having to inspect those clinical trials wherever they might be held.

In addition, as you alluded to, this would have an impact on our ability to promote innovation in new drug regulation and in drug development, which is something that is very dear to my heart.

Mr. ENGEL. Let me ask you—as you know, many doctors and hospitals are struggling to cope with unprecedented drug shortages in the United States. Drug shortages obviously lead to delays in treatment and force the use of alternative drugs, which can result in unintended consequences. This shortage is endangering cancer patients, heart-attack victims, accident survivors, and many other ill people.

So let me ask you this. Before I ask you this, I want to ask the chairman for unanimous consent to put into the record a statement from the American Hospital Association on behalf of our hearing today.

Mr. PITTS. Without objection, so ordered.

Mr. ENGEL. OK, thank you. Thank you, Mr. Chairman.

[The information follows:]

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Statement for the Record

of the

American Hospital Association

before the

United States House Energy and Commerce Committee

Subcommittee on Health

"PDUFA V: Medical Innovation, Jobs, and Patients"

July 7, 2011

On behalf of our more than 5,000 member hospitals, health systems and other health care organizations, and our 42,000 individual members, the American Hospital Association (AHA) appreciates the opportunity to comment on the reauthorization of the *Prescription Drug User Fee Act* (PDUFA), and we applaud the Subcommittee for holding this hearing.

Drug Shortages and the Reauthorization of the *Prescription Drug User Fee Act*

In 2010, a record number of drug shortages – more than 200 – were reported by the Food and Drug Administration (FDA), and in the first six months of 2011, there has been more than 150 drugs reported in shortage. These shortages occurred across drug classes, including critical drugs used in surgery/anesthesia, emergency care and oncology.

Hospitals and health systems are deeply concerned about chronic and increasing drug shortages because they have serious consequences for patient safety, quality of care and access to therapies. Drug shortages lead to delays in treatment and force the use of alternative drugs with which the provider may not be as familiar. Using unfamiliar alternative drugs can result in unintended harm to the patient through errors in dosing and administration and in unexpected side effects.

Shortages also are costly to hospitals and health systems in terms of staff time and other resources to manage the shortages and the increased cost of buying alternative drugs "off contract." The majority of the 2010 drug shortages were critical sterile injectible drugs, mostly older generic drugs. From the hospital perspective, these shortages often came with little or no advanced notice from the manufacturers.

Drug shortages is a complex issue with many causes ranging from raw material sourcing, manufacturing problems (quality control and compliance issues), manufacturer consolidation and business decisions that result in drugs being discontinued. While there are some steps the FDA can take to mitigate or resolve drug shortages, the agency's current statutory authority in this area is limited.

The AHA, together with other national pharmacy, physician, drug manufacturer and patient safety organizations support the *Preserving Access to Life Saving Medications Act* (H.R. 2245), introduced by Reps. Diane DeGette (D-CO) and Thomas Rooney (R-FL), Sens. Amy Klobuchar (D-MN) and Robert Casey (D-PA) have introduced companion legislation, S. 296, in the Senate. The legislation would help address the issues leading to shortages and provide the FDA with additional authority and information to prevent further drug shortages. Specifically, the bill would:

- Require drug manufacturers to notify the FDA at least six months prior to a planned discontinuance or interruption of the manufacture of a drug that would likely result in a shortage; or as soon as practicable upon becoming aware of such interruption or adjustment. The FDA may modify reporting timeframes, if appropriate.
- Require the establishment of civil monetary penalties for failure to submit a notification as required.
- Ensure that the FDA protects proprietary information submitted by manufacturers.
- Require the FDA to publish on its website information about actual drug shortages and distribute such information to appropriate health care provider and patient organizations.
- Require the FDA to implement evidence-based criteria for identifying drugs that may be vulnerable to shortages. The FDA must notify and collaborate with the manufacturers of such vulnerable drugs in order to establish and improve their plans and processes for averting and addressing drug shortages.
- Require the FDA to submit reports to Congress describing its actions to address drug shortages.
- Require the Government Accountability Office to conduct a study and submit a report to Congress examining the causes of and the FDA's response to drug shortages; assessing the adequacy of stakeholder communications; analyzing the impact of the provisions of the bill and identifying other steps to prevent drug shortages.

While this legislation is a critical first step in addressing a serious public health problem, there are many other changes that could be made to help to alleviate drug shortages. Other steps include removing obstacles so that the FDA is able to streamline approval of drugs in shortage.

An example would be to develop a fast track for approval of new production lines, alternate manufacturing sites or new suppliers of raw materials for medically necessary drugs in shortage. Improved communication among stakeholders also would help. For example, more formal communication between the FDA's Drug Shortage Program, Office of Generic Drugs and the Office of Compliance could help to minimize unnecessary delays in resolving quality systems issues for shortage drugs. Further, Congress should explore incentives to encourage drug manufacturers to stay in, re-enter or initially enter the market, such as, tax credits to manufacturers that agree to continue to produce drugs vulnerable to shortage or to upgrade manufacturing plants to meet or exceed quality standards in exchange for a guarantee of continued production of these products.

The reauthorization of the *Prescription Drug User Fee Act* presents an opportune vehicle for making some of the policy changes needed to address drug shortages. The FDA has been meeting with drug industry and non-drug industry stakeholders, including the AHA, to develop recommendations for the next *Prescription Drug User Fee Act.* Initiatives to prevent and address drug shortages have been raised in this context as well as other drug-related issues of interest to hospitals.

The AHA will continue to work with Congress, the FDA and with other interested organizations in effort to address the serious issue of drug shortages and keep patients safe.

Mr. ENGEL. So let me ask you this, Doctor. From the FDA's perspective, what is the problem with drug shortages, and how can we address it?

Ms. WOODCOCK. Drug shortages have multifactorial problems, all right? They are related, often, to drugs that are off-patent, that only have one manufacturer that is approved in the United States, and that eventually have aging facilities.

We work tirelessly to try and ameliorate drug shortages in the United States. And, from our point of view, although there are these structural problems, what would help us the most would be to have early notification if a company is planning to stop making an essential drug or temporarily go out of production, so that we could make arrangements to substitute something else, to get another drug available for doctors and patients. And we have been able to do that many times when we have actually had advanced notice.

Mr. ENGEL. Let me ask you—the final question is, you mentioned in your testimony that the FDA allows access to investigational products through clinical trials. And this allows patients who may need a treatment that is not currently on the market to access innovative treatments. You mentioned also in your testimony that are times when patients cannot enroll in critical trials.

Could you explain why and what some of the challenges are that these patients face when considering the clinical trial?

Ms. WOODCOCK. Well, there is difficulty in the U.S. in accessing clinical trials. But there is a broader issue of treatment access, which is a person who lacks alternative therapy and there is no other approved drug that might work for them, so they would like to access an investigational product—drug.

We recently passed regulations about a year ago that broadened and liberalized and rationalized access protocols for investigational drugs. The FDA believes that people with serious illnesses who lack alternative therapy should be able to get investigational drugs on a treatment basis.

Mr. ENGEL. Thank you, Mr. Chairman.

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

Mr. GINGREY. Mr. Chairman, thank you.

And, Dr. Woodcock, thank you very much for your testimony.

Let me ask you a couple of quickies. Did you tell the committee that your specialty is rheumatology?

Ms. WOODCOCK. Yes.

Mr. GINGREY. OK, thank you.

In regard to my colleague from North Carolina, in regard to the question on Avastin, can you assure the committee the decision on Avastin—and I guess that final decision is in the hands of the commissioner at this point; it looks like it probably will not be approved for advanced breast cancer, although it will continue to be approved for colon, and you mentioned a type of brain cancer that it is still approved for—this decision, can you assure us, is not based on the cost of that drug?

Ms. WOODCOCK. We never look at the cost of drugs when we are doing our decisions. It is not within our mandate, and it is not something that we look at.

Mr. GINGREY. You never look at the cost of the drug?

Ms. WOODCOCK. No.

Mr. GINGREY. OK.

Mr. Shimkus brought up a question about the need for new antibiotics, and I think that your response to his questions was reassuring to me. And I think you probably know that Mr. Shimkus and myself and others on this committee, in a very bipartisan way, have introduced H.R. 2182, the GAIN Act, to try to get more antibiotics to the market and the problems that we have in regard to that, because if they are used properly, then the market for the sales of those drugs is very limited——

Ms. WOODCOCK. Right.

Mr. GINGREY [continuing]. As it should be, if they are used properly.

Can you also give me your thoughts on the need for new diagnostics to properly identify infectious diseases? For example, would new diagnostics have helped in the recent E. coli outbreak in Germany?

Ms. WOODCOCK. Certainly. We feel that, particularly, point-of-care diagnostics that could be used at the bedside by clinicians to rapidly identify the bacteria and also potentially resistance profiles would be just an outstanding advance in infectious disease. And we have certainly talked to the Infectious Disease Society about this and others.

So if we could target our antibiotics better—as you well know as a clinician, we do a—whatever you call it—a shotgun approach to treatment until we have the cultures and we know what the patient has. And so, for many days or maybe total course of treatment, it may be empirical, and so we don't know what we are treating. And this leads to a more widespread resistance, I believe.

Mr. GINGREY. And that, of course, is part of our bill, as well. And I thank you for that response.

Very quickly, my last point, I wanted to address the Sentinel Initiative, the post-market risk identification/analysis system.

And the reason I wanted to be sure of your specialty of rheumatology, there is a drug—I think it is pronounced "Remicade." Am I correct?

Ms. WOODCOCK. Yes, uh-huh.

Mr. GINGREY. —Remicade, that was approved. And I wanted to ask you, if you know, was that approved under orphan drug status? I know it has been on the market maybe for as much as 20 years—well, maybe not quite that long. But the drug being used for Crohn's disease and with pretty good results. But my understanding is that up to 5 percent of individuals will eventually, if they have taken that drug for Crohn's disease, they will eventually come down with leukemia. And, you know, to me, that seems awfully high. And maybe I am being affected because it happened to a family member just recently, who ended up dying of her leukemia. She was helped tremendously several years ago by use of this drug.

What is the threshold? A 5 percent, to me, risk from taking a drug and then ultimately developing leukemia, which is pretty life-threatening—in her case, it was definitely life-threatening and life-ending—where is the threshold in regard to what we are looking

at in the Sentinel Initiative, the post-market analysis of these drugs?

Ms. WOODCOCK. Well, generally what we are doing with all the immunosuppressant drugs is having registries and long-term follow-up. So we can also use Sentinel for evaluating these longer-term outcomes. But we are also watching patients observationally over time.

And we can get back to you on what we know right now about the occurrence of malignancies as well as infections, opportunistic infections, as a result of all the classes of immunosuppressive drugs that are used.

Mr. GINGREY. Dr. Woodcock, I would really appreciate that, both as a Member of Congress and personally. I would really appreciate you getting back to me with a report on that. And I thank you very much.

Ms. WOODCOCK. I would be happy to do that.

Mr. GINGREY. I yield back.

Ms. WOODCOCK. And if I may say one thing about this, this really illustrates the balance of benefit and risk, because malignancies are not apparent immediately, all right? And so, you could say, well, this is a wonderful drug, we should just get it out there, and everyone should take it. But what we find out is, yes, there are breakthrough—tuberculosis, whatever, and there are also cancers that occur late. And this is where we have an obligation to patients to find out as much as we possibly can, so they can make their decision.

Mr. GINGREY. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman, Mr. Latta, for 5 minutes for questions.

Mr. LATTA. Well, Doctor and Director, thanks very much for being with us today. I really appreciate your testimony today.

And just to kind of maybe follow up a little bit of the questioning that has already been asked, but one of the areas that I would like to go into is about especially on the obesity and diabetes side, with the drugs out there and the therapies that are being brought forth, and especially with the FDA approval process. Because, as we all know, especially young and old alike, both these, diabetes and obesity, are affecting a huge portion of our population and increasing our costs. Especially, it is a huge driver on the Medicare side.

And the question is, what are you doing to encourage the development of new therapies to treat these diseases, especially using your authority under REMS——

Ms. WOODCOCK. Pardon me. I am having trouble hearing you.

Mr. LATTA. OK. You know, this is sometimes also the room that we use for our telecommunications subcommittee. And I am sorry—is that better?

Ms. WOODCOCK. Yes.

Mr. LATTA. OK. The way some of our mikes pick up.

But the question I have then is, what are you doing encourage the development of new therapies to treat these diseases, especially using your authority under REMS to follow the drugs closely after their approval?

Ms. WOODCOCK. We share the understanding of the need for new treatments for diabetes and for obesity. And I would point out that

for diabetes, in early 1990s, there were only two types of therapies available for the treatment of Type 2 diabetes, and now we have 11 new classes of drugs that are out there. So there has been a tremendous blossoming of attempts to get new therapies for diabetes out there.

And, in fact, we are seeing the pipeline continue. And we have put out guidance about cardiovascular risk in diabetes drugs that companies have been able to deal with and follow, and we have approved new diabetes drugs recently. So we see a robust pipeline there.

In obesity, the problem is different. We have had to take three obesity drugs off the market because they cause stroke. We have had to take another class of obesity drugs off the market because of heart-valve disease. And you can see with young people, if we expose them to an agent widespread that causes heart-valve disease, we would have another epidemic on our hands. So we must make sure that these products have adequate safety.

But we recognize the obesity epidemic. And what we are doing is we are going to have a scientific meeting about obesity and cardiovascular safety. And we are also planning to have a series of stakeholder meetings, where we bring in the very attritions and the patient groups and the FDA and other experts to talk about how diabetes drugs should be developed. And I think this will be very helpful to the industry.

Mr. LATTA. Let me ask this. I think you said that you took several off the market last year. I believe also, if my information is correct, that the FDA also denied three consecutive applications for approval of new obesity drugs last year.

Ms. WOODCOCK. That is correct.

Mr. LATTA. Now, was that for the same reasons, or what was the cause of that?

Ms. WOODCOCK. Different—well, one drug had a blood-pressure problem, which was the reason we had to remove other diabetes drugs off of the market. They were causing strokes. Last year, we removed a drug, Meridia, from the market because of stroke. A trial was done that showed that even though people lost weight, they still got an increased number of strokes when they took this weight-loss drug. So it was removed from the market.

So one of the problems that we are identifying is many of the weight-loss drugs increase blood pressure, and we have to make sure they are not causing an excess of strokes, OK? But some of the other weight-loss drugs have other types of problems that we are looking at.

Mr. LATTA. Thank you very much.

And, Mr. Chairman, I yield back.

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

Mr. GUTHRIE. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock.

I know you all have a difficult job anytime you approve a drug as you go forward. And just think about the long term as you move forward, of course there is a—so it is a quandary. But there are a lot of people waiting on the approvals as you move forward.

And my friend, Ms. Myrick, Representative Myrick, covered some of it, but I just got a text this morning from my brother, and I am going to share this a little bit. Well, first, my brother called me yesterday. He has a best friend in the Navy, was in the Navy, whose wife had breast cancer. And they were one of the ones who flew from Seattle, Washington, to, I guess, Baltimore a couple of weeks ago. And the text says, "Thanks for talking to Nancy yesterday. She knew we were having this meeting. They are great people, and thanks for the quick response. The bottom line is, they have been through a lot, and she has lived much longer than she was supposed to." And I really read that to give you that line.

And it seemed like with Avastin that—I talked with her quite a while on the phone yesterday, and she said her mother has breast cancer but very localized. And she realizes Avastin wouldn't be something that her mother should be taking. But she did say, when she discovered she had breast cancer, when they found the breast cancer, she had four tumors on her liver. I think that is what she said. And so, therefore, it looked like she had made the decision. She realizes the toxicity, but she really believes that Avastin is—and she is distraught—has really increased her life expectancy.

So the question—and maybe this wasn't your area, as you said—was Avastin not approved for breast cancer because of the side effects or because there is no clinical proof that it actually works?

Ms. WOODCOCK. Avastin was approved under accelerated approval for breast cancer. It was already on the market for other cancers, all right?

Mr. GUTHRIE. Right, right.

Ms. WOODCOCK. And then, subsequently, it was approved under accelerated approval.

What that means is, then the drug developers have to prove that the promise, OK, that was approved under accelerated approval is real, all right? And so the company did additional trials, and they did not show any survival advantage.

The original trial it got approved on showed something called progression-free survival. What that means is you live longer with your tumors not growing on scans.

Mr. GUTHRIE. OK.

Ms. WOODCOCK. All right? It doesn't mean you live longer. It means that your tumors are stable longer. And so the original trial showed, in women getting Avastin, their tumors stayed stable longer, all right?

Mr. GUTHRIE. OK.

Ms. WOODCOCK. What we asked the company to say—well, show that means something, show that translates to either quality of life, better quality of life of the people or longer life of people, all right? And they were not able to show either of those in the subsequent trials that were done.

That does not mean that Avastin is not an active drug, perhaps, for some women, but we do not know what women. And it does have very serious, potentially fatal side effects.

Mr. GUTHRIE. Right. She recognized that. We had talked on the phone—and so the issue really wasn't just the side effects and it could be fatal. But you are saying it really didn't show that it extended the life as you move forward.

Ms. WOODCOCK. It did not. In that population. And that is not a population that is selected by some marker to respond well to Avastin. It may well be if they could come up with a biomarker and say, "These women are the women who should take this drug," then it might be possible to figure out who the drug is good for.

Mr. GUTHRIE. Uh-huh. So it could be a—and she could be one——

Ms. WOODCOCK. That is right.

Mr. GUTHRIE [continuing]. A select group of circumstances that it affects—because drugs interact with all of us differently—that would actually—and I know from our conversations she is convinced that she is still here because she was on Avastin.

And one other thing a lot of people have said—I only have about a minute, so I will just ask it really quick. You know, I do hear from a lot of our people in the drug field, pharmaceutical field, saying that they are having difficulty getting things approved. You have heard that from several of us here. You all must be hearing the same thing. And maybe what you are saying is 2011 has been better than 2010 and 2009 and 2007.

So are you already acting to the fact that people said they are getting things difficult—like you said, 2011 has been pretty successful, but I am really not hearing people saying that, "We have had difficulty in the past, but it seems to be getting better." So I don't know if you are hearing the same thing. And just comment on that. I have about 40 seconds left.

Ms. WOODCOCK. Well, I would propose to you that the people who come into your office are not the people who have had a successful experience. And so you have what we call a biased sample, all right? And even if, like, 90 percent of the people are getting through and we are having a tremendous—I am not saying all this will continue, but this year we are having an extremely high approval rate because the drugs that are coming in are—many of them are very significant advances, all right?

But the people I think who come to talk to you continue to be the people who are having a difficult time. And so I don't know that you would see any change in your experience.

Mr. GUTHRIE. So they are not coming by to see us just to say, "Thanks, it really went well"? We hear that sometimes too.

Thanks a lot.

Ms. WOODCOCK. Thank you.

Mr. PITTS. The chair thanks the gentleman, recognizes the ranking member emeritus of the committee, Mr. Dingell, for 5 minutes.

Mr. DINGELL. Mr. Chairman, I thank you for the hearing.

And I thank you for your courage.

Ms. WOODCOCK. Thank you.

Mr. DINGELL. I wanted to ask a "yes" or "no" question. I hope you will respond.

Do you have the ability to fully control the safety of imported pharmaceuticals, yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the authority to control the safety of raw materials or imported pharmaceuticals?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the authority and the resources you need to address the safety of components now being imported into this country, yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the necessary authorities and resources to see to it that drugs are only imported from facilities overseas that are properly observing good manufacturing practices—that is a word of art—yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the ability to see to it that raw-materials suppliers also engage in good manufacturing practices abroad?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the resources needed to conduct foreign drug-facility inspections with the same frequency as domestic drug-facility inspections?

Ms. WOODCOCK. No.

Mr. DINGELL. How often can you get by to see a foreign drug manufacturer?

Ms. WOODCOCK. Every 9 years or so.

Mr. DINGELL. Every 9 years?

Ms. WOODCOCK. Yes.

Mr. DINGELL. You get by to see dog-food manufacturers every year or so.

Ms. WOODCOCK. Yes, probably a little more—a little over a year.

Mr. DINGELL. Do you need additional resources to increase inspections of foreign drug facilities?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you need additional authorities to be effective in that?

Ms. WOODCOCK. Absolutely.

Mr. DINGELL. Do you have the ability to freely share information about a drug with your trusted domestic and foreign counterparts in the instance of something like another heparin crisis, yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you need this ability?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you have a clear authority to require manufacturers to assure the safety of their food chain, yes or no?

Ms. WOODCOCK. Their food chain?

Mr. DINGELL. Yes—I am sorry, the supply chain. I apologize.

Ms. WOODCOCK. Thank you. No, we do not.

Mr. DINGELL. Do you need this authority?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you have the authority to require manufacturers to notify you if they suspect their drug may have been counterfeited, misbranded, or adulterated?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have the ability to properly assure the safety of both raw materials for the manufacture of pharmaceuticals and pharmaceuticals as they are imported into this country?

Ms. WOODCOCK. No. And I think we are one of the few countries that does not have that authority.

Mr. DINGELL. Do you need this authority?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you have the authority to require companies to recall a drug, yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have that authority with regard to imports?

Ms. WOODCOCK. No.

Mr. DINGELL. Do you have that authority with regard to raw materials and things like that?

Ms. WOODCOCK. No.

Mr. DINGELL. And components?

Ms. WOODCOCK. No.

Mr. DINGELL. Now, let's go to the question of heparin. A lot of bad heparin got out because, currently, you couldn't get over to China to see what the raw material was like and what was safe or unsafe with it. Is that right?

Ms. WOODCOCK. That was part of the problem.

Mr. DINGELL. What was the other part?

Ms. WOODCOCK. I think the tests were out of date for heparin.

Mr. DINGELL. The what?

Ms. WOODCOCK. The testing standards, the U.S. standards, international standards.

Mr. DINGELL. Were they adequate or inadequate?

Ms. WOODCOCK. They were inadequate.

Mr. DINGELL. OK. Do you have authority to address that problem?

Ms. WOODCOCK. No, not fully.

Mr. DINGELL. Not fully or just not at all? If you can't do it fully, you can't do it at all, can you?

Ms. WOODCOCK. Can you repeat the question?

Mr. DINGELL. Would you submit a brief monograph to this committee for the purposes of the record——

Ms. WOODCOCK. Certainly.

Mr. DINGELL [continuing]. Explaining what happened in the heparin case and what abilities you need to address imports not just of finished products, pharmaceuticals, but also raw materials and components, please?

Ms. WOODCOCK. We would be happy to do that.

Mr. DINGELL. Thank you.

I ask unanimous consent that the additional matters requested be inserted in the record at the appropriate point, Mr. Chairman.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy.

And I thank our witnesses.

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

Mr. LANCE. Thank you, Mr. Chairman.

Good morning, Doctor.

I have the honor of being the Republican co-chair of the Rare Disease Caucus. And I want to thank the progress that the FDA has made regarding the advancement of orphan product development. And given the fact that a large number of products approved by the agency are for orphan indications, it is clear to me that the FDA's increased focus on development and approval of orphan

products is important to all stakeholders in the rare-disease community.

I am particularly interested in learning more about the Office for Rare Diseases, created last year. As I understand it, the goal of that office is to facilitate and support research, product development, regulations and approval of biopharmaceuticals for the treatment of rare disorders and to serve as a focal point for stakeholders and developers of drug and biological products.

If one of the primary objectives of the Office for Rare Diseases is to ensure collaboration among scientists and clinicians throughout CDER, what steps are being taken and what are the plans for the future to ensure adequate resources that are allocated to this office?

Ms. WOODCOCK. Thank you.

Yes, as part of enhancing regulatory science and expediting drug development within the proposals we have for the new user-fee program, we have a portion on rare diseases, which would improve resources, add additional resources to our attention to rare diseases, including to that office.

Mr. LANCE. And will you be engaged in that activity? And what time frame, Doctor?

Ms. WOODCOCK. The new user-fee program hopefully will be passed and be able to be implemented in 2013. And, at that point, we would have additional resources to put——

Mr. LANCE. So this would be an action probably we would take next year regarding PDUFA, next year?

Ms. WOODCOCK. Yes.

Mr. LANCE. Thank you. Well, I look forward to working with you and other interested stakeholders in this issue. It is important, I think, to the entire Nation and certainly important to the district and State I serve, which we believe is one of the medicine chests of the world.

On a different topic, on biomarkers, innovative drug development is increasingly dependent on the use of new biomarkers of disease to target the right patients. Could you tell us what you are doing to encourage the use of biomarkers in drug development?

Ms. WOODCOCK. Thank you.

I think since 2004 FDA has really been in the forefront of this; we have been encouraging the use of biomarkers. And we have published numerous guidances. We have done a lot on something called pharmacogenomics, because a lot of these would be genetic markers.

And we also now have a proposal in the new user-fee enhancements where we would like to enhance our activities on biomarkers and pharmacogenomics, because we feel this does have tremendous promise for patients and for drug development.

Mr. LANCE. Well, thank you, Doctor. This is my first opportunity to meet you. I am new to the committee, and I look forward to working with you.

And I yield back the balance of my time.

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

Mr. CASSIDY. Thank you, Dr. Woodcock, for testifying.

Newly active substances, just so I am clear on the definition, if somebody has a drug and they make it a single-day therapy, a prolonged release if you will, as opposed to a QD, does that qualify the new—so it is just a truly new drug?

Ms. WOODCOCK. Yes, it has to be first, you know, time and first exposure to humans of this molecule, basically.

Mr. CASSIDY. Got you.

Secondly, just to follow up on what Mr. Dingell asked about, man, if you are inspecting dog-food factories a little bit over a year but only going abroad every 9, couldn't you redirect resources from the dog-food factory—I am saying that as a pet owner—to—and, of course, it sounds tongue-in-cheek, but, actually, it is a very serious question.

Ms. WOODCOCK. Well, Congress directs resources to drug programs separately from foods or veterinary medicine. So they are all separated out, and we have to expend those based on the appropriation, OK?

Mr. CASSIDY. So, would it be—not to put you in a box, but if Congress redirected some of the funds currently used for dog food, as an example, metaphorically if you will, to inspecting companies abroad to make sure they have good clinical or good manufacturing practices, would that be a reasonable thing?

Ms. WOODCOCK. Well, I think, then, that is a tradeoff. The Congress has recently asked FDA to accomplish a great deal more tasks under food safety, with their new food-safety bill. And those inspectors are all busy trying to accomplish those activities.

So we have tried—we are trying to redirect domestic inspection resources to do overseas inspections. And that has been the main effort that we are working on.

Mr. CASSIDY. So, then, to follow up that, one thing you could do within this silo, almost, of funding is—because I have had domestic drug manufacturers complain, "Listen, I am checked every 6 months, and yet my competition is checked every 9 years." It isn't a competitive issue for them; it is a drug-safety issue.

So could you elaborate a little bit more on that occurring? Because it seems a very reasonable approach.

Ms. WOODCOCK. Yes, I think that we are moving—we have been trying to move in that direction. That is a desirable thing to do, to have a uniform level of inspection around the world that is also risk-based, OK? So the riskiest plants should receive the most frequent inspections, whether they are in the U.S. or whether they are in China or elsewhere. It has just been logistically very difficult to accomplish this.

Mr. CASSIDY. Now, again, just to, again, pursue—it just seems so logical. I mean, you are going to go buy a ticket to go to Bangalore and inspect the plant there. Why would that be logistically complicated instead of going to New Jersey? Granted, New Jersey is a train ride and Bangalore is a trip. But, nonetheless, it does seem as if maybe it is a prejudice, that probably the people in New Jersey have better practices or one that we trust more than maybe just a startup in Bangalore?

Ms. WOODCOCK. Yes, the inspections are done by our field organization. It is not a part of the Center for Drugs. And they have a

union, and they have agreements about foreign travel and how much you can get people to go and do things overseas.

Mr. CASSIDY. You mean there is a union agreement which is keeping us from being able to inspect foreign manufacturers?

Ms. WOODCOCK. Partly. That is my understanding.

Mr. CASSIDY. You mean the union agreement is keeping us from inspecting these more frequently than every 9 years?

Ms. WOODCOCK. Well, the work conditions. It is just very difficult—my understanding; I don't supervise that organization—to shift resources to have a larger number of foreign inspections done.

Mr. CASSIDY. I have to admit, as a physician practicing, it gives me great concern for the safety of my patients that that is what is limiting our ability.

Ms. WOODCOCK. We would be happy to get back to you with a more complete explanation.

Mr. CASSIDY. Please. Because that is so incredibly troubling. Which union is that?

Ms. WOODCOCK. Pardon me?

Mr. CASSIDY. Which union is that?

Ms. WOODCOCK. NTEU.

Mr. CASSIDY. I only have 50 seconds left. Let me gather my thoughts after that.

If we had not had that union agreement, would the heparin tragedy have been avoided?

Ms. WOODCOCK. I think it would still be difficult to move people from their established inspection routine and get them to travel repeatedly overseas.

Mr. CASSIDY. Why don't we just——

Ms. WOODCOCK. But we are moving in that direction.

Mr. CASSIDY. It may be difficult with the current employees, but it sounds like, if that is where the problem is, then we just need to find employees that will go, correct?

Ms. WOODCOCK. Well, there is also a problem with resources. I don't want to understate that, OK? That it is going to take more people to do all of these inspections overseas, and it would—it is not as efficient as inspecting a certain number of plants in a certain geographic area.

Mr. CASSIDY. I accept that. But, on the other hand, if you are going to find out where the problems are, and if we can trace them—the bulk of them to these companies overseas, manufacturing plants overseas, it just seems that is where you should be looking.

Ms. WOODCOCK. Well, we definitely should go where the money is. But I would say that we have certainly found manufacturing problems domestically recently. Some of them have been high-publicity problems. And we have to maintain good coverage of those firms, as well.

Mr. CASSIDY. I accept that. On the balance, what would be the percent of the domestic versus foreign that have resulted in deaths?

Ms. WOODCOCK. I don't think we have that kind of data.

Mr. CASSIDY. OK.

I yield back. Thank you.

Mr. PITTS. The chair thanks the gentleman, recognizes the gentleman from Pennsylvania, Dr.——

Mr. DINGELL. I forgot to ask one question. Could I ask just one question?

Mr. PITTS. Go ahead. Please.

Mr. DINGELL. To the witness, if you please, H.R. 1438, the Drug Safety Enhancement Act of 2011, would this afford you the authorities you need to deal with the heparin problem?

Ms. WOODCOCK. Yes.

Mr. DINGELL. It would.

Ms. WOODCOCK. Yes.

Mr. DINGELL. Would you give us a little memo on why that is, for inclusion in the record?

Ms. WOODCOCK. We would certainly be happy to.

[The information appears at the conclusion of the hearing.]

Mr. DINGELL. Mr. Chairman, you have been enormously courteous, and I thank you.

And I apologize to my colleague for having interfered with his time.

Mr. PITTS. That is all right.

The chair thanks the gentleman and recognizes Dr. Murphy of Pennsylvania for 5 minutes.

Mr. MURPHY. Welcome, Doctor. It is good to have you here.

Ms. WOODCOCK. Thank you.

Mr. MURPHY. There was an article in yesterday's Wall Street Journal written by Roger Bate. I don't know if you had a chance to see that. But in that, he pointed out a number of things about the risks that come to western firms from these small, hard-to-detect flaws, with the trace impurities from unhygienic practices, which seems to summarize what we are dealing with here.

The FDA—excuse me—the Federal Food, Drug, and Cosmetic Act provides a drug is adulterated unless the methods used for the manufacturing of a drug product conform to current good manufacturing practices. Can you explain the role and importance of the good manufacturing practices that FDA looks at in their approved products?

Ms. WOODCOCK. Good manufacturing practices are a quality system, and you are probably familiar with quality systems from other areas of manufacturing. These really apply to mass production. So it is one thing to make a drug in a laboratory and have a lot of scientists looking over it. It is another thing to make it in a factory and make millions of doses and make them repeatedly sterile, potent and uncontaminated, and that requires adherence to a quality management system.

The good manufacturing practices is a set of codified regulations that FDA has that establishes kind of the minimum standards for doing that.

Mr. MURPHY. Now, you have talked about the supply chain. I know Mr. Dingell brought that up, too. So what is preventing the FDA from updating its GMPs, requiring drug companies to verify their suppliers are complying with the law on providing quality ingredients? Can you tell me a couple of items there that are preventing you from doing that?

Ms. WOODCOCK. Well, it is possible with a very long process, we could modify some of the good manufacturing practices regulation, but others—I think of the things that Mr. Dingell—other authorities that he was referring to would require legislative authorization.

Mr. MURPHY. In part of looking at that, you understand that this entire Nation is looking upon Congress to find ways to save money and also to look at health care costs, particularly Medicare and Medicaid which is spinning out of control.

Is the FDA involved in or do you know of any other Federal agencies looking at a number of aspects? For example, when we look at some of these medications, and the estimates are, as an example, as much as 5 percent of ingredients may be impure, may have impure drug content, and we are looking at $1.74 billion and rising of imports here.

Does anybody have any information on the impact on health care, such as drug shortages, and what that means to health care costs, tainted drugs that then effect extended stays in hospitals, return visits to physicians office and emergency rooms? Is that something that you or anybody else is studying the impact on health care costs?

Ms. WOODCOCK. I wish we had that kind of data, but we do not. It is very difficult to link drug quality health problems with health outcomes, and Heparin was a dramatic example where we saw that. But we don't have overall data like that, and I don't know that anybody else does.

Mr. MURPHY. Well, that is certainly troubling. While we are looking at this, I know that studies have said just when patients—when patients, we have looked at something like 75 percent of people don't take their medication properly and a study recently said that is a $250 billion drain on the system. But then when they do take medications according to doctors orders, and we find out there are flaws with some of the content of generic drugs, I don't want to malign generics because we are also encouraging physicians to write prescriptions for generics, and yet at the same time if we are not inspecting these plants properly we end up with causing more problems.

So, does FDA have any positions they recommend then in terms of what other branches of government, Medicare and Medicaid should be doing? Are they requiring doctors to write prescriptions for generics while at the same time we can't assure that those are pure?

Ms. WOODCOCK. Well, I would point out that Heparin was not a generic drug. There were various versions of Heparin on the market, but that was not a generic drug. This is not necessarily a generic drug problem. This is pervasive drug quality problem, and we don't have evidence that generics particularly have additional quality problems over innovator drugs.

So I think physicians should write for generic drugs with confidence. But we do need to make sure we manage the supply chains, that we and mainly the companies have the systems in place to make sure that they maintain the quality of their drugs that are sold in the United States.

Mr. MURPHY. I appreciate you pointing that out about generics. That is a very important fact. We don't want people to be worried about that. It has to do with the content that comes over.

You had mentioned that plants can be inspected about once every 9 years. The GAO says it is more like every 13 years or so. Plus isn't it true that when you are inspecting a plant in the United States, you can just show up on a surprise visit if you wish?

Ms. WOODCOCK. Correct.

Mr. MURPHY. And the chances of surprising someone in China is slim and none?

Ms. WOODCOCK. Right.

Mr. MURPHY. So they have a chance to change that. And so on this globalization of drug manufacturing and supplies, are there caveats that the FDA is saying then to manufacturers in the U.S. that even though you cannot inspect this, other standards you are asking them to handle on their own with this as well?

Ms. WOODCOCK. Yes. Basically we feel that the ultimate responsibility lies with the manufacturer. We are not their quality assurance group. We are auditors to make sure that they are obeying the rules and that they are maintaining quality, and we audit all around to make sure they do that.

There is also testing, which isn't everything, but having good analytical tests for potency, sterility and making sure the manufacturers conduct those tests, and for impurities, can go a long way to help ensure the safety of the drug supply.

Mr. MURPHY. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Michigan, Mr. Rogers, for 5 minutes.

Mr. ROGERS. Thank you, Mr. Chairman. Thank you, Doctor, for being here.

Is venture capital important in the development of the next generation of pharmaceuticals, do you believe?

Ms. WOODCOCK. Yes, venture capital is very important to a segment of the drug development industry, the smaller and arguably more innovative side of the industry.

Mr. ROGERS. They are targeting special treatments for cancer or for sepsis or all of those things, right? That is where the venture capital kind of flows to those innovative—so you are arguing it an important part hopefully of the next cure, we would hope?

Ms. WOODCOCK. Certainly for innovation. The biotech sector depends on venture capital.

Mr. ROGERS. I happened to be reviewing the testimony of someone on the panel, Jonathan Leff. I am just going to read some things from here just to get your perspective on this.

"During 2010 and 2011 to date, first time fundings of life sciences ventures, a key leading indicator of the health of the innovation ecosystem, has decreased by more than 50 percent due to prior years."

That is a problem, isn't it?

Ms. WOODCOCK. Yes.

Mr. ROGERS. What would you attribute that problem to?

Ms. WOODCOCK. The problem is due to the failure rate and the fact that—again, I am not an economist, but what I have been told is that these firms are not successful enough to merit the return

on investment, and also there is a longer term development cycle, that venture capital prefers a shorter return, and so biotech has become less attractive.

Mr. ROGERS. So it is all the investors that are pulling out of the market. It wouldn't have anything to do—here is his assessment. "The FDA's shift in recent years to an increasingly cautious risk-averse posture towards new drug approvals has the unintended consequence of reducing investment in life sciences innovation due to the significant additional time," which you mentioned, "cost and uncertainty it has added to the drug development process." True?

Ms. WOODCOCK. Well, there is uncertainty in the drug development process, and that is the main problem. To lay it all at the feet of the FDA I don't think is correct. McKenzie has recently done a study where they looked at failures in Phase III development, which is clinical—the last stage of clinical trials, and of products that failed there, fifty percent failed because they had no benefit compared to placebo. It is really hard to attribute that to the FDA.

Mr. ROGERS. I certainly understand. But if the FDA doesn't recognize it has a problem, we will never get any segment of that fixed?

Ms. WOODCOCK. I recognize it. As I said in my oral testimony, I think there is a crisis in the industry, and it is pervasive and it is very concerning.

Mr. ROGERS. What would be your recommendation for Congress to try to help us through that particular process? Can you clearly say that the added time and bureaucracy and investment is gaining—it is worth the sacrifice of losing innovation and attracting capital? Is it worth it?

Ms. WOODCOCK. We feel that the scientific challenges are the problem, not the regulatory challenges. So I would disagree with Mr. Leff on this. And our data shows that we have a very high rate of first cycle approval. So it is hard to lay this at FDA's feet.

I was hesitating in responding to you because I have a whole list of prescriptions for this problem that I have been promulgating for some time, and I would be happy to share those with you outside of this venue, because they are fairly extensive.

Mr. ROGERS. I would be delighted. With your permission, I would receive that at your earliest convenience. I think that would be helpful.

The lines in the sand are hard things, and when you look at the real decrease in investment, to say that the FDA isn't a part of that problem is a little concerning. Let me give you some other statistics here I find shocking.

The venture capital funds raised have decreased 25 percent in 2010 just over 2009, and that is the third consecutive year of decline. The share of venture capital invested in biotechnology declined from 18 percent in 2009 to 12 percent in 2010. From 2008 to 2010, investment in U.S. Life sciences companies declined by $2 billion.

That is significant. And I agree with you, it is a crisis that we are going to have to deal with. As a cancer survivor myself, I hope somebody is willing to put up the capital to go through the process, and I want the FDA to understand that there are risks involved

and they should be part of the process to help quickly determine the efficacy of that particular drug.

I am concerned that the risk aversion has crept into the FDA to a point that it is costing us innovation in the United States, and to me that is an unacceptable outcome.

Do you think there would be any value in having a category of drug, and I heard the discussion earlier, you know, if I am sitting with my oncologist and my oncologist tells me that this is the particular drug that I have seen work, it has saved someone's life, it has added years to their life, but the FDA says I can't give it to you even if I explain all the risks involved, is there a better way to do that?

Ms. WOODCOCK. Well, I don't think the FDA—that is the FDA's posture, that people can't give drugs to patients. As I said earlier——

Mr. ROGERS. Well, if you take it off the market, it clearly is.

Ms. WOODCOCK. Are you talking about Avastin?

Mr. ROGERS. Yes. As an example. I just used that as an example.

Ms. WOODCOCK. Avastin is on the market for other indications and will remain on the market.

Mr. ROGERS. I don't want to debate if you feel that is the right decision. But shouldn't there be the opportunity—I tell you that, because many a Member will run into a constituent who will fly out of the country to get access to a drug because they have made the conclusion that their life is at a point where they are willing to take that risk.

Ms. WOODCOCK. Right.

Mr. ROGERS. Is there some value in that in the United States? Do we have to force people to go to Mexico to do this?

Ms. WOODCOCK. We don't stand between people getting investigational drugs if they have no other options, and we passed regulations about 18 months ago that provide a broad range of ways to access totally investigational drugs, especially for people who have exhausted other types of therapies. So we agree that people have a right to take substantial risk.

Mr. ROGERS. At their own risk.

Ms. WOODCOCK. Yes.

Mr. ROGERS. I would love to work with you on the expansion of that. I think there have been some problems in the past and currently that I think we can, working together, solve this problem for literally thousands and thousands of people who are at a pretty emotional place in their life and are willing to take some risks.

With that, I yield back.

Mr. PITTS. The chair thanks the gentleman.

That concludes our first panel. Dr. Woodcock, thank you very much for your testimony, for your answers to our questions.

At this point, we will call the second panel. I think we will take 5 minutes here just to check the mikes and then we will reconvene.

[Recess.]

Mr. PITTS. I think we are ready to reconvene. Our second panel has a number of witnesses, and I will introduce them and ask them to testify in this order.

Paul Hastings is the President and Chief Executive Officer of OncoMed Pharmaceuticals. Jonathan Leff is the Managing Director

of Warburg Pincus. Mark Boutin is the Executive Vice President and Chief Operating Officer of the National Health Council. Dr. Ellen Sigal is the Chair and Founder of Friends of Cancer Research. Lastly, Allan Coukell is the Director of Medical Programs of the Pew Health Group of the Pew Charitable Trust.

Your written testimony will be made a part of the official record. We ask that you summarize your opening statements in 5 minutes.

Mr. Hastings, you may begin.

STATEMENTS OF PAUL J. HASTINGS, PRESIDENT AND CHIEF EXECUTIVE OFFICER, ONCOMED PHARMACEUTICALS, INC., ON BEHALF OF BIOTECHNOLOGY INDUSTRY ORGANIZATION; JONATHAN S. LEFF, MANAGING DIRECTOR, WARBURG PINCUS, LLC; MARC BOUTIN, EXECUTIVE VICE PRESIDENT AND CHIEF OPERATING OFFICER, NATIONAL HEALTH COUNCIL; ELLEN V. SIGAL, CHAIRPERSON AND FOUNDER, FRIENDS OF CANCER RESEARCH; AND ALLAN COUKELL, DIRECTOR OF MEDICAL PROGRAMS, PEW HEALTH GROUP, THE PEW CHARITABLE TRUSTS

STATEMENT OF PAUL J. HASTINGS

Mr. HASTINGS. Thank you. Chairman Pitts, Ranking Member Pallone, members of the committee, my name is Paul Hastings. I am the President and Chief Executive Officer of OncoMed Pharmaceuticals. I am here testifying on behalf of the Biotech Industry Organization's 1,100 members, where I serve as Vice Chairman of the Emerging Company Section; that would be small companies. I also chair the Bay Area Life Sciences Association, and I am a member of the board of the California Health Care Institute. All of these organizations represent innovative life science companies.

I have over 25 years of experience in the biotechnology and pharmaceutical industry. My current company, OncoMed Pharmaceuticals, is developing molecules based on new understandings of how tumors grow and spread. Specifically, we are trying to block biological pathways critical for the survival of tumor initiating cells. These cells are more resistant to current therapies and promote the growth of cancerous tumors. Thus, our products offer real advancement in the treatment of cancer. We presently have three products in Phase I and Phase I–A clinical trials after being in existence for 6 years.

Companies like mine are generating many new therapies to treat patients suffering from a myriad of unmet medical needs. Of the 172 scientifically novel and orphan drugs approved from 1998 to 2007, 52 percent of them were discovered or developed by biotechnology companies. We offer tremendous hope to patients, with over 3,700 new biotherapeutics in development.

Biotechnology is an American success story. Our life science sector accounts for over 7 million in direct and related jobs. We create high-paying jobs in our companies and support employment and provide vital revenue for our universities and medical centers through the clinical trials we conduct, thus employing people in those important State and local universities and medical centers. We have a national imperative to foster the development of innovative treatments and therapies.

By 2030, almost one out of every five Americans will be 65 years or older, which means dramatically increased costs associated with treating chronic disease. Innovative medicines can help offset these costs by preventing or delaying the need for other costly services such as emergency room visits and hospitalizations. If you just simply reduce cancer deaths by 10 percent, that is equal to $4 trillion in economic value.

Our position as global leadership is a position we can no longer presume to keep. We face international threats, such as India and China and the European Union increasing funding and incentives for biotech companies, while at the same time investment in the U.S. has decreased markedly.

To encourage innovation and maintain U.S. leadership, we must have an FDA that is empowered and able to effectively and consistently review breakthrough treatments and therapies. There are several troubling trends that threaten to severely hamper our ability to innovate. For example, only half of the products submitted to the FDA are approved on the first submission. From the average of the previous PDUFA rounds of 2003 to 2007 to today, drug and biologic approval times have increased 28 percent, and between 1999 and 2005 the average length of clinical trials grew by 70 percent.

Regulatory uncertainty deters future venture investment in biotechnology companies. This results in longer time for development, not time for approval once drugs are submitted, longer time for development when you start the development process in Phase I; lower investment, fewer cures for patients, and not as many life science jobs.

It is important to maintain a balanced and consistent regulatory system. To that end, among BIO's top priorities throughout the PDUFA technical discussions was to promote innovation by fostering scientist-to-scientist dialogue between FDA and sponsors concerning high priority rate limiting scientific issues that arise during drug development. We are pleased that FDA agreed to adopt a new policy that timely interactive communication with sponsors during the drug development is a core activity to help achieve the agency's mission.

BIO believes that PDUFA should be reauthorized in a timely and expeditious manner. However, additionally, last week during the BIO international convention, we unveiled a package of policy proposals entitled Unleashing the Promise of Biotechnology: Advancing American Innovation to Cure Disease and Save Lives. This is a BIO initiative, with the thought in mind to come with you with not complaints but solutions. The FDA policy recommendations described in my written testimony are designed to ensure a clear and effective pathway for turning ideas into realities that will benefit patients and improve public health. The proposals are focused on creating a modern, forward looking FDA and creating more effective clinical research and development processes.

Some of the highlights of our proposals include updating the FDA mission statement to reflect its role in advancing medical innovation; providing FDA with the management, budgetary and advisory authorities reflective of its role in regulating a quarter of our country's GDP; providing FDA with authorities, expertise, imple-

mentation mechanisms to ensure the development of forward-thinking strategies and implementation of modern regulatory science into their review practice; expanding and improving the accelerated approval pathway into a progressive approval mechanism for innovative products for unmet medical needs that would also serve to ensure a risk-benefit analysis that incorporates the safety and needs of patients in the real world.

Lastly, proposals to further empower the FDA to utilize a weight of the evidence approach and ensure that the FDA communicates to sponsors in clear terms why risk was determined to outweigh benefits and why other agency authorities, such as REMS, are insufficient.

Thank you for the opportunity to share with you our thoughts today.

[The prepared statement of Mr. Hastings follows:]

TESTIMONY OF PAUL HASTINGS, PRESIDENT AND CEO OF ONCOMED PHARMACEUTICALS
REDWOOD CITY, CA

ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION

BEFORE THE U.S. HOUSE OF REPRESENTATIVES
ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH HEARING

PDUFA V: MEDICAL INNOVATION, JOBS, AND PATIENTS

JULY 7, 2011

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, my name is Paul Hastings and I am the President and Chief Executive Officer of OncoMed Pharmaceuticals. I am here testifying on behalf of the Biotechnology Industry Organization where I serve as the Vice-Chairman of its Emerging Companies Section, comprised of more than 480 companies. BIO represents over 1,100 members involved in the research and development of innovative healthcare, agricultural, industrial, and environmental technologies.

Ninety percent of BIO's research and development company members have fewer than 100 employees. Additionally, 43 percent of typical biotech companies have less than a year's worth of cash on hand and 48 percent are at least three years away from having product revenue.[1]

I have over 25 years of experience in the biotechnology and pharmaceutical industry. My current company, OncoMed Pharmaceuticals, is working at the cutting edge of oncology research, focusing on a specific set of cells within tumors that drive the growth of the

[1] BIO Emerging Companies Section Membership Survey, 2011.

tumor and can morph into various cell types within the tumor. We have developed the ability to isolate and monitor these tumor initiating cells using specific surface markers and technologies. Our studies have shown that tumor initiating cells are more resistant to standard chemotherapy agents and radiotherapy. So, some current treatments may succeed at initially decreasing the size of a cancer, but leave behind an increased proportion of the most malignant cells. We have developed a portfolio of antibodies and have tested them within xenograft models derived from freshly resected human cancers. These antibodies target biologic pathways critical for survival of tumor initiating cells. We believe these models are more representative of the effects of these treatments in cancer patients than traditional models using cancer cell lines, which may no longer accurately reflect the properties of the original tumor. Currently we have one antibody that targets tumor initiating cells in Phase I and are developing other promising therapeutic candidates.

The U.S. biotechnology industry is poised to be a major driver in an innovation-driven economy. And while we are currently the global leader in the development of biotechnology treatments and therapies, intense competition from China and India means this a position we have to fight to keep. Indeed, when it comes to venture-backed start up biotechnology discovery companies, our industry is facing a crisis. Regulatory uncertainty, longer drug development timelines, and an increasing regulatory and Congressional focus on risk instead of reward in pharmaceutical innovation deters limited partners from investing in biotech venture capital firms and subsequently deters venture capitalists from investing in biotechnology discovery companies.

Today, I will briefly discuss PDUFA, but the focus of my testimony will be on developing a policy environment that will support the one industry, biotechnology, which is offering 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. Despite the extraordinary promise offered by biotechnology, government policies restrain our industry's ability to meet its full potential to serve patients.

The bioscience sector accounts for over 7 million direct and related jobs.[2] Not only do we create high paying jobs for scientists, clinicians, manufacturing technicians, and support staff internally at our companies, we also create jobs and vital revenue for our universities and medical centers through the clinical trials we conduct.[3]

We are also innovators. Of the 172 scientifically novel and orphan drugs approved from 1998-2007, 52% were discovered and/or developed by biotechnology companies.[4] We offer tremendous hope to patients with over 3,700 new biotherapies in development that have the potential to offer significant advances in treatments for patients suffering from cancer, diabetes, Alzheimer's, cardiovascular disease, and rare genetic disorders.

The public benefit of medical innovation is well-documented.

- Medicines can help offset overall medical costs by preventing or delaying the need for other costly services, such as emergency room visits and hospitalizations. For example, a 2009 Medicare study found that use of prescription drugs reduced hospitalization costs for Medicare beneficiaries.[5]
- Medicare ultimately saves $2.06 for every additional dollar it spends on drugs.[6]
- Reducing cancer deaths by 10% would be worth approximately $4 trillion in economic value.[7]
- Medicare spends $91 billion each year caring for individuals suffering from Alzheimer's disease and delaying the onset of Alzheimer's by just five years would save $50 billion per year.[8]

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[2] The Batelle Technology Partnership Practice. 2010. "Gone Tomorrow? A Call to Promote Medical Innovation, Create Jobs and Find Cures in America." Prepared for the Council for American Medical Innovation.
[3] Battelle Technology Partnership Practice. 2010. Battelle/BIO State Biosciences Initiatives.
[4] Kneller, Robert. 2010. "The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs." Nature Reviews/Drug Discovery.
[5] B. C. Stuart, J. A. Doshi, and J. V. Terza. 2009. "Assessing the Impact of Drug Use on Hospital Costs." *Health Services Research* 44, no. 1: 128–144.
[6] Shang, Baoping and Dana P. Goldman. 2007. "Prescription Drug Coverage and Elderly Medicare Spending." NBER Bulleting on Aging and Health.
[7] Murphy, K.M. and R.H Topel, 2003. "Measuring the Gains from Medical Research." University of Chicago Press
[8] Alzheimer's Association

We have a national imperative to foster the development of innovative treatments and therapies. Baby boomers are now entering into the Medicare system. By 2030, almost one out of every five Americans – some 72 million people – will be 65 years or older.[9] Currently, Medicare is projected to equal 5.1% of the U.S. GDP by 2030.[10] One of the main drivers of rising health care costs is treating chronic disease, with approximately 75 cents of every health care dollar spent on taking care of individuals suffering from a chronic disease.[11] This is even more concerning when you take into account that 45% of the population (133 million Americans) has at least one chronic disease.[12]

Developing innovative treatments and cures is a time- and capital-intensive endeavor reliant on private investment. It generally costs over $1 billion and 8-10 years to research and develop an FDA-approved drug.[13] In order to encourage innovation, we must have an FDA that is empowered and able to effectively and consistently review breakthrough treatments and therapies. There are several troubling trends that threaten to severely hamper our ability to innovate. For example, only half of the products submitted to the FDA are approved on the first submission.[14] From the average of the previous PDUFA rounds of 2003-2007 to today, drug and biologics approval times have increased 28 percent.[15] Between 1999 and 2005, the average length of clinical trials grew by 70%.[16] And despite the extraordinary advances in science over the last two decades, the number of new drug approvals per year remains flat (i.e., an average of 23 NME approvals per year over the past decade).[17]

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[9] Alliance for Aging Research
[10] 2010. Medicare Trustees' Report
[11] Partnership for Chronic Disease
[12] Partnership for Chronic Disease
[13] J Dimasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: is Biotech Different?" Managerial and Decision Economics No 28 (2007): 469–79
[14] BIO. Biomed Tracker. 2011.
[15] CHI. BCG. 2011. "Competiveness and Regulation: The FDA and the Future of America's Biomedical Industry."
[16] Tufts Center for the Study of Drug Development. 2008. "Growing Protocol Design Complexity Stresses Investigators, Volunteers." Impact Report. 10.1.
[17] FDA. http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf

We are in danger of losing our position as a global leader in medical innovation and our ability to keep private investment dollars and jobs in the United States as Europe, China, and India continue to develop aggressive strategies to entice companies to take their research and development enterprises abroad. In 2007, the European Union and the European Pharmaceutical Industry Association (EFPIA) sought to attract life sciences companies to Europe by establishing the $2 billion Innovative Medicines Initiative (IMI), which is described as "Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients…[which] supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe." A March 2011 press release indicates that the IMI has recently launched a second wave of research projects (focusing on areas including cancer, infectious disorders and electronic health), with a total of 23 current research projects and over €450 million (approximately USD $658 million at the time of publishing) committed by the European Commission and the EFPIA. In 2010, while the amount of capital invested in private U.S. biotechnology companies declined 3.2%, Europe saw a 29% increase.[18]

Additionally, last year, the Chinese government unveiled a 5-year plan for national economic and social development, and the biopharmaceutical industry was identified as one of the seven strategic emerging industries that China would target. The plan includes a $1.5 billion commitment and the establishment of new venture funds to invest in emerging start-up companies. India has similar plans to expand biopharmaceutical activities and in 2010 announced a plan to establish a $2.2 billion venture fund for supporting drug discovery and research infrastructure development projects.[19]

We as a nation need to focus policy discussions on how to unleash the promise of biotechnology so that the American public can realize the benefits it has to offer. Small biotechnology companies like my own depend on private investment to advance our innovative treatments and therapies programs and ultimately make it through the FDA

[18] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011
[19] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

approval process. A fundamental part of our ability to innovate and raise private investment is having an FDA with the resources and mechanisms required to effectively and consistently review and approve innovative products in a timely manner. These decisions must be understood by stakeholders – industry, investors, patients, and physicians – and then must be made in the context of patients and diseases being treated. The FDA is rarely praised for approving a novel therapy, yet they are often maligned if there are unforeseen adverse events that occur once a product is approved. It is imperative that policymakers understand the scientific realities of approving novel medicines. When determining if the benefits of a novel product outweigh the risks, examination of current standard of care and what level of risk patients and physicians find acceptable must be part of the analysis. It is important to maintain a functioning regulatory system. Increasing requirements and associated costs without a balanced assessment of what is reasonable to accomplish and in the best interest of patients risks slowing innovation in the U.S.

The remainder of my testimony will focus on solutions. I will discuss some of the positive outcomes of the PDUFA technical negotiations as well as describe a set of policy proposals/recommendations BIO has developed to address a key policy area required to encourage innovation: the creation of a 21st century FDA. Commissioner Hamburg said it best – "Discoveries in biomedical research are slow to find their way into patient care because the agency relies on 20th century methods to evaluate 21st century science." It is imperative that we have an FDA that is empowered and able to consistently and effectively review innovative treatments and therapies. It must be an agency which has review processes and requirements that are understood by patients, physicians, industry, investors, and policymakers. And lastly, it must be an agency that takes the diseases and patients being treated into account when evaluating innovative treatments and therapies.

PDUFA TECHNICAL RECOMMENDATIONS

As you are aware, the PDUFA V technical discussions between the FDA and industry have concluded. FDA, BIO, and PhRMA have agreed on a package

of proposed technical recommendations that seek to restore FDA's review performance and get "back to basics" for patients by strengthening scientific dialogue and transparency between FDA and the Sponsor with the goal of minimizing review issues that can delay patient access to novel treatments.

Among BIO's top priorities throughout the technical discussions was to promote innovation by fostering scientist-to-scientist dialogue between FDA and Sponsors concerning high-priority rate-limiting scientific issues that arise during drug development. We are pleased that FDA agreed to adopt a new philosophy that timely interactive communication with sponsors during drug development is a core Agency activity to help achieve the Agency's mission.

BIO also supports enhancements under PDUFA V that will strengthen the timeliness, transparency, and predictability of the review of novel medicines, advance regulatory science initiatives, and enhance post-market safety surveillance. Through increased FDA-Sponsor scientific dialogue and interaction during the review process, the proposed New Molecular Entity (NME) review program will help to identify and resolve issues earlier in the review and reduce the potential for a second review cycle, thereby facilitating earlier patient access to needed treatments.

PDUFA V also makes significant contributions in the field of regulatory science. Modern approaches to drug development and evaluation, such as through the application of new tools for rare disease drug development, greater utilization of biomarkers and patient reported outcome scales, and structured benefit/risk assessment, will introduce new efficiencies in the drug development enterprise and provide FDA with additional tools to evaluate the benefits and risks of pharmaceutical products.

Additionally, 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, standardized approaches

to Risk Evaluation and Mitigation Strategies (REMS), and further validation of the Sentinel Network will promote patient confidence in drug and biologics.

BIO believes that PDUFA should be reauthorized in a timely and expeditious manner because the program supports the patients that the biotechnology industry serves.

POLICY PROPOSALS TO RE-INVENT THE IDEA-TO-MARKET PATHWAY

In addition to work that was accomplished within the confines of PDUFA technical discussions, last year BIO began the process of interviewing thought leaders in our industry with the purpose of envisioning game-changing strategies. Following those conversations, BIO began a rigorous policy development process to develop a forward-thinking set of policies focused on revamping incentives for investment and improving the regulatory approval pathway. As part of this process, BIO sought, and will continue to seek, input from Members of Congress, federal agencies and institutes, patient organizations, former high-level government employees, former Members of Congress, and other policy experts. The culmination of all of these efforts to date are described in a document entitled "*Unleashing the Promise of Biotechnology: Advancing American Innovation to Cure Disease and Save Lives*," which was unveiled last week during BIO's 2011 International Convention and is the focus of my testimony today.

The policy recommendations we developed are designed to ensure a clear and effective pathway for turning ideas into realities that will benefit patients and improve public health. The proposals are focused on creating a 21st century FDA and creating more effective clinical research and development processes. With an increasingly aging population, it has never been more critical to support an American industry that offers solutions to the most pressing health care needs of today and tomorrow. It is imperative that FDA be an agency that recognizes its national role in advancing innovation, maintains the ability to effectively review innovative products in a timely manner, and promotes a consistent and science-based decision making process that is reflective of patient needs. The proposals described below are designed to address each of these

principles. They are organized under three main headings: Elevating FDA and Empowering Operational Excellence; Advancing Regulatory Science and Innovation; and Enabling Modernized Patient-Centric Clinical Development.

ELEVATING FDA AND EMPOWERING OPERATIONAL EXCELLENCE

Update the FDA Mission Statement

FDA needs a clear mandate to encourage the development of innovative products. In addition, FDA must have the capacity and commitment to incorporate the latest scientific advances into its decision making so that regulatory processes can keep pace with the tremendous potential of companies' leading edge science. Congress can help by updating FDA's statutory mission to underscore the need for FDA to advance medical innovation by incorporating modern scientific tools, standards, and approaches into the Agency's work, so that innovative products can be made available to those who need them and in a timely manner.

Establish a Fixed Term of Office for the Commissioner of Food and Drugs

The Commissioner of Food and Drugs is charged with leading a science-based regulatory agency to advance the public health. As required by statute, the President appoints the Commissioner with the advice and consent of the U.S. Senate. However, a presumption of replacement with each new President has politicized the appointment and confirmation process. The Federal Food, Drug, and Cosmetic Act (FFDCA) should be amended to provide that the President appoint the Commissioner to a six-year term of office. Once confirmed, the Commissioner would be removable by the President only for pre-specified reasons – neglect of duty, malfeasance in office, or an inability to execute the agency's mission. Encouraging consistent and stable leadership at FDA, with protection from political influence that typically occurs during a presidential administration transition, better equips the Agency to fulfill its mission to protect and promote the public health.

Grant FDA Status as an Independent Agency

FDA regulates nearly a quarter of the consumer goods supplied to the American public. As such, the Agency should have the same authorities to make budget, management and operational decisions as afforded other independent agencies such as the Environmental Protection Agency. This would empower the Agency to work more effectively with the President and Congress to carry out its mission to promote and protect the public health. Creating an independent agency would also enhance the Agency's ability to obtain quality and consistent leadership.

Establish an External Management Review Board for FDA

FDA is a large, complex organization, and in order to fulfill its responsibilities effectively, it must be well-organized and well-managed. It is critical that the Agency's organization and management capabilities be periodically analyzed, and that the Commissioner of Food and Drugs be provided with fresh, visionary, and independent thinking on how to improve the ability of the Agency and its centers to promote and protect the public health, as well as the support necessary to implement recommendations. An external advisory board composed of individuals with experience in organizational management could help the Agency address operational challenges. Current law should be amended to establish a Management Review Board (MRB) to conduct periodic reviews of FDA's management and organizational structure, and to provide recommendations to the Commissioner about ways to improve FDA operations. This idea is modeled upon the Scientific Management Review Board at the National Institutes of Health, which was developed and passed by this Committee and the Congress as part of the NIH Reform Act of 2006.

ADVANCING REGULATORY SCIENCE & INNOVATION

Support Regulatory Science Public-Private Partnerships

Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress established the Reagan-Udall Foundation for the Food and Drug Administration, an independent non-profit organization intended to support public-private partnerships for the purpose of advancing the mission of FDA to "modernize medical [and other] product

development, accelerate innovation, and enhance product safety." The Foundation could, for example, form collaborations to advance the use of biomarkers, surrogate markers, and new trial designs to improve and speed clinical development. However, Congressional appropriations bills for the Agency have subsequently restricted FDA's ability to transfer federal funding to the Foundation. These funding restrictions should be lifted so that the Reagan-Udall Foundation can fulfill its promise.

Create an FDA "Experimental Space," led by a Chief Innovation Officer, to Pilot Promising New Scientific and Regulatory Approaches

FDA has developed several initiatives to advance regulatory science. These include the FDA/NIH Joint Leadership Council, the academic Centers of Excellence in Regulatory Science, and FDA's Critical Path Initiative. However, FDA's ability to incorporate modern science into its regulatory processes has been limited because there is no entity within the Agency with unified responsibility for systematically analyzing the findings and recommendations from these groups, and with clear authority to pilot promising scientific and regulatory approaches. An FDA "Experimental Space," led by a new Chief Innovation Officer, should be established with the responsibility and authority to ensure that promising new approaches are integrated into Agency operations at all levels.

Enhance FDA's Access to External Scientific and Medical Expertise

FDA is the preeminent federal agency charged with evaluating cutting-edge science as it is applied to the prevention, diagnosis, and treatment of human disease. FDA also has been perceived by many as the global standard bearer for regulatory review of drug and biologic applications. However, scientific and medical knowledge, techniques, and technology are advancing at a more rapid pace today than at any other time, and FDA's capacity to access information about these advances has not kept pace. It is essential that FDA's access to scientific and medical advice be enhanced by improving the operations of FDA Advisory Committees, establishing Chief Medical Policy Officers in the immediate offices of the Center Directors, and providing FDA staff with additional avenues for accessing external scientific and medical expertise.

ENABLING MODERNIZED PATIENT-CENTRIC CLINICAL DEVELOPMENT

Increase Access to Innovative Treatments and Therapies through Progressive Approval

Patients, industry, Congress, and others are eager to find ways to deliver safe and effective new drugs and biologics to patients. Patients, particularly those with illnesses for which no adequate therapy exists, want access to promising new therapies earlier in the drug development process. Smaller biopharmaceutical companies that develop those therapies are sometimes unable to maintain operations through extensive phase III testing without revenue from the sale of products. Expanding and improving the accelerated approval pathway into a progressive approval mechanism would help provide patients more timely access to needed therapies. This pathway would be limited to innovative products for unmet medical needs, significant advances to standard of care, targeted therapies, and those that have been approved by the European Medicines Agency (EMA) or other mature regulatory agencies. This pathway also would ensure risk-benefit analysis that incorporates the safety and needs of patients in the real world.

Empower FDA to Utilize a Weight-of-Evidence Approach

FDA's current statutory authority requires that the Agency approve applications for new drugs when they have been demonstrated to be safe and effective under the intended conditions of use. The law provides that effectiveness is established where FDA is satisfied that there is "substantial evidence" that the new drug has the intended effect that it is purported to have. FDA typically requires two "adequate and well controlled" studies under this standard. A weight-of-evidence approach to data analysis, however, would allow the decision-maker to look at all data and information, whatever its value, and give each appropriate consideration.

Leverage Electronic Health Records to Facilitate Clinical Research

Every new drug's sponsor spends years designing and conducting clinical trials to show their drug is safe and effective. Using health information technology (IT) such as electronic health records (EHRs) in clinical research will improve and speed up the drug development process, and decrease costs. However, there are significant barriers

preventing wide-spread use of health IT in clinical research, including slow adoption by providers and lack of standards development. FDA can help remove those barriers. Congress should create a Clinical Informatics Coordinator in the Office of the Commissioner of Food and Drugs charged with developing processes to validate and encourage the use of health IT in clinical research, and establishing pilot projects to use health IT in clinical research.

Require FDA to Disclose to the Sponsor Reasons for Non-Approval

The FFDCA implies that licensing or approval applications contain a binary question – approve or deny – due to phased, investigational review of applications; however, there is in practice a third response. In this case, FDA neither approves nor officially denies the application (which would require FDA to give the sponsor specific procedural rights such as a hearing); rather it finds the application to be incomplete in some way that makes the application ineligible for approval. When FDA makes such a finding, it should communicate to sponsors in clear terms why risk was determined to outweigh benefits, and why other Agency authorities such as Risk Mitigation and Evaluation Strategies (REMS) – which are designed to mitigate risk for approved products – are insufficient (in addition to indicating what must be done to address any deficiencies). Such an approach would help create a consistent and transparent evaluation of risk-benefit, and provide the sponsor with better information on what, if any, additional studies are required to achieve approval.

Conclusion

We have a national imperative to support and foster advances in medical innovation. The full potential of biotechnology industry to cure disease and offer real solutions to our nation's most pressing health care needs has yet to be realized. We look forward to working with you on developing policies for a 21st century FDA that will serve to unleash the promise of biotechnology in the United States.

Mr. PITTS. The chair thanks the gentleman.

Mr. Leff, you are recognized for 5 minutes.

STATEMENT OF JONATHAN S. LEFF

Mr. LEFF. Thank you. Chairman Pitts, Ranking Member Pallone, and members of the committee, my name is Jonathan Leff. I am a managing director at Warburg Pincus, where I lead the firm's investment efforts in biotechnology and pharmaceuticals. I have more than 15 years of experience as a life sciences venture investor and have served on the boards of and helped build more than 15 small entrepreneurial companies involved in developing novel therapies for a range of diseases, companies not unlike the one that Mr. Hastings described. It is my privilege to be here today.

Venture capital provides the essential fuel for medical innovation by funding the development of novel therapies, an endeavor that requires hundreds of millions of dollars over many years or even decades. Venture capital has been a primary source of this vital risk capital, has funded the development of an entire generation of important new medicines, and has financed and helped build almost every successful biotechnology company in the U.S., creating well over 1 million high quality jobs.

Today, however, the U.S. medical innovation ecosystem is in jeopardy. Life sciences venture capital is experiencing an alarming decline. The primary reason is that the cost, time and risk involved in developing new drugs and biologics have increased to unsustainable levels. As a result, vital risk capital is being diverted to other industries and to other countries. At a time when medical research is exploding with potential, many scientific discoveries are not being developed into new medicines due to lack of investment capital.

While many factors have contributed to the escalating cost, time and risk of drug development, a changing regulatory environment at the FDA is the most significant. In the early 1990s, Congress and the FDA worked together to shape a new drug approval system designed to balance the goal of ensuring drug safety with the desire to speed new therapies to seriously ill patients. As a result of this balanced regulatory environment, for example, HIV is no longer a death sentence, cancer patients have access to many dozens of important new medicines, and the U.S. has established itself as the world's leader in life sciences innovation.

By the middle of the last decade, however, the political backdrop and public consensus that made all of this possible had changed. Following the safety issues with Vioxx, the public discourse began to heavily emphasize drug safety. Far from being congratulated for speeding new treatments to sick patients or for advancing medical innovation, FDA has instead come under heavy criticism for failing to do enough to ensure patient safety.

Naturally, FDA officials have responded to this changing environment, including congressional hearings and media attention, and have shifted to a more cautious, risk averse posture in the new drug approval process, emphasizing the potential risks of new treatments more than their benefits to patients. My written testimony provides examples of how this shift has become evident.

Without question, protecting patients from harm is an essential element of what the public expects from the FDA. But so too is enabling the timely development and availability of new therapies. Finding the right balance is the central challenge of the new drug approval process. However, I want to emphasize that the way this balance is struck by regulators and by policymakers has tremendously important implications for U.S. leadership in medical innovation.

FDA's shift in recent years to an increasingly cautious posture toward drug approvals has had the unintended consequence of reducing investments to life sciences innovation due to the significant additional time, cost and uncertainty it has added to the drug development process.

In the face of new hurdles to FDA approval, investors are moving away from critical areas, including cancer, diabetes, rare diseases and many others. I believe these problems are fixable if we act now. Twenty years ago, U.S. policymakers and the FDA rose to the challenge. We have the opportunity to do the same today.

My recommendations are as follows: Strengthen FDA's mission statement to reflect the importance of innovation; expand the accelerated approval pathway into a progressive approval system for new drugs that offer a significant advance; empower FDA to weigh all evidence in the context of the disease being treated in assessing benefit versus risk in new drug approvals; fully detail the FDA's benefit-risk calculus when denying or delaying approval in favor of collecting more data; and, finally, ensure that FDA is provided with the resources that it needs to accomplish its mission.

I look forward to working with the committee to reinvigorate and strengthen U.S. leadership in medical innovation. Thank you.

[The prepared statement of Mr. Leff follows:]

HEARING TESTIMONY

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New York City, New York

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

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PDUFA V: Medical Innovation, Jobs, and Patients

Chairman Pitts, Ranking Member Pallone, and Members of the Committee, my name is Jonathan Leff. I am a Managing Director at Warburg Pincus, where I am a member of the firm's Healthcare Group. I joined Warburg Pincus in 1996, and for the past 12 years, I have led the firm's investment efforts in biotechnology and pharmaceuticals. Established more than 40 years ago, Warburg Pincus has invested over $7.5 billion in more than 130 healthcare companies. I personally have more than 15 years of experience investing in innovative life sciences companies and have served on the boards of more than 15 companies involved in developing novel therapies for a wide range of diseases. I am also a director of the Spinal Muscular Atrophy Foundation and a member of the Executive Committee of the Board of Visitors of Columbia University Medical Center as well as a member of the Board of Directors of the National Venture Capital Association (NVCA) and of the Biotechnology Industry Organization (BIO) Emerging Companies Section Board.

It is my privilege to be here today to share my perspective as a venture investor on the impact that the Food and Drug Administration's (FDA) approval process for new drugs and biologics has on innovation in the discovery and development of new treatments for disease. I am also pleased to present a set of policy recommendations related to the FDA approval process that will help bring a new generation of breakthrough therapies to patients and will help sustain and grow the essential ecosystem that has established the U.S. as the global leader in life sciences innovation.

Venture capital provides the essential fuel for medical innovation, by funding the discovery and development of novel therapies to treat disease. In order to develop new drugs, innovative companies require many hundreds of millions of dollars in capital over a period of many years or even decades. For the past three decades, venture capital has been a primary source of this vital risk capital, has funded the

development of an entire generation of important new medicines, and has financed and helped build almost every successful company in the world-leading U.S. biotechnology industry.

Today, however, the U.S. medical innovation ecosystem is facing severe strains. The cost, time, and risk of developing novel therapies for important diseases have all grown to the point where, increasingly, investors can no longer earn returns on these investments. As a result, the vital risk capital that for the past several decades has funded U.S. medical innovation is being diverted to other industries and other countries. At a time when medical research is exploding with potential, many promising scientific discoveries are not being developed into new treatments for disease due to lack of investment capital.

While many factors have contributed to the escalating cost, time, and risk of new drug development, a changing regulatory environment at the FDA is the most significant. In the late 1980s and early 1990s, patient groups highlighted delays in getting new medicines to patients and pushed for more rapid access. In response, Congress and the FDA worked together to shape a new drug approval system designed to balance the goal of ensuring drug safety with the desire to speed new therapies to seriously ill patients. Throughout the 1990s and through the first part of the last decade, the FDA generally struck this benefit-risk balance effectively and maintained an efficient, predictable review process. This balanced regulatory environment helped bring a generation of vital new treatments to patients in need and helped establish the U.S. as the world leader in life sciences innovation, fostering the rapid growth of a vibrant biotechnology industry and creating more than a million high-quality U.S. jobs.

By the middle of the last decade, however, the political backdrop and public consensus that made all of this possible had changed dramatically. Following the emergence of safety issues with Vioxx in 2004 and other similar high-profile developments, the public discourse about drug regulation began to heavily emphasize drug safety. Far from being congratulated for speeding new treatments to sick patients or for advancing medical innovation, the FDA has instead come under increasingly heavy criticism for failing to do enough to ensure patient safety. Naturally, FDA officials have responded to this changing environment and have shifted to a more cautious, risk-averse posture in the new drug approval process, emphasizing the potential risks of new treatments more than their potential benefits to patients.

Without question, protecting patients from harmful drugs is an essential element of what the public expects from the FDA. But so too is enabling the timely development and availability of new therapies for those in need. Finding the right balance between these important objectives is the central challenge of the new drug approval process.

As a long-standing investor in the development of innovative new therapies, I want to emphasize that the way this balance is struck, by regulators and by policymakers, has tremendously important implications for the health of the U.S. medical innovation ecosystem. The FDA's shift in recent years to an increasingly cautious, risk-averse posture toward new drug approvals has had the unintended consequence of reducing investment in life sciences innovation due to the significant additional time, cost, and uncertainty it has added to the drug development process.

I am especially pleased to have the opportunity to testify today, because I believe the problems are fixable. Twenty years ago, U.S. policymakers and the FDA rose to the challenge and implemented policy solutions that genuinely benefited patients as well as the innovation ecosystem. We have the opportunity to do the same today. I offer a set of specific policy recommendations designed to give FDA the tools and resources it needs to rebalance the new drug approval process in a way that continues to ensure the safety of new products, but also reflects the great benefits of new therapies as well as the immense value of a vibrant U.S. medical innovation ecosystem.

Venture Capital Fuels Medical Innovation

Over the last several decades, venture capital has provided the fuel for U.S. medical innovation. Venture capital has played a central role in creating, financing, and building an entire generation of new companies that have been at the heart of the discovery and development of almost all of the new biotechnology drugs and medical devices of the last 30 years. Venture-backed companies have delivered breakthrough treatments to patients with cancer, diabetes, HIV, multiple sclerosis, orphan diseases, and many other serious conditions. These investments are not only driving innovation; they are also helping to create jobs and grow the economy. In 2010, venture capital-founded and -developed life sciences companies employed more than 1.7 million people in the United States.[1]

Venture-backed biotechnology companies are small, emerging growth companies that require continuing investment of risk capital. In fact, more than 90 percent of all biotechnology companies employ fewer than 100 people.[2] These companies are central to the U.S. medical innovation ecosystem, but they are small businesses whose ability to survive and innovate can be impacted by seemingly minor regulatory factors that increase the cost, time, and risk required to develop new products.

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[1] IHS Global Insight 2011

[2] BIO Emerging Companies Section Membership Survey, 2011.

A Challenging Environment for Medical Innovation

Currently, America's medical innovation ecosystem is under intense strain. At a time when scientific research is generating unprecedented opportunities for breakthrough therapies that improve treatment while bringing down healthcare costs, the venture capital dollars that have been the vital fuel of U.S. innovation are fleeing the life sciences sector and even leaving the country. Fewer new drugs are being developed and making it to the marketplace, and those that do succeed take longer and cost more than in the past. Today, it requires an average of 10 to 15 years and $800 million to over $1 billion to develop a new drug, and not only is that cost increasing, but it is increasing at an accelerating rate.[3 4 5 6] As a result, fewer biotechnology ventures than ever before provide favorable returns to their investors, and venture investors in life sciences struggle to raise funds to create and nurture the next generation of innovative companies.

While other measures of investment are bouncing back from the difficult economic environment, life sciences venture investment is declining. Increasingly, limited partners (the endowments and pension funds and other institutions that provide the capital for venture funds to invest) are telling the National Venture Capital Association that they are reducing or even eliminating the share of investment that they allocate to life sciences venture capital. As a result, a number of the most established venture firms dedicated to life sciences have been unable to raise new funds and have had to reduce or even cease operations. Many other venture capital partnerships are being forced to reduce or abandon life sciences investing, and instead focus on other areas such as information technology, social networking, and, more than ever before, emerging markets such as China.

The following statistics illustrate the depth of the problem facing U.S. life sciences venture capital and the medical innovation ecosystem that it supports:

- During 2010 and 2011 to date, first-time fundings of life sciences ventures – a key leading indicator of the health of the innovation ecosystem – have decreased by more than 50 percent compared to prior years.[7]

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[3] Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics 13, no. 4 (1994): 383–406
[4] H.G. Grabowski, J. Vernon, and J.A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," Pharmacoeconomics 20, supp. 3 (2002): 11–29
[5] J. Dimasi and H Grabowski J "The Cost of Biopharmaceutical R&D: is Biotech Different?" Managerial and Decision Economics no 28 (2007): 469–79
[6] Munos, Bernard. "Lessons from 60 years of pharmaceutical innovation." *Nature Reviews Drug Discovery* 8, 959-968 (December 2009).
[7] BioAdvance, MedTRACK Venture Finance Database

- The total amount of capital raised by venture capital funds decreased by 25 percent in 2010 compared to 2009, representing the third consecutive year of decline.[8]
- The share of venture capital invested in biotechnology declined from 18 percent in 2009 to 12 percent in 2010, the lowest level since 2001.[9]
- From 2008 to 2010, venture investment in U.S. life sciences companies declined by $2 billion.[10]

FDA's New Drug Approval Decisions Have Adversely Impacted Innovation

A strong FDA that makes scientifically rigorous decisions is an essential element of the medical innovation ecosystem. For many decades, the FDA has been the world's highest-performing and most scientifically advanced regulatory body. While other countries have steadily improved their regulatory capabilities, they have done so largely by emulating the FDA, and the world continues to look to the FDA for leadership in regulatory science. Nevertheless, when asked what is the biggest factor driving the increased cost, time, and risk of drug development, almost every venture capital investor and drug developer points, without hesitation, to the way FDA approval requirements have changed over the past decade.

Ultimately, decisions about when and whether to approve new drugs are not just scientific judgments, but also value judgments. All drugs present risks as well as benefits to patients. Rigorous science helps to identify and measure the benefits and the risks, but the question of how to balance the benefits versus the risks, and the question of how much uncertainty to accept when releasing a new product to the market, is inherently a value judgment.

On this score, while the FDA continues to bring great scientific rigor to its decision-making, the last decade has witnessed a major shift in the nature of the value judgments the FDA is making. Compared to a decade ago, the FDA of today is on the whole more risk-averse, and tends to emphasize the risks of new products more than their benefits to patients. This leads the Agency to demand more and more data – larger trials, longer follow-up, and greater statistical certainty about efficacy and safety – before being willing to approve a new product.

This evolution in the value judgments being made by the FDA has not happened in isolation. Rather, it reflects the tenor of the public discourse about the benefits and risks of new therapies. In the late 1980s

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[8] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011
[9] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011
[10] PricewaterhouseCoopers/National Venture Capital Association Money Tree Report: Thompson Reuters.

and early 1990s, patient organizations argued passionately that patients with deadly diseases value new therapies and are willing to accept some risk and uncertainty in exchange for rapid access. At the same time, many observers highlighted the existence of a "drug lag," noting that novel drugs were generally reaching the market faster in Europe than in the U.S.[11] Congress and the FDA responded, implementing a number of forward-thinking regulatory initiatives – including the Accelerated Approval Pathway, Fast Track designation, Priority Review, and regulatory performance metrics and goals – designed to streamline the approval process and speed new drugs to patients. Throughout the 1990s and into the first half of the last decade, the FDA's decision-making about new drug approvals reflected this broader societal consensus about the benefits of new therapies as well as the importance of safety and rigorous scientific evaluation.

However, the political and public backdrop has changed markedly in recent years. Ever since Vioxx was pulled from the market in 2004, the public discourse about the FDA – reflected in Congress and amplified by the media – has been less about the promise of new drugs, and more about their risks. The FDA has been increasingly criticized for not doing enough to ensure safety, and for taking too much risk in approving new products. Rarely over the past decade has one heard FDA officials being congratulated for speeding new therapies to patients in need or for encouraging innovation. Not surprisingly, the FDA has responded to this environment, shifting to a more cautious decision-making posture, and requiring more and more data to provide a higher degree of statistical proof of both efficacy and safety, before allowing new drugs to market.

While it is undeniably important to assure the safety of new drugs coming to market, it is equally important to recognize the benefits of new therapies. It is also essential to recognize that the way in which these objectives are balanced has enormous implications for our country's ability to maintain leadership in turning science into breakthrough products. As the FDA becomes more cautious, demands more and more data, and emphasizes the risks of new products over their benefits, the cost, time, and risk of investment in medical innovation all go up, driving investment capital away from U.S. life sciences and into other industries and other countries.

While this is surely an unintended consequence of a cautious, risk-averse regulatory environment, its impact is very real. Notably, the FDA approved an average of 36 new drugs and biologics per year from

[11] CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry

1996 to 2004, but an average of only 21 per year from 2005 to 2010.[12] The most recent data for 2011 to date show the FDA on pace to approve more new drugs and biologics this year than in recent years.[13] This is certainly welcome news, but there is little evidence yet of a sustained change in the underlying issue, which is the way the Agency balances the benefits versus the risks of new therapies. Investment in the development of novel therapeutics is being impacted as well. Total R&D investment by the U.S. biotechnology industry is down an alarming 27 percent from $30 billion in 2007 to $22 billion in 2010.[14]

Investing in Novel Therapies is Increasingly Challenging

The shift in new drug approval standards directly impacts the calculus of investors when deciding whether or not to make the high-risk, long-term investments needed to develop new therapies. As an investor in innovative life sciences companies for the past 15 years, I now find it increasingly difficult to make the math work for investment in novel therapeutic product development. I am certainly not alone in this. This is an experience that is widely shared and frequently discussed among venture capitalists and other life sciences investors. Simply stated, promising scientific breakthroughs – ones that a decade ago would have readily secured ample venture capital investment – now languish for lack of investment.

In recent years, along with other life sciences investors, I have watched the calculus for investment turn markedly less favorable in one disease category after another. This has been happening across a wide range of different therapeutic areas. Here, I will briefly highlight three areas – diabetes, obesity and rare diseases – where the investment calculus has been adversely impacted by an increasingly risk-averse posture at the FDA. In each case, my aim here is not to second-guess the FDA's scientific judgments nor its decisions about any specific product. Rather, it is to illustrate the profound impact that these decisions can have on investment in development of innovative new therapies.

Diabetes. Type 2 diabetes is among the largest and most rapidly growing serious health conditions in the U.S., and is a significant driver of increasing healthcare costs. However, due to new FDA requirements, it has recently become a very difficult area in which to invest. In a 2008 guidance document, the FDA notified sponsors of new type 2 diabetes drugs that they will now be required to conduct additional large, long-term safety studies in advance of approval, on top of what were already stringent requirements. While the FDA's goal of more tightly defining the cardiovascular risk profile of new diabetes drugs is clearly a worthy one, this new approval requirement has had major unintended consequences. Due to the

[12] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011
[13] FDA, NMEs approved, 2011.
[14] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

requirement, the development of a new diabetes drug today costs as much as several hundred million dollars more than in the past, and takes as much as several years longer. This additional burden in time and cost has significantly reduced investment in diabetes drug development. The impact has been especially crippling for the kinds of small, venture-backed companies which have been so critical to the life sciences innovation ecosystem. Just within the past few years, as a result of these new FDA approval hurdles, several venture-backed companies with promising diabetes therapies have been forced out of business, and many others have abandoned diabetes and shifted focus to other areas.

Obesity. Like diabetes, obesity is recognized as a major public health challenge and a key driver of escalating healthcare costs. Over the past decade, venture capital-backed companies took up the challenge of advancing novel obesity therapies to the market. During the past year, however, the FDA denied three consecutive applications for approval of new obesity drugs. One of those drugs, developed by a small company financed with venture capital, was rejected despite an Advisory Committee vote recommending approval. According to the public statements of the sponsor, the FDA is requesting a pre-market cardiovascular safety study that will require between 60,000 and 100,000 patients – a study which would be cost-prohibitive and, for all practical purposes, impossible to conduct. Investors will be unable to justify further investment in obesity therapeutics in the face of requirements such as this.

Rare Diseases. While the FDA's pre-market safety requirements have shaken the innovation ecosystem in areas such as diabetes and obesity, the Agency's escalating requirements for statistical proof of efficacy have taken a toll on the calculus for investment in innovation in many other disease areas. Rare diseases are a case in point.

By definition, the smaller the number of patients affected by a disease, the more difficult it is to enroll any given number into clinical trials. Yet increasingly, the FDA has held treatments for serious orphan diseases to the same level of statistical proof of efficacy as is required for non-orphan diseases. In general, the FDA requires two randomized controlled clinical trials demonstrating a statistically significant and clinically meaningful benefit as the basis for new drug approval. This is an entirely reasonable standard in most situations. However, when applied inflexibly, it drives innovation capital away from certain areas, such as rare diseases, where the small numbers of patients make it difficult and often impossible to enroll multiple clinical trials large enough to meet the traditional definition of statistical significance.

A recent example is Firazyr, a novel treatment for hereditary angioedema ("HAE"), a rare but very serious condition. Firazyr was originally developed by a small venture capital-backed company, which conducted two randomized controlled studies in support of approval. The results of both studies appeared to suggest a benefit for Firazyr, but one of the two studies fell short of meeting the conventional definition of statistical significance. In 2008, citing the need for additional evidence of efficacy, the FDA denied the sponsor's application for approval of Firazyr.

At the same time, however, the European Medicines Agency ("EMA") approved Firazyr for marketing in the EU. In contrast to today's FDA, the EMA has proven to be less wedded to the requirement for two statistically significant randomized controlled studies. While that remains the usual standard in the EU as in the U.S., the EMA is empowered to employ a "weight of evidence" approach, evaluating all available evidence, and interpreting that evidence in the context of the disease and the unmet need, in order to determine whether the benefit of a new therapy outweighs its risks.[15] This "weight of evidence" approach to EU approval decisions, in contrast to the more statistically rigid principles generally applied by the FDA, has profound implications and is a major reason that many observers increasingly consider the EU regulatory environment to be more conducive to life sciences innovation than the U.S.[16]

The FDA's rejection of Firazyr in 2008 is one of a number of FDA actions that have forced investors to reassess the economics of investing in rare diseases. The FDA's decision on Firazyr jolted investors not only because it came on the very same day that EU regulators decided to approve Firazyr, but also because it appeared to reflect a different balance from what the FDA itself might have struck a decade ago, when regulatory principles were applied in a more flexible manner that aligned with the unique challenges of developing drugs for rare conditions.[17]

Over the years, my firm has made a series of significant investments in a variety of orphan diseases, and I am proud to have played a part in the successful development and commercialization of a number of drugs for rare diseases where no prior therapy existed. Unfortunately, as a direct result of the evolution of FDA approval requirements over the past decade, my firm has in recent years been forced to decide against making investments in several potential breakthrough therapies for rare diseases, where 10 years ago, we would have jumped at these opportunities.

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[15] Module 5 of Part I of Annex I to Directive 2001/83/EC
[16] CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry
[17] "Icatibant: Mixed bag for US & EU approval." Credit Suisse, 25 April 2008.

Cancer Innovation Is at a Crossroads

Over the past two decades, cancer has attracted far more investment capital than any other disease, and potential breakthrough anti-cancer medicines in the pipeline today vastly outnumber those for other therapeutic areas.[18] While many factors have helped create this situation, a central element has been the FDA's approach to approval of new cancer drugs – an approach that has historically struck an effective balance between the benefits and risks of new cancer treatments. However, since late 2009, the FDA has initiated what appears to be a fundamental re-evaluation of the standards for approval of new cancer therapies. The resulting uncertainty has chilled investors' enthusiasm for oncology, as investors fear that the FDA's decision-making in oncology may already be in the process of veering toward the same risk-averse, cautious approach that has impacted other disease areas.

In 1992, with patient groups pushing for earlier access and a public discourse that valued the benefits of new treatments for patients, the FDA implemented the Accelerated Approval pathway, which was designed to allow for earlier approval of new drugs that provide benefit over existing therapies for serious and life-threatening diseases, based on "surrogate endpoints" that are deemed "reasonably likely to predict clinical benefit." [19] In effect, rather than having to wait for definitive statistical proof that a drug extends patients' survival, the FDA could make the drug available to seriously ill patients in the market based on a more limited package of data, with a commitment from the sponsor to conduct further post-market studies to more completely document the patient benefits.

The Accelerated Approval pathway has been a great success story. While its applicability has been limited only to certain disease areas and certain situations, the pathway has stimulated an explosion of investment in innovation in those diseases, most notably HIV/AIDS and cancer, and has brought immense benefit to patients. In HIV/AIDS, for example, there are now over 20 new medicines on the market. In oncology, the FDA has granted Accelerated Approval to 49 new indications for 37 novel oncology drug products since 1995.[20]

While recent studies have suggested that innovative medical devices are increasingly reaching the market years earlier in the EU compared to the U.S. and that FDA review times for new drugs may be beginning

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[18] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

[19] 21 C.F.R. § 314.500; 21 C.F.R. § 601.40

[20] Dr. Paul Kluetz. ODAC. February 8, 2011, the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC))

to lag behind those of the EU regulators,[21] [22] the U.S. has continued to lead the world in cancer drug approvals. A study released last month by Friends of Cancer Research ("FOCR") found that during the period from 2003 to 2010, more new cancer medicines were approved in the U.S. than in Europe, and new cancer drugs typically became available to patients earlier in the U.S. than in Europe.[23] These welcome results reflect the success of the Accelerated Approval pathway in oncology, along with the willingness of the FDA through most of the decade to take a balanced approach to the assessment of benefit versus risk in cancer drug approvals. Notably, of the 32 novel cancer drugs approved by the FDA from 2003 to 2010, 14 obtained Accelerated Approval, of which 11 were based on single-arm studies without a control group.[24]

However, an active debate is underway today about approval standards for cancer drugs, and there is serious concern among investors and oncology drug developers that the FDA may be moving away from the balanced approach to oncology of the past two decades and toward the same kind of cautious, risk-averse mindset that has impacted FDA approval decision-making in other disease areas. In particular, recent actions and public statements from the FDA's Office of Oncology Drug Products have introduced significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway in the future. For example, at an Oncology Drugs Advisory Committee ("ODAC") meeting in February 2011 and other recent settings, the FDA has raised fundamental questions about the range of situations in which single-arm studies (i.e., studies without a randomized control group, typically using tumor response rate as primary endpoint) and studies using measures of disease progression (such as Progression Free Survival) as primary endpoint should be sufficient to support Accelerated Approval for cancer drugs. During this same time period, companies developing oncology drugs have increasingly reported that in their interactions with the FDA, the Agency has begun demanding overall survival studies in situations where single-arm studies or progression-free survival studies would in the past have supported approval.

While no new formal guidance has been issued on these topics, the uncertainty about the FDA's direction has cast an alarming shadow over the cancer drug innovation ecosystem and has chilled investment in innovative cancer therapies. The reason for this becomes apparent when one realizes that of the 47

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[21] Josh Makower, "FDA Impact on U.S. Medical Technology Innovation, A survey of over 200 medical technology companies, November 2010. http://www.medicaldevices.org/node/846

[22] CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry

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

[24] Johnson, John R., et. al. "Accelerated Approval of Oncology Products: The Food and Drug Administration Experience." JNCI, Vol. 103, Issue 8. 20 April 2011.

Accelerated Approvals granted to cancer drugs since 1992, 44 have been based on either single-arm studies using tumor response rate as primary endpoint, or randomized studies using measures of disease progression or tumor response as primary endpoint.[25] In short, these endpoints and trial designs have been the basis of essentially *all* of the oncology innovation that has been encouraged and facilitated by the Accelerated Approval pathway over the past two decades. Indeed, many of the most important new cancer drugs of the past 20 years – including Gleevec, Alimta, Velcade, Erbitux, and many others – owe their approvals, at least in part, to the Accelerated Approval pathway and to these trial designs and endpoints.

Thus, while it is appropriate for the experts to review and debate the merits of these endpoints and designs, it is essential that this discussion reflect the practical realities of oncology drug development and the incentives for investment in innovation. It must be remembered that the Accelerated Approval pathway has stimulated an explosion of investment in innovative cancer drugs over the last 20 years precisely because it reduced the cost, time, and risk of investment required to get a new cancer drug to market. While randomized studies measuring overall survival are clearly the gold standard in terms of scientific certainty, the Accelerated Approval pathway, and the trial designs and endpoints that have made the Accelerated Approval pathway work in oncology, are essential to the oncology innovation ecosystem.

This debate over cancer drug approval standards is happening as we speak. In light of the unique status of cancer – its devastating impact for patients, its position as the most heavily invested area of drug development, and the explosive pace of basic scientific progress in understanding its mechanisms – the stakes of this debate for the future of U.S. leadership in medical innovation could not be higher.

Policy Recommendations

As I have described, the fundamental challenge facing the U.S. innovation ecosystem for new drugs and biologics is the way in which the FDA balances the benefits versus the risks of new therapies. Fortunately, this problem is eminently fixable. The FDA remains the most scientifically rigorous regulatory agency in the world, and has demonstrated its commitment to continuously improving its processes and scientific foundation. It has also proven over the past two decades that it has a great ability to adapt and respond to intelligent policy and to the values of the public. Therefore, I offer the following policy recommendations designed to rebalance the benefit-risk assessment in the new drug approval process and to help jumpstart the U.S. medical innovation ecosystem.

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[25] Johnson, John R., et. al. "Accelerated Approval of Oncology Products: The Food and Drug Administration Experience." JNCI, Vol. 103, Issue 8. 20 April 2011.

Strengthen FDA's Mission Statement

The FDA's statutory mission should reflect the centrality of its role in the life sciences innovation ecosystem, as well as the degree to which the public values, and benefits from, medical innovation. Currently, the FDA's mission, as stated in the Federal Food, Drug, and Cosmetic Act, is to "promote and protect the public health."[26] Congress should update the FDA's mission statement to explicitly reflect that the advancement of medical innovation is one of several core aspect of the FDA's undertaking and is essential to the public health. Such an updated mission statement would provide the basis for the Agency to routinely assess the consequences of its decisions, policies and priorities on unmet medical needs and medical innovation, and would serve as a powerful reminder to FDA staff and to all stakeholders that the FDA's actions and decisions have enormous impact on the life sciences innovation ecosystem.

Expand the Accelerated Approval Pathway into a Progressive Approval System

Congress should expand the highly successful Accelerated Approval pathway into a Progressive Approval system for new drugs and biologics that offer a significant advance in the treatment of serious or life-threatening diseases. While the Accelerated Approval pathway has given the FDA the ability to speed certain products to market based on "surrogate endpoints," the Progressive Approval system should build on the success of Accelerated Approval by addressing the overall benefit-risk balance directly, rather than just the question of endpoints. The FDA should be empowered to grant Progressive Approval at the earliest possible point in development, as soon as the available evidence suggests that a new therapy is more likely than not to provide benefits to patients that exceed its risks. As with the Accelerated Approval pathway, sponsors would be required to conduct post-marketing studies designed to further elucidate the benefit-risk balance, and the FDA would be able to rescind a drug's Progressive Approval status if the available evidence comes to suggest that the benefit-risk balance is unfavorable. Importantly, the implementation of a Progressive Approval pathway would make explicit that the FDA has the authority and the public mandate to behave flexibly, without a "one-size-fits-all" standard of evidence, in approving breakthrough drugs in the context of unmet medical needs.

Empower FDA to Incorporate All Available Evidence in Assessing Benefit versus Risk

Under the Federal Food, Drug, and Cosmetic Act, the FDA is directed to approve a new drug or biologic when "substantial evidence" exists that it is safe and effective when used as intended. Except in certain limited circumstances (such as the Accelerated Approval of new oncology drugs), the FDA has generally interpreted this language to require at least two randomized controlled clinical studies meeting the

[26] Federal Food, Drug, and Cosmetic Act, Section 1003.

conventional definition of statistical significance. As illustrated above in the context of treatments for rare diseases, this requirement at times fails to reflect the realities of drug development and lacks flexibility in situations such as orphan conditions, drugs that address major unmet needs in serious and life-threatening diseases, and drugs that present minimal safety risk to patients.

Congress should clarify the standard to make explicit that the FDA is empowered to use a "weight-of-evidence" approach to the assessment of benefit versus risk, taking into account the full context of the disease, the patients being treated, and the nature of evidence available. While placebo-controlled studies with statistically significant outcomes would clearly remain the gold standard form of evidence, this proposal would further empower the FDA to apply rigorous scientific judgment in a flexible manner, in line with circumstances. The weight of evidence approach has worked for the new drug approval process in Europe and for the FDA itself, when it is necessary and appropriate to make decisions without the benefit of statistically significant, randomized controlled data.

Make FDA's Benefit-Risk Assessments Explicit When Refusing Approval of New Products

It is easy for a regulatory agency to fall into the trap of excessive caution, requiring more and more data and certainty rather than being willing to take risk. To be sure, drug safety is of the utmost importance and is central to the FDA's mission, but so too are the benefits of new drugs to patients and the health of the U.S. innovation ecosystem. The FDA should be required to fully detail its benefit-risk calculus when it decides to deny or delay approval in favor of collecting more data. This would make explicit the basis on which critical decisions are being made, would help ensure that regulators assess the tradeoff between benefit and risk in a manner that reflects the values of patients and the public, and would facilitate investment in innovation by providing enhanced clarity about the standards against which approval of potential new therapies will be measured.

Ensure Adequate Funding for FDA

A vibrant life sciences innovation ecosystem requires a strong, science-oriented FDA. The FDA's scope of responsibility continues to expand, and the complexity of medical science continues to grow. Congress should ensure that, through the reauthorization of PDUFA and appropriations, the FDA is endowed with the resources it needs to advance the public health, maintain its position at the cutting edge of regulatory science, and promote U.S. leadership in life sciences innovation.

Conclusion

As I have described, the U.S. medical innovation ecosystem is in jeopardy. Life sciences venture capital, which for the past four decades has provided the basic fuel for medical innovation, is experiencing an alarming decline. Without risk capital, breakthrough science cannot be developed into treatments that cure disease, ease suffering, and reduce healthcare costs. The cost, time, and risk involved in developing new drugs and biologics have increased to unsustainable levels. If investors are unable to earn returns investing in the development of innovative new therapies, investor capital will be diverted to other industries and other countries, and many of the small venture capital-backed businesses that have made the U.S. the world leader in life sciences innovation and have created more than a million high-quality jobs in the process, will cease to exist.

While many factors have contributed to driving up the cost, time, and risk of drug development, the regulatory benefit-risk balance is the key. As the FDA has grown more cautious and risk-averse, and has emphasized the dangers of new therapies over their benefits, the innovation ecosystem has suffered. Fortunately, this is a fixable problem. As Congress debates the PDUFA reauthorization, and as policymakers focus on the need to modernize regulations, streamline government, and enhance innovation, a tremendous opportunity exists to reinvigorate and strengthen U.S. leadership in life sciences innovation. Thank you for the opportunity to share my thoughts and proposals with you today.

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

STATEMENT OF MARC BOUTIN

Mr. BOUTIN. Thank you, Mr. Chairman, Ranking Member Pallone, and distinguished members of the committee. My name is Mark Boutin, and I am the Executive Vice President and Chief Operating Officer at the National Health Council, which represents approximately 133 million people with chronic diseases and disabilities.

Our membership includes large patient advocacy organizations like the American Cancer Society, the American Heart Association, as well as smaller organizations like the Alpha One Foundation and the Children's Foundation. We provide a united voice for people with chronic diseases and disabilities.

Our membership also includes organizations such as the American Academy of Cardiology, nonprofits with interests in health, including family care giving organizations, and business and industry. Our governance is controlled by the patient advocacy organizations, and we represent patients, not consumers.

I make that point because often patients and consumers are confused. While we have a lot in common, we are at opposite ends of the same spectrum. We define patients as people with chronic diseases and disabilities. They are people who will use the health care system to manage their daily lives. They will use the health care system until they die.

Consumers use the health care system on an ad hoc basis, often for acute instances. An easy way to put your arms around it is imagine that you have mild hay fever. It acts up in spring. There are many options to address hay fever, over-the-counter prescriptions. But I can tell you if a new product comes to market and it has serious side effects, perhaps it causes severe headaches, rashes, diarrhea, vomiting, you are not going to be willing to take a risk on that new medicine.

But if you discover that you are having intestinal problems, you go to your doctor after putting it off for some time and you are diagnosed with pancreatic cancer and you are told you have 11 months to live, your willingness to take a product that might extend your life by 6 months will dramatically increase. You might be quite happy to take that same product that causes the rash, severe headaches, diarrhea, vomiting. It doesn't change your tolerance for risk for the hay fever medicine. Benefit-risk is an incredibly complex issue and one of the things I would like to address today.

As has already been referred to earlier, the patient advocacy community actually chained themselves to the fence at FDA and NIH nearly 20 years ago asking for significant change, and as a result of that, they went to the FDA and said, let's be allowed to have early access to treatments. And the FDA appropriately said, no, we are not going to allow you to have access to those treatments. We don't know what the risks of them are.

The patient community said, you know what? I am going to be dead in 2 years, I am willing to accept that risk. And the FDA responded and Congress responded with the first iteration of PDUFA.

As a result, we have seen dramatic improvements in terms of early access to new treatments and the development of new treatments, and we in the patient community have been very pleased with the success of these products.

Unfortunately, the patient communities, somewhat naively, thought we were done. We are relatively new to advocacy. We really only started about 25 years ago. We actually stepped back to a large extent from the FDA and the environment shifted, and what we have seen is significant change. We are back at the table now saying that we need to look at these issues in different ways.

What I would like to do is address two interrelated issues, the first being benefit-risk, the second being conflict of interest.

As I said, benefit-risk is a complex issue. The FDA is charged with looking at benefit-risk from a population-based model. But as we know, benefit-risk is very much an individual decision. It is very personalized to the individual person and their family caregivers.

Take for example Mark Stecker, who is somebody that about 7 years ago was walking in Manhattan and realized he had a limp. Shortly thereafter he was diagnosed with MS. He is now confined to a wheelchair, and he runs a blog, and he is very articulate about saying that he is very interested in assuming far greater risk than he is currently allowed.

I would say to you, many people in the disability and disease community feel the same way. While we had great success for HIV and AIDS, to some extent cancer and to a lesser extent heart disease, there are many conditions, from rare diseases to larger conditions like Alzheimer's, MS and other neurologic conditions without effective treatments, with many people willing to accept risk that they are often not allowed to.

As I said, this is complex, and risk determinations can vary from condition to condition. Somebody with Alzheimer's is probably more likely to take a risk than somebody with heart disease. It can change even within an individual. If you think about somebody with breast cancer that is in their late twenties and they have two children, their willingness to take a risk that might extend their life long enough to see their children grow up and get married, because it is very pronounced. But you could have another woman in her eighties with the same diagnosis who might choose a different product that is going to allow her to have better quality and perhaps less longevity.

At this point in time, it is important to recognize that there is no Federal regulatory body anywhere in the world that has identified benefit-risk or crafted a clear framework for benefit-risk. As part of the PDUFA negotiation, the stakeholder community was involved, and this was a huge priority for the patient community, and we were able to work with the FDA and industry to insert a benefit-risk analysis into the agreement. This will allow for a great deal of consistency, transparency and effective communication. It will allow for the benefits to be more clearly defined and it will allow for contacts and credibility.

I apologize for running over my time. Thank you.

[The prepared statement of Mr. Boutin follows:]

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Testimony before the
House Energy and Commerce Subcommittee on Health

PDUFA V: Medical Innovation, Jobs, and Patients
July 7, 2011

Marc Boutin, JD
Executive Vice President and Chief Operating Officer
National Health Council

SUMMARY

The Prescription Drug User Fee Act (PDUFA) has facilitated significant improvements in the drug development process. However, more must be done to encourage the development of new treatments and to ensure that patients with chronic diseases and disabilities have access to these drugs in a timely manner. To meet this need, Congress should

1. Develop as part of PDUFA V a framework for benefit-risk assessment of new drugs that incorporates input from stakeholders, including patients.

    - Historically, benefit-risk assessments have taken the perspective of the greater public good. However, individual patients make judgments based on their own preferences and circumstances.
    - The patient community asks for the development of a qualitative framework for benefit-risk assessment of new drugs that incorporates input from patients and that takes into consideration the size of the population affected, the range of existing treatment alternatives available to those patients, and the risks of living with that specific condition.

2. Reevaluate conflict of interest policies related to the selection of panelists for FDA advisory committees.

    - The conflict of interest regulations play an important role in ensuring transparency and credibility in the FDA approval process. However, they should not delay access to safe and effective medicines, especially if the product is designed to treat a significant unmet need.
    - Conflict of interest restrictions should be reevaluated to ensure the most qualified experts are not precluded from participating in advisory committees.

INTRODUCTION

Good morning Chairman Pitts, Ranking Member Pallone, and distinguished members of the Subcommittee. I am Marc Boutin, Executive Vice President and Chief Operating Officer of the National Health Council (NHC). Today, I speak on behalf of the more than 133 million people living with chronic diseases and disabilities. We appreciate this opportunity to present our views on the reauthorization of the Prescription Drug User Fee Act (PDUFA).

The National Health Council is an umbrella organization of patient advocacy organizations and provides a united voice for people with chronic conditions and their family caregivers. Our core membership includes 50 of the nation's leading patient advocacy organizations, ranging in size from large groups such as the American Cancer Society and the American Heart Association, to smaller organizations such as the Alpha-1 Foundation and the Sjögren's Syndrome Foundation. Other members include professional and membership associations, nonprofit organizations with an interest in health, and major pharmaceutical, medical device, health insurance, and biotechnology companies. Our governance is controlled by the patient advocacy organizations. We provide a place where all stakeholders meet for meaningful and reasoned dialogue.

The NHC represents patients and not consumers. I want to make that distinction because while patients and consumers are part of the same stakeholder group and share many common concerns, we are at opposite ends of the same spectrum. People with chronic diseases and disabilities use the health care system to manage their daily lives. They use the health care system on a continuing basis to stay alive. Consumers are people who use the health care system

largely on an ad hoc basis, so their perception or focus on health care issues and access to new treatments is often very different.

Since its enactment in 1992, PDUFA has facilitated significant improvements in the drug development process, accelerated the delivery of life-altering treatments to patients by reducing review times for new drug applications, and improved patient safety.

Despite this progress, more must be done to encourage the development of new treatments and to ensure that patients have access to these drugs in a timely manner. We need to place the discussion of PDUFA reauthorization into the context of meeting the needs of people with complex health issues; those that are most affected by the availability of new treatments. So, today, I would like to speak to you about two issues related to PDUFA V:

1) Developing a framework for benefit-risk assessment of new drugs that incorporates input from stakeholders, including patients, and
2) Reevaluating conflict of interest policies related to the selection of panelists for the Food and Drug Administration (FDA) advisory committees.

BENEFIT-RISK ASSESSMENT OF NEW DRUGS

The NHC strongly supports the work of the FDA to bring safe, effective, high-quality treatments to patients. To fulfill its mission to promote and protect public health, the FDA is responsible for weighing the potential risks of drugs against their benefits. Historically, these benefit-risk assessments are conducted from a population based perspective. But as you know, individual patients make judgments based on their own preferences and circumstances.

Marc Stecker of New York is such an example. Seven years ago, he noticed he was limping. Not long after that, he was diagnosed with multiple sclerosis. Today, he is confined to a

wheelchair. "Because my disease is so aggressive," Stecker said, "I have been very willing to be equally aggressive in trying to combat it."[1]

A patient with a life-threatening disease with limited treatment options is likely to have a much higher tolerance for "riskier" drugs than health care consumers who are not using medicines to manage their daily lives.

Even among patients with the same disease, risk tolerance may vary based on individual values. A mother in her 40s diagnosed with breast cancer may seek treatments that will help her stay alive to see her children grow up; however, a woman in her mid-80s with the same diagnosis may focus more on the quality of her days ahead, rather than longevity.

While the FDA is committed to serving the greater public good, the agency must also address the individual needs of the entire spectrum – from consumers to patients. Just as we know that different people respond differently to the same medications, so, too, we need to recognize that patients and consumers can have vastly different perceptions of benefits and risks.

In PDUFA V, the patient community asks for the development of a qualitative framework for benefit-risk assessment of new drugs that incorporates input from stakeholders, including both patients and consumers. The NHC recommends developing and implementing a plan to integrate a benefit-risk framework in the drug review process that places the drug's intended recipient into the equation. Such a framework would be conducted with robust input from all the relevant stakeholders such as patients and health care consumers. Such a framework would increase credibility and, perhaps more importantly, provide context to the review process.

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[1] Kroen G, Doctor challenges cause of MS and treatment, National Public Radio, 2011. Available at: www.npr.org/2011/01/31/133247319/doctor-challengescause-of-ms-and-treatment

When evaluating the risk of drugs, the FDA must take into consideration the size of the population affected, the range of existing treatment alternatives available to those patients, and the risks of living with that specific condition. To ensure this perspective is incorporated in decision making, the NHC believes it is imperative that patients are consulted. For patients with a rare or incurable condition, especially those with few or no treatment options, restricting access to a new drug is potentially devastating.

For example, patients with systemic lupus erythematosus (SLE) rely on corticosteroids to alleviate flares. Despite significant side effects, such as osteoporosis, hepatoxicity, glaucoma, artery damage, weight gain, and serious skin irritation, corticosteroids remain an essential component of the treatment regimen for a patient with lupus because their use can substantially reduce the symptoms associated with inflammation. That is, many patients with SLE accept risks of major negative side effects because the alleviation of symptoms and prevention of flare ups outweigh these other risks.

Far too often adverse events are framed from the point of view of someone without a disease or disability or someone who has never relied upon medication to improve or extend their life. Creating a better system to balance the benefits and risks of new drugs is a complex task. But, the engagement of people with chronic conditions and their representatives will be paramount to making it successful.

To relegate patients to a silent or hidden status in the assessment of new drugs limits the agency from receiving valuable input from those most affected. Their perspective and best judgment should be fully considered and valued. Benefit-risk assessments of a drug may look considerably different when taking in the perspective of a patient with a debilitating chronic

condition – a patient who is willing to take a risk on a medication for a chance at a more healthy and functional life.

CONFLICT OF INTEREST POLICIES

Equally important as acknowledging the differences in the benefit-risk analysis of drugs by the intended user, we must also ensure that the conflict of interest rules are not so strident as to delay the review and approval of new drugs for people with few or no treatment options.

The conflict of interest regulations play an important role in ensuring transparency and credibility in the FDA approval process. However, they should not delay access to safe and effective medicines, especially if the product is designed to treat a significant unmet need. The conflict of interest rules and their application must reflect this much needed balance.

FDA advisory committees provide expert advice that is critical to enabling the FDA to fulfill its mission. The NHC appreciates the need for conflict of interest screening to maintain public trust in the role of advisory committees in providing independent advice to the FDA. However, we are concerned that efforts to maintain the public's trust may now be superseding the need to secure necessary expertise to the detriment of the advisory committee process as a whole.

The NHC is particularly concerned that restrictions currently placed on the agency are creating challenges in convening advisory committees on highly specialized topics, such as rare disorders. On these topics, very few experts exist.

When we look at the unmet needs of targeted and smaller patient populations, there are fewer individuals with the relevant expertise and experience. The FDA is hard pressed at times to identify experts with the appropriate training and background to provide the agency with

informed advice, as experts in these specialized fields are likely to receive research grants for their studies, including grants from pharmaceutical and biotechnology companies, or serve as consultants to industry.

The FDA's conflict of interest policy appears to be in need of re-assessment when considering that nearly one quarter of the more than 600 seats on the FDA's 49 advisory committees remain vacant. According to data published by the FDA[2], the rate of vacancies on FDA advisory committees was 23 percent as of March 31. For example, at the Center for Drug Evaluation and Research (CDER), vacancies on committees were 24 percent in March. At the Center for Biologics Evaluation and Research (CBER), the vacancy rate was 38 percent. And at the Center for Devices and Radiological Health (CDRH), vacancies were 18 percent. These vacancy rates are alarming in light of the significant responsibility placed on advisory committees to inform FDA decision making. While we understand that there are numerous factors leading to these vacancy rates, it is clear that conflict of interest disqualifications strongly contribute to them.

We are deeply concerned that the challenges in identifying experts for advisory committees are leading to delays in patient access to new treatments. In fact, during a PDUFA V stakeholder meeting held on November 17, 2010, the FDA noted that there have been cases in which late recusals from an advisory committee due to a conflict of interest have led to a meeting cancellation and a delay in the FDA's approval of the application.[3] In a communication to individuals inquiring about the FDA's review of a new drug application, the FDA wrote

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[2] http://www.fda.gov/AboutFDA/Transparency/track/ucm216403.htm. Accessed on June 30, 2011.
[3] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM235777.pdf. Accessed on June 30, 2011.

"Although FDA strives to have broad representation of appropriate medical and scientific specialties on its advisory committees, optimal representation is often difficult to achieve given the strict conflict-of-interest regulations that apply ..."[4]

We fully support disclosure requirements so that conflicts of interest are transparent. However, conflict of interest rules should not be so strict as to preclude the most qualified experts from serving on advisory committees. Such preclusions can cause delays or cancellations of committee meetings. Patients are anxiously awaiting new treatments to manage, prevent, or delay their disease or disability. We urge you to consider how overly stringent conflict of interest rules may be doing more harm than good.

CONCLUSION

The reality is we are still not getting new treatments to market as quickly as the patient community would like or need. By working together with the FDA and all stakeholders we can do better in getting safe and effective treatments through the regulatory process if we take into consideration the perspective of the intended user – whether it be a person with a chronic condition or an average consumer.

We need a system that is flexible enough to meet the specific needs of the people who will ultimately use the medicine.

To conclude, on behalf of the National Health Council, the patient advocacy community, and the people living with chronic conditions that we represent, we recommend that Congress enact PDUFA V reauthorization legislation which includes the development of a framework for

[4] http://blogs.forbes.com/matthewherper/2010/10/22/fda-responds-to-outraged-arena-investors/

benefit-risk assessment that incorporates meaningful patient input. In addition, the National Health Council also calls on Congress and the FDA to reevaluate conflict of interest policies as they relate to the FDA advisory committees to ensure they do not impede the delivery of new, safe, and effective treatments to patients.

Thank you again for this opportunity to appear before this subcommittee. I look forward to your questions.

Mr. PITTS. The chair thanks the gentleman, and recognizes Dr. Sigal for 5 minutes.

STATEMENT OF ELLEN V. SIGAL

Ms. SIGAL. Good afternoon, Chairman Pitts, Ranking Member Pallone, and all members. It is a great honor for me to testify today.

My name is Ellen Sigal. I am chair of Friends of Cancer Research. Friends of Cancer Research is a Washington-based think tank. We publish. We are involved with the American Cancer Society, professional societies, patient groups, advocates. Our sole mission is really the integration of science for better treatment for patients.

This is very personal for me, as it is for all of you. Friends started 15 years ago when I lost my 40-year-old sister, leaving a 4-year-old child. Since then, my mother died of pancreatic cancer, my father died of prostate cancer, my husband has cancer, and there is no one that we all don't know that isn't impacted. So this mission is quite personal for me and for all of you.

My testimony today is intended to give a perspective on what can be done. First of all, the urgency of getting new life-saving treatments to patients in the safest and quickest possible way; the importance of maintaining our global competitiveness; and finally to realize the full potential of biomedical research and the role that all sectors play. None of these things can be accomplished without a fully resourced and scientifically vigorous FDA.

For many years we have been hearing about the slowness of FDA and particularly in oncology, so the agency has been portrayed by many critics as slow and inefficient compared to other countries. The criticism is particularly concerning in the field of cancer, where severely ill patients have few effective options. A new Friends of Cancer Research study published in Health Affairs revealed that FDA is approving anti-cancer drugs much faster than its overseas counterpart, the European Medicines Agency. What is important is the standard is high. It is the gold standard on both.

Of its findings, our study revealed that FDA not only approved more cancer drugs than Europe, but they did so at a significantly faster rate. FDA approved average drugs in 182 days, while EMA averaged 350 days. Access to new medications 5½ months sooner has undoubtedly improved the lives of 1.5 million Americans diagnosed with cancer every year.

While we praise this and we think this is very important, this cannot be accomplished nor sustained without appropriations needed to continue this effort. I have very specific recommendations that are in my testimony, and I would like to talk about a few of them.

First and foremost, FDA has to have the scientific tools, the regulatory science programs better to enable them to make these very complicated decisions. Whether it is adaptive trial design, validation of biomarkers, it is urgent that they have the resources to really have this. We believe very strongly and support the continuance of accelerated approval process. Ten of the 32 new oncology products in our study utilized this mechanism.

We also are recommending expedited development programs to address challenges to the current multi-phase sequential development process. This could be particularly important to ensure scientific rigor for targeted therapies. We want to ensure that FDA has the highest quality access to the best expertise possible in making informed decisions, and we believe patients have a very important role at that table and that role has to be accelerated.

A weakened, underfunded FDA will cause companies to take research overseas, creating a loss of jobs and billions of dollars in investment, it will threaten our standing as global leader, and, most importantly, it will delay getting potentially lifesaving treatment to patients battling disease and illness.

The role of the Food and Drug Administration as a component of medical innovation is critical, but successful innovation does not solely include the FDA. Our data indicates that the end stage review is on average half the duration of the FDA U.S. and EMA. While this indeed translates to American cancer patients gaining access to new drugs, it does not address the fundamental challenges to advancing health innovation that are currently facing our society.

In order to resolve the larger problem, all of the sectors represented at this hearing today and several of those that are not must at all times set aside the individual interests and work towards the common goal of improving the health of the country, both economic and personal, through innovation. As patients, we all have been and we all should demand it. The people will all work on behalf of the deserved. We are asking that everyone work together towards these goals.

Thank you.

[The prepared statement of Ms. Sigal follows:]

PDUFA V: Medical Innovation, Jobs, and Patients

Energy and Commerce Subcommittee on Health

July 7, 2011

Testimony of Ellen V. Sigal, PhD

Good morning, Chairman Pitts, Ranking Member Pallone, and Members of the committee. I am Dr. Ellen Sigal, Chair and Founder of Friends of Cancer Research, a cancer research think tank and advocacy organization based here in Washington. I would like to thank the staff of this committee who has worked tirelessly in putting together this hearing. It is an honor to testify before you today on the important role that the Food and Drug Administration (FDA) plays in getting life-saving treatments to patients.

I started Friends of Cancer Research over 15 years ago after having lost a sister to breast cancer, my father to prostate cancer, and mother to pancreatic cancer. This is as personal for me, as it is for you Mr. Chairman, and likely everyone in this room who have been deeply affected by illness.

My testimony is intended to give perspective on the urgency of getting new lifesaving treatments to patients in the safest and quickest way possible, the importance of maintaining our global competitiveness, and to realize the full potential of biomedical research. None of these things can be accomplished without a fully resourced and rigorous Food and Drug Administration that has the necessary scientific capacity to continue to evaluate new approaches to treating different diseases.

While compelling progress has been made within the field of oncology, there is much more to be done to alleviate the burden of cancer. It is estimated that, in 2011, nearly 1.6 million Americans will have been diagnosed with some form of cancer. As a result, our healthcare system will be strained an additional $228 billion.[1] Most importantly, this disease will claim the lives of 571,950 mothers, fathers, grandparents, sisters, brothers, and friends, this year.[2]

Advancements in basic science do not always translate to new medication as rapidly as many would desire. In fact, recent estimates indicate that it could take upwards of 12 years and over $1 billion to

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[1] The American Cancer Society: http://www.cancer.org/docroot/MIT/content/MIT_3_2X_Costs_of_Cancer.asp Accessed 6/30/11

[2] http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029819.pdf Accessed 6/30/11

develop a new drug.[3] While there are many factors that make development of new drugs complex and increasingly expensive, assessments of the process often focus on the Food and Drug Administration (FDA).

For many years the U.S. FDA has been portrayed by many critics as slow and inefficient compared to other countries. Anecdotally, some critics have indicated that the pathway to market approval for new medicines is more collaborative, consistent, and transparent in Europe compared to the U.S. This criticism is particularly concerning in the field of cancer, where severely ill patients have few effective treatment options. In order to explore such claims, Friends of Cancer Research conducted a study released in *Health Affairs* on June 16th that revealed the FDA is approving anti-cancer drugs in a more timely fashion than its overseas counterpart, the European Medicines Agency (EMA).

STUDY:

Our study shows that between 2003 and 2010 the FDA has approved 32 new cancer drugs versus only 26 by the EMA.[4] FDA not only approved more cancer drugs, but they did so at a significantly faster rate; FDA approval averaged 182 days while EMA averaged 350 days. Access to new medicines five and a half months sooner has undoubtedly improved the lives of many of the 1.5 million Americans diagnosed with cancer each year.

The intent of this study is not to conclude that one regulatory agency is approaching drug review in the best possible manner and the other is not. It is simply to provide information about current trends in oncology drug review. It should also be noted that the review period prior to approval is only one component of a multi-step process to develop new medicine. In order to truly accelerate the pace in which patients are able to utilize innovative medicines, the entire drug development process will need to be examined.

While the FDA should be praised for their contribution to ensure efficient access to new medicine, the responsibility to ensure that this continues extends beyond the agency. Unquestionably, FDA should maintain its high evidentiary standards and rapidly evolve to include new scientific advancements, however, strong public support and additional Congressional appropriations are necessary for the FDA to be able to continue this trend and strengthen its scientific foundation.

As Congress begins to examine priorities that would support the FDA through the reauthorization of Prescription Drug User Fee Act (PDUFA), we believe that three areas in particular would strengthen the agency's role as a vital component in medical innovation. These areas include advancement in regulatory science, innovative approaches to drug development and approval, and novel mechanisms for FDA to obtain external input.

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[3] Adams, C. P. and Brantner, V. V. Health Economics, 19 (2010), 130–141. doi: 10.1002/hec.1454

[4] Roberts, S., Allen, J., and Sigal, E. Health Affairs 30, No. 7 (2011) Published online: June 16, 2011

Advancement in Regulatory Science

With great advances in molecular research, the field of drug development is becoming increasingly complex. In order capitalize on the promise of new discoveries, the FDA, and its global counterparts, must keep pace with scientific advancement and be a catalyst to medical innovation for patients in need.

As recently as 2007 the FDA's own Science Board declared the agency's "mission at risk" due to its eroded scientific foundation.[5] In response to this stark assessment, the FDA's 'Regulatory Science Initiative' has outlined areas for additional research and the development of new tools to support regulatory decision making for the scientific challenges of the future. Advanced scientific methods to evaluate both safety and efficacy will ultimately help the new products reach the right patients in the timeliest manner. This is increasingly important as new medicines continue to employ advanced approaches - such as the ability for new drugs to be designed for a select population based on genetic characteristics – which may require novel designs of the clinical trials to demonstrate safety and efficacy.

Each year billions of dollars are invested in biomedical research, through the federal government, philanthropic foundations and private sector industry. This investment has and continues to create tens of thousands of jobs, and generate incredible new understanding of how to battle diseases like cancer.

However, that research, and the promise and hope it brings to patients, will not be able to be translated into medical solutions at a fast enough rate if the resources and science at the FDA cannot keep pace with discovery. **Congress should ensure that FDA is provided with additional resources, particularly those that can support regulatory science programs.**

A weakened and underfunded FDA will cause companies to take their research overseas, creating a loss in jobs and investment, and threaten our standing as the global leader of science and innovation. Most importantly, an under resourced agency will mean delays in getting potentially life-saving treatments to patients battling disease and illness.

Innovative Approaches to Drug Development and Approval

The Prescription Drug User Fee Act was originally enacted as a program to increase the efficiency of the FDA drug review process and ultimately provide patients access to new products sooner. It has been largely successful in accomplishing this goal. As a part of the original Act, the 'Accelerated Approval' pathway was established. Under this program new drugs and biologics that treat serious or life-

[5] Report of the FDA Subcommittee on Science and Technology: FDA Mission at Risk. November, 2007: http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf Accessed 6/30/11

threatening illness and provide meaningful benefit over existing therapies can be made available based upon demonstrated improvement of a surrogate endpoint.[6]

Accelerated approval is accompanied by the requirement for post-market studies in order to confirm the long-term benefit that was initially indicated by the surrogate marker. This program has proven extremely valuable for patients, particularly those facing a situation in which they may have had no treatment options for their disease. Our research indicates that of the 32 new oncology drugs approved by the FDA from 2003-2010, 10 were approved by accelerated approval.

The FDA must continue to utilize this process and Congress should encourage FDA to explore novel regulatory paradigms and provide clarity on how existing frameworks can be applied to advanced science. In oncology, and several other genetically-driven diseases, new products are being developed for use in particular subclasses of patients based on the presence of a molecular marker. These "targeted therapies" may be highly effective (and less toxic than treatments that are unable to differentiate between normal and abnormal cells) in the molecularly identified patient set, yet ineffective in patients without the marker. In situations that a marker is known and characterized prior to approval of a new drug, a modified approach to the overall development program could be explored and expedited. In general, new drug research is currently conducted in a manner where a phase 1 study is performed and analyzed, followed by a phase 2 study, and culminating with large randomized phase 3 studies. However, for therapies that show a large-magnitude of clinical benefit in their target population early in the development process, the traditional multi-phase, sequential development approach may not be appropriate, particularly if current treatment options for those patients have limited efficacy.

An 'Expedited Drug Development Program' could be employed to abbreviate or combine traditional phases of development, thereby shortening the pathway to approval and avoid giving larger numbers of patients a potentially harmful or ineffective drug. In addition, a robust capacity for on-going post-market research to better collect and understand emerging evidence about a new product will allow increased use of an expedited drug development program and ensure that new medicines can be made available to patients without compromising their safety. There are historic examples where the traditional Phase 1-3 stepwise development has been modified. For example, Gleevec™ (imatinib mesylate) was approved in 2001 based upon Phase 2 data due to its early demonstrated clinical benefit;[7] however such an expedited pathway is not fully defined as to when and how a similar approach that condenses different phases of development could be utilized. Establishment of an 'Expedited Drug Development Program' could help to provide guidelines applicable to the entire development process (not just the approval process) in order to facilitate the development of targeted therapies.

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[6] 21 CFR 314.500

[7] Cohen, MH, Williams, G, et al. Clin Cancer Res. Vol. 8 (2002) 935-942

Novel Mechanisms for Input

To fulfill its mission to protect the public health, FDA needs to interact with stakeholder groups including patient advocacy organizations, disease specialty societies and others to obtain the information necessary to address difficult scientific and policy questions. Currently, as established by the Federal Advisory Committee Act, FDA uses its standing advisory committees as the primary source of scientific advice.[8] While the advisory committee process has shown to be a valuable venue to aid scientific decision making, it should be just one way in which FDA can participate in discussions with scientific experts. FDA should have the ability to convene and actively interact with qualified subject-matter experts that are able to provide input on larger scientific and policy issues, rather than solely drug specific situations. Interactions could include participation in scientific conferences, task forces, and public meetings. This would provide FDA rapid access to multiple sources of high-quality, scientific expertise.

In addition to scientific input, appropriate channels should be created to facilitate input from patients with greater frequency. The decisions made by the FDA ultimately impact the people using medical products. Developing methods for interactions between medical reviewers and patients or care givers to discuss their direct experiences would improve the understanding of difficult to quantify metrics such as risk-tolerance, disease impact on quality of life, or symptomatic burden.

Congress should ensure that mechanisms are put into place to allow FDA rapid access to diverse scientific expertise and direct patient viewpoints. This type of input could increase transparency and greatly aid difficult decisions that may need to be made at all stages of the drug review process.

Conclusion

The role of the Food and Drug Administration as a component of medical innovation is critical. Our data indicate that the end-stage review is on average half the duration by the US FDA than the EMA. While this indeed translates to American cancer patients gaining access to new drugs sooner, it does not address the fundamental challenges to advancing health innovation that are currently facing our society. In order to begin to solve this larger problem, all of the sectors represented at this hearing today, and several of those that are not, must at times, set aside our individual interests and work toward the common goal of improving the health of the country, both economic and personal, through innovation. As patients, which we all have been or will be, we should demand it. The people we all work on behalf of deserve it.

I would conclude today by asking the members of this committee, and your colleagues on both sides of the aisle, to keep the best interest of patients in mind and support the agency that plays such a vital role in bringing new hope and potentially lifesaving treatments to them everyday.

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[8] 21 CFR Part 14, Subpart A

Mr. PITTS. The chair thanks the gentlelady, and now recognizes Mr. Coukell for 5 minutes for an opening statement.

STATEMENT OF ALLAN COUKELL

Mr. COUKELL. Mr. Chairman, Ranking Member Pallone, members of the subcommittee, thank you for the opportunity to present testimony.

My name is Allan Coukell. I am a pharmacist by training and Director of Medical Programs in the Pew Health Group, whose mission is to improve the health of all Americans through research and critical analysis.

Pew's work addresses a range of FDA-related issues, but my focus today is the safety and security of the pharmaceutical supply chain. Next week we will release a report entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs." Our research for that report included dozens of interviews with industry and regulatory experts and was informed by a recent public meeting that brought together pharmaceutical manufacturers, distributors, pharmacies, the FDA, State regulators and other analysts and stakeholders.

The meeting heard that while the vast majority of drugs in our pharmacies and medicine cabinets are not counterfeit or adulterated, drug manufacturing has changed dramatically in recent years. It has become globalized and increasingly outsourced, and this creates new risks, risks dramatically illustrated not long ago with the intentional adulteration of the blood thinning drug Heparin.

In 2007, health officials began to receive the first of what would ultimately be more than 500 reports of patients who experienced unusual adverse events, some of them fatal, after receiving this drug. The problem was traced to a contaminant, a substance introduced in place of the pure drug, and this occurred not in the premises of the U.S. manufacturer, but in China where the drug's raw ingredient was sourced from a complex network of suppliers.

The evidence suggests that the adulterant was introduced deliberately on a large scale and for economic gain. Whoever made it must have known that the substance wouldn't be detected by the standard tests. By one estimate, the crime netted more than $1 million in profit.

Later investigations pointed to other failures that underlined the need for systemic improvement. In particular, the manufacture did not audit its supplier over several years. The FDA approved the Chinese plant without an inspection, partly because agency databases confused two different facilities. Inspectors later found manufacturing quality issues, including poor control of incoming materials. And neither the FDA nor the manufacturer was ever able to gain complete access to that upstream supply chain.

The incident represents a clear breach of the U.S. drug supply, and to this date no one in any country has been held accountable nor has Congress acted to update the statutes that govern drug manufacturing.

What we heard at our meeting from a variety of experts was that without changes to the system, another such event is inevitable, not if, but when.

The number of drugs and ingredients made at non-U.S. sites doubled over the past decade. About 40 percent of our finished drugs and 80 percent of their active ingredients now come from overseas, often from developing countries. Current law requires FDA to inspect every 2 years here in the U.S., but is silent on the frequency of foreign inspections and the FDA lacks the resources to do regular foreign inspections.

When manufacturing shifts to low cost environments with reduced oversight, consumers are at risk, from the deliberate acts and also from failures to meet quality standards.

Our report reviews some other recent examples, including the problem of so-called show shadow factories, where drugs are coming from a hidden source instead of the official factory. We discussed cases in which manufacturers falsified or concealed records, and we note the risk of U.S. patients receiving counterfeit or stolen drugs that penetrate our domestic distribution system.

Let me give you one more example, a substance called DEG that has been linked to numerous mass poisonings around the world. Five years ago, this sweet-tasting liquid was mistakenly used to make cough syrup, killing dozens. The syrup had been labeled as something else. It had passed through a series of brokers in China and in Europe, each relabling it presumably without testing. Many of those who died were children. This occurred outside the U.S., but 70 years ago this same substance killed more than 100 Americans and led Congress to pass the Food, Drug and Cosmetic Act.

So recently there have been important steps by the FDA and by individual companies to tighten the supply chain. Nevertheless, we must update the act for the 21st century. Pew advocates a number of key reforms, including measures to ensure that manufacturers themselves better assess risk and ensure safety and steps to ensure they are held accountable; increased inspections overseas and new enforcement tools for the FDA, including the ability to order drug recalls; and improved oversight of drug distribution, including national standards for wholesalers and assistance to track and verify the authenticity of drugs.

I will conclude just briefly with a recent poll, a poll we commissioned last year among likely voters, that showed Americans are concerned about this issue, and across the political spectrum they overwhelmingly, upwards of 80 and 90 percent, favor many of the provisions I have outlined.

This committee has long taken a bipartisan interest in the safety of the drug supply. The American public supports those efforts, and we should not await another tragedy.

Thank you, and I welcome your questions.

[The prepared statement of Mr. Coukell follows:]

One Page Summary:
Testimony before the
House Committee on Energy on Commerce, Subcommittee on Health
United States House of Representatives
July 7, 2011

Allan Coukell, Director, Medical Programs, Pew Health Group, The Pew Charitable Trusts

A major focus of the Pew Health Group is identifying ways to address risks to the U.S. pharmaceutical supply chain. In March of this year, we hosted a two-day conference 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) and state regulators, and independent supply chain experts. The convening was structured around a discussion draft of a white paper entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," which was shared with conference participants in advance. The final report will be issued on July 12.

The presenters at our meeting explained that while the vast majority of drugs in our pharmacies and medicine cabinets are not counterfeit or adulterated, pharmaceutical manufacturing has changed dramatically in recent years, becoming increasingly globalized and outsourced. This creates new risks which were dramatically illustrated not long ago with the intentional adulteration of the common blood-thinning drug, heparin.

Despite globalization of manufacturing, FDA oversight is largely domestically focused. The Food, Drug and Cosmetic Act (FDCA) requires inspections of U.S. plants every two years, but specifies no inspection frequency for foreign plants. The FDA lacks the resources to inspect foreign sites with any meaningful regularity. The Government Accountability Office (GAO) has also found that FDA foreign inspections are shorter than inspections of U.S. plants and, unlike inspections at U.S. facilities, are pre-announced, because of cost and resource considerations.

Poor adherence to quality standards has been observed both in the U.S and abroad, but the shift of manufacturing to low-cost environments with reduced oversight creates an increased risk. According to one estimate, ignoring Good Manufacturing Practices (GMPs) can save up to 25% of a factory's operating costs. The expectation of inspections is an incentive for compliance with quality standards. Compliance failures may be the result of poor performance, or they may be deliberate.

Additional legislative changes are now needed to give the FDA the tools it needs and to ensure that every manufacturer is held to the highest standard. Pew prioritizes the following reforms:

1. Pharmaceutical companies must have comprehensive systems in place to assess risk and ensure the quality and safety of their manufacturing supply chains.
2. Overseas inspections by FDA must be significantly increased.
3. FDA authority and enforcement gaps must be addressed.
4. Improve the information flow to FDA.

Testimony before the

House Committee on Energy on Commerce, Subcommittee on Health

United States House of Representatives

July 7, 2011

Allan Coukell, Director, 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.

The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public and stimulate civic life. Based on research and critical analysis, the Pew Health Group seeks to improve the health and well-being of all Americans.

A major focus of the Pew Health Group is identifying ways to address risks to the U.S. pharmaceutical supply chain. In March of this year, we hosted a two-day conference 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) and state regulators, and independent supply chain experts. The convening was structured around a discussion draft of a white paper entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," which was shared with conference participants in advance. The final report will be issued on July 12.

The presenters at our meeting explained that pharmaceutical manufacturing has changed dramatically over the past decade. While the vast majority of drugs in our pharmacies and medicine cabinets are not counterfeit or adulterated, increasing globalization and reliance on outsourced manufacturing create new risks.

Heparin

The contamination of the blood thinner heparin dramatically illustrates the risks we face. In late 2007,

health authorities at the U.S. Centers for Disease Control and Prevention (CDC) and the FDA began receiving reports of unexpected allergic-type reactions in patients undergoing dialysis.[1] The events were subsequently linked to heparin, a widely used blood thinner.[2] Additional analysis led to the identification of an adulterant that standard tests were unable to detect.[3] The heparin active ingredient had been sourced from a Chinese factory, which in turn relied upon a network of small suppliers. The FDA and others believe that persons in China added the cheaper adulterant to crude heparin to cut costs.[4,5] The toxic material eventually reached at least 11 countries. Based on an estimated three tons of product, this substitution has been estimated to have yielded $1 million to $3 million in gains for the individual or company that sold it.[6] The FDA received reports of deaths and serious injuries associated with use of heparin.[7]

While failure to detect the contaminant during manufacture was a key factor, the case also illustrated other systemic problems, including:[8],[9],[10]

- An absence of timely supplier audits and FDA inspections,
- Limits and errors in the FDA database of manufacturing facilities,
- The discovery of manufacturing quality issues, including poor control of incoming raw materials, and
- The fact that – even in the period after the deaths – neither the manufacturer nor the FDA was able to gain complete access to the upstream supply chain.

This incident represents a clear breach of the security of the U.S. pharmaceutical supply. To this day, no one in any country has yet been held accountable. Nor has Congress acted to update the statutes that govern drug manufacturing. Numerous experts have asserted that, absent changes to the system, another such event is inevitable.

Globalization/outsourcing

Heparin is far from the only pharmaceutical that is produced outside the U.S. for American consumers. The number of U.S. drugs and ingredients made at non-U.S. sites has doubled since 2001.[11] An estimated 40% of all finished pharmaceuticals,[12] and 80% of the active ingredients and bulk chemicals in U.S. drugs, are now sourced by industry from foreign countries,[13] and up to half are purchased from plants in India and China.[14] The U.S. is the number one destination for Chinese pharmaceutical raw material exports.[15]

Despite globalization of manufacturing, FDA oversight is largely domestically focused. The Food, Drug and Cosmetic Act (FDCA) requires inspections of U.S. plants every two years, but specifies no inspection frequency for foreign plants.[16] The FDA lacks the resources to inspect foreign sites with any meaningful regularity.[17] The Government Accountability Office (GAO) has also found that FDA foreign inspections

are shorter than inspections of U.S. plants and, unlike inspections at U.S. facilities, are pre-announced, because of cost and resource considerations.[18]

Quality/compliance

In the case of heparin, it appears that criminals deliberately sold unsafe product into the supply chain. At other times, consumers may be at risk because of failures by manufacturers to comply with quality standards. Poor adherence to quality standards has been observed both in the U.S and abroad, but the shift of manufacturing to low-cost environments with reduced oversight creates an increased risk. According to one estimate, ignoring Good Manufacturing Practices (GMPs) can save up to 25% of a factory's operating costs.[19] The expectation of inspections is an incentive for compliance with quality standards.

Compliance failures may be the result of poor performance, or they may be deliberate. One Chinese company was found to have exported heparin to the U.S. that they claimed to have made at their own factory, but was in fact made entirely at two external plants.[20] The FDA has said that some of this heparin may have contained the same contaminant associated with the deaths in 2007 and 2008.[21] Falsification of manufacturing location poses risks to patients, because regulators cannot ensure a product's quality without knowing the conditions of its manufacture.

In 2008, an Indian manufacturer was cited by the FDA for alleged falsification of stability testing records and use of active ingredients made at unapproved sites, according to a Department of Justice subpoena motion. [22],[23] In 2010, another Indian manufacturer was found to have falsified batch manufacturing records for an anti-platelet medicine. E.U. inspectors discovered at least 70 batch-manufacturing records in the plant's waste yard. All of the records had been re-written, and in some cases original entries had been changed.[24]

In Panama in 2006, dozens of people died after taking a cough medicine that had been made with diethylene glycol,[25,26] a sweet-tasting, but poisonous solvent.[27] It had been wrongly labeled in China and passed through a series of Chinese and European brokers, who repeatedly re-labeled it, presumably without performing independent tests. The same problem has occurred with products in Africa, Haiti and India, and has been identified in consumer products in this country as recently as 2007.[28] Students of FDA history will know that diethylene glycol poisoning in the United States in 1937 was the disaster that lead directly to the enactment of the FDCA.[29] It is now time to update that statute for 21st century manufacturing.

Gaps and Solutions

At the Pew convening in March, we heard clearly that real risks exist, and that the system can – and must –

be improved. We heard that serious limitations to FDA's oversight of foreign plants making drugs and ingredients for the U.S. must be remedied. Representatives from several drug manufacturing groups agreed to back new industry fees to cover additional foreign inspections.

Experts also called for industry audits of every supplier and sub-supplier. Some companies already have best practices in place, but it is important that every company have systems in place to ensure the safety and quality of its upstream supply chain.

Some steps can be taken now. The FDA has opened offices in India, China, and other countries, and pursuing changes to standards to improve supply chain oversight. The agency is also implementing a new risk-based screening system for imports to speed the clearance of low-risk shipments and increase the predictive efficacy for identifying and targeting high-risk imports. In addition, FDA has entered into 22 confidentiality agreements with regulatory bodies in different countries and shares inspectional information with the European Union and Australia.[30] Finally, just last month, the FDA released an important strategy paper outlining its intent to form a global consortium of regulators and to increase the agency's reliance on third-party sources of information.

Many individual companies have also taken steps. Nevertheless, additional legislative changes are now needed to give the FDA the tools it needs and to ensure that every manufacturer is held to the highest standard. Pew prioritizes the following reforms:

1. Pharmaceutical companies must have comprehensive systems in place to assess risk and ensure the quality and safety of their manufacturing supply chains. Companies must audit suppliers on-site prior to engagement and institute supplier quality agreements.[31] Company management must be held accountable for implementing these systems.
2. Overseas inspections by FDA must be significantly increased. Inspections do not guarantee quality, but the reasonable expectation of inspections is an incentive for compliance with quality standards. We can and should ensure that inspection frequencies domestically and internationally are meaningful. The FDA has recently expressed its intention to increase its reliance on third-party sources of information, particularly inspections by other regulators, to supplement FDA's own ability to conduct inspections. This is a necessary step to preserve the integrity of the U.S. drug supply, but the agency also needs additional resources to conduct overseas inspections.
3. FDA authority and enforcement gaps must be addressed: FDA authorities and enforcement tools are often inadequate to properly regulate the pharmaceutical industry, particularly overseas. FDA does not currently have the authority to mandate a drug recall, nor may it halt product distribution (it can do both for medical devices) and must instead go through the courts to request a seizure.[32] In

addition to mandatory recall authority for drugs, the FDA needs the authority to subpoena documents and witnesses, and an improved set of enforcement tools such as civil penalties for violations of the FDCA.

4 Improve the information flow to FDA: Drug companies are not currently required to inform FDA of many types of quality or safety issues that could present risks to U.S. patients, such as suspected counterfeiting or theft. Industry whistleblowers wishing to bring information to FDA are not currently covered by specific whistleblower protections. FDA is also limited in its ability to share information protected under the trade secrets provision of the Freedom of Information Act (FOIA) with other government agencies, which can hamper international investigations, and should be given clear authority to do so.

Protect American Consumers

The public expects that FDA will ensure that the drugs they take every day are safe from contamination and, at the same time, there is increasing concern about the safety of imported drugs. A poll commissioned by The Pew Charitable Trusts found that Americans are concerned about the safety of drugs from developing countries.[33] And Americans across the political spectrum overwhelmingly support giving FDA increased authority in order to protect the domestic drug supply. For example, 86% of respondents supported inspecting foreign facilities every two years; 94% supported mandatory recall authority for the FDA. We can avoid future tragedies by adopting policies that are supported by drug manufacturers, health professionals, and the vast number of Americans who take medicines such as prescription and over the counter drugs at their peril. Congress should act now.

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Mr. PITTS. The chair thanks the gentleman and thanks the panel for the testimony. We will now begin questioning, and I will recognize myself for 5 minutes for that purpose.

First of all, Mr. Hastings, I have had the opportunity to talk to many small and mid-sized American biotech companies, and they are struggling right now partly because of increasing review times at FDA and the lack of predictability at FDA.

Have you experienced these problems or do you know a company who has, and what issues are biotech companies facing today related to FDA?

Mr. HASTINGS. We work very—is this on? No. There we go. Sorry about that.

Whenever there are regulatory uncertainties, there are delays. A big piece of data that is missing today is not the speed of approval once an NDA is filed, but the speed to which we can enter a drug into the clinic, file an IND, get it through Phase I, get it into Phase II. Many of us who are lucky enough to get it into Phase III would be happy with approval times that are faster and more expedient than other countries. That would be great. But there is a whole process that occurs before the drug even is filed for an NDA, and I think it is important for us to work with the FDA, as we have.

As I mentioned, the biotech industry's focus here is on streamlining the whole process, not just the approval process once the NDA is filed.

Mr. PITTS. Mr. Leff, would you like to comment on that?

Mr. LEFF. Sure. Thank you, Mr. Chairman, I would be happy to.

I think the central issue, the central impact that FDA is having on investors in medical innovation is, as I said in my statement, the increase in the time, the cost, and the risk of development. So it is not review times per se, although obviously we all want fast and efficient review times. It is the requirements that FDA is increasingly imposing for developers of drugs to move their drugs through clinical trials and get them in front of FDA.

So when Dr. Woodcock made the observation that FDA is having a problem approving more drugs because they are not seeing more drugs, they are seeing fewer drugs submitted than in the past, I think that is absolutely right. The reason FDA is seeing fewer drugs submitted than in the past is because people like me and hundreds of other people like me making investment decisions on drugs that are in development or discoveries that are being turned into drugs are increasingly deciding that the cost, time and risk have become too high, and that is a function of the risk averse decisionmaking that has increased at FDA over the past decade.

Mr. PITTS. Mr. Hastings, how many jobs does the bioscience sector account for, both direct and indirect?

Mr. HASTINGS. I think I mentioned 7 million jobs indirectly and directly.

Mr. PITTS. Seven million total. What else can we do in the FDA space to help create jobs? How would fixing the issues at FDA help these companies create jobs?

Mr. HASTINGS. Mr. Chairman, I believe that the way to create jobs is to foster innovation, not at the expense of safety or efficacy. One of the proposals which is to make innovation a part of the mission statement, which, by the way, the European Union has in

their mission statement, and then hold people accountable for innovation.

You know, innovation could be when somebody is going through the process of—I will give a very practical example. I am running a startup company and I file an IND and I get my drug into Phase I. In the middle of my Phase I trial, there is an issue. Any kind of issue could come up in Phase I. The way the system is set up is I can pick up my phone or my regulatory person can pick up the phone and call the FDA. And the FDA are bound by these guidelines, by the way. The phone call takes place. It needs to be followed up by a letter, which comes usually 30 days later. Then you have 30 days to respond to that letter. Then they have 30 days to respond to that letter.

Now, in that whole process, which in my mind could be handled in a phone call, I spent as a startup biotech CEO $4 million a month on the burn of the company while the letter writing campaign was going back and forth.

This is not the FDA's fault. These guidelines are guidelines that have been put in place, and I think they should be looked at as, you know, how can we streamline communication. Again, not once the NDA is filed, but how do we help companies innovate by making the process smoother in areas which are not going to create more risk? I think this would be a major.

So if that occurs, I don't have to go to my venture capitalist and say I am writing a letter now and $4 million of burn is looking at us right down the face. He hears that $4 million and says if I could invest that $4 million in Facebook, I could get a return in a month. You are going to burn that. I am going to need to give you—now, for me I need $1 billion to develop a drug, right? So that $4 million, which is huge in the early stages of a drug company's evolution, is just a tiny portion of what it is going to take.

So each dollar is very, very important. So for innovation and streamlining, making processes and helping the FDA, by the way, make processes that are less bureaucratic, providing them with the staff they need to actually answer the phone calls, which is something we have been working on together, would be very helpful.

Mr. PITTS. The chair thanks the gentleman.

My time has expired, and the chair recognizes the ranking member, Mr. Pallone, for 5 minutes.

Mr. PALLONE. Thank you, Mr. Chairman. I am going to start with Mr. Hastings also.

BIO recently released policy recommendations contained in the document "Unleashing the Promise of Biotechnology: Advancing American Innovation to Cure Disease and Save Lives." I appreciate the need for the kinds of proposals listed under the heading of Advancing Regulatory Science and Innovation. But I wanted to focus on one as an example, the need to enhance FDA's access to external scientific and medical expertise.

The FDA has repeatedly cited the need to make improvements in the area of regulatory science, and as the BIO policy document mentions, FDA has struggled to keep up with the rapid pace of scientific and medical knowledge techniques and technology. And you know FDA launched a major regulatory science initiative designed to build on the achievements of programs like the critical path ini-

tiative. The other proposals in that section also seem to make a lot of sense to me.

But my problem is that each of these concepts that you mentioned or that, I should say, the document mentions would demand a significant infusion of resources if there is any hope for the FDA to implement them. That is my opinion.

I just wanted to ask you if you agree with that, that we need more resources to do these kind of things?

Mr. HASTINGS. I think respectfully——

Mr. PALLONE. I think you lost the mike. The reason I am asking you this is—go ahead. I am sorry.

Mr. HASTINGS. Somebody up there where you folks are a few minutes ago had an overreaction to an issue with a union, right? So I think if we can all work together to look at ways to prioritize.

First of all, there is no question that our industry supports the FDA being adequately staffed. We actually had an initiative a few years ago to help them get staffed. So we would be all for helping them get staffed. But we also understand there are budget crises under way right now.

So I would submit, running a business, and having run many businesses, private and public businesses, that there are always ways to reallocate resources to do things.

External advisory boards are external people. You pay them when they walk through the door. When they leave, you stop paying them. That is a much more efficient use of capital than head count. So if there are opportunities to use external advisers to help keep regulatory science moving. In the case of FDA, by the way, they have very few regulatory science employees. They would like to have more. Again, we are working on this initiative. So there are many ways to do this.

Mr. PALLONE. The only problem that I have though, now we have this FDA funding bill that the House Republicans just passed, and that guts the FDA's funding by $570 million. It is a cut of 21 percent from the administration's request. So obviously I think there should be more resources. But if this goes through, we will have 21 percent less than what the administration is requesting.

How are we going to implement these types of things that are in this BIO document if we make cuts? It is one thing to add. But what about now if they cut 21 percent?

Mr. HASTINGS. Again, I would argue that one could look at reallocation, and one could also look at the risk-benefit of where one invests one's money.

Mr. PALLONE. All right. I know that you are part of this—or I should say your organization is part of this alliance for a stronger FDA whose mission is to get increased resources for FDA. So, again, I think you can always find more efficiencies, but I think it is going to be very difficult to do any of these new innovations if we see a 21 percent cut, and I think that is why the Alliance for a Stronger FDA is trying to increase resources.

Mr. HASTINGS. May I respond to that? No offense, but, you know, in our organization, when I hear an answer like that, I say to the organization, figure it out.

Mr. PALLONE. It is one thing to be able to do what they are doing now. But to go into totally new areas with cuts in funding, I don't

see how. But whatever—let me go to Dr. Sigal, because I only have 40 seconds left here.

I found the results of your study very interesting, the one comparing cancer approvals in the U.S. versus Europe, and I was surprised, given the claims about FDA's role in the innovation downturn, to see a document like that.

What prompted you to do that study and what did you expect to find? Were you surprised by what you found?

Ms. SIGAL. I was very surprised. What prompted me was that we were hearing consistently from academic institutions, from developers, from biotech, from patients that the FDA is slower and things were getting approved faster in Europe, and we know the standards were very high in Europe. So we were very concerned and we did the initial research in house, we did it solely in house. And we were very shocked. As a matter of fact, we were so surprised that we had to validate it.

I did not expect it. And I want you to know if in fact what we were told as urban legend were true and in fact we were slower, we would have published. So this was not a matter of getting data that we suspected was going to—we thought we were going to get data that showed that Europe was more innovative and faster, so we were very surprised at it and clearly it was very important. But there is still a lot more that needs to be done, because the science is complex and the agency is significantly underfunded for the innovation that they need to go forward.

Mr. PALLONE. Thank you, Doctor.

Thank you, Mr. Chairman.

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

Mr. BURGESS. I thank the chairman.

Just as a follow-up to Ranking Member Pallone's observations, last year twice Dr. Sharfstein came before this subcommittee, once with the DeCoster egg farm hearing and once with a hearing about are there problems with the pipeline and restrictions in the pipeline of getting drugs and products from NIH to the consuming public and is the FDA part of that obstruction. And both times Dr. Sharfstein testified in response to a direct question by me, do you need more money, and he assured me that the FDA had all the money that it needed.

I knew that that must be right, because for those of you who sit up nights reading the Federal Register, you may know that we passed, Congress passed, I voted against it, but there was a big health care law about a year and a half ago, and it included no new money for the Food and Drug Administration in that big new health care law.

Mr. Hastings and Mr. Leff, let me just ask you a question. If an innovator comes to the FDA and they have got something, a drug or device, characterize it as a black box, if you will, it does something good for patients, if that innovator comes to the FDA and asks for the pathway, what are my steps to go through getting this drug or device approved? Are they going to get clear direction and clear instruction from the FDA as to what procedures to follow?

Mr. HASTINGS. We will get guidance, some guidance or recommendations on what to do in a situation like that.

Mr. BURGESS. If it is truly innovative, maybe something that hasn't happened before, are they likely to get an answer, "we are not sure and you need to start and then we will provide you guidance as go along."

Mr. HASTINGS. Well, it is very difficult in the case of a brand new innovation when there are no benchmarks to sometimes give guidance, because everybody is looking at the same thing and wondering what to do. I think that would therefore argue for the ability to communicate scientist-to-scientist and work together. This is also where some of these external advisers could come in and be very helpful experts in the field in terms of creating not a validated instrument that may take years to do this, but to create a risk-reward model to move that drug forward since it is the first in its class. That would be the ideal thing to do.

Mr. BURGESS. Forgive me for interrupting, but time is very limited. On this risk-reward model that you just articulated, does that exist within the FDA? If an innovator comes to the FDA and says I have got this, help me know the stems I must take to develop this and have it approved by the FDA, is that model in fact in place? Does it work?

Mr. HASTINGS. I mean, I can't speak for the FDA. I think that model would probably work differently division by division, depending on who the reviewer is, depending on who runs the division.

Mr. BURGESS. That is the regulatory uncertainty. Again, I have people come to my office all the time with these complaints that I don't get clear direction about what I am going to need to provide and then it all changes in the course of development, and that obviously extends the timeline significantly.

Mr. HASTINGS. Well, you made a very good point about changing it. And, again, I don't think this is anybody's particular fault, but I know of CEOs who are running diabetes companies where endpoints were changed in the middle of their Phase III clinical trials as they were ongoing and had to redo their Phase III clinical trial. Some of those companies shut down.

Mr. BURGESS. Sure. I wish we had more time to explore that, but Mr. Coukell, I need to ask you, you talked about the Heparin issue which we have studied in this committee, and I just wanted to reassure you that we do have an active and open investigation now.

Last Congress it was a little bit difficult to get information from the FDA. Margaret Hamburg went to China and presumably talked to some of these individuals who were involved with the companies that produced the product that was contaminated with the adulterant. And you are correct, the adulterant was a very clever molecule that could hide behind the normal active pharmaceutical ingredient in Heparin on the normal testing with the mass spec. It almost had to be a criminal mind that decided to do this. I don't think it was accidental.

But we have had significant difficulty in getting the data from the FDA as to where they are in this investigation, why the labs were confused and issues that you mentioned. I wanted to reassure you that the legislative remedy really is hard to come up with if you don't have the results of your investigation. Unfortunately, this investigation has taken a lot longer than I would have ever thought

possible, but at the same time you run the risk of legislating with incomplete information.

Mr. COUKELL. Yes, sir. I commend your ongoing interest in drug safety. I think it is very important. I think it would be highly desirable to find the culprit in that case.

Nevertheless, I think Heparin illustrates, as I outlined in my testimony, a lot of weaknesses that we know about now, and it was a wake-up call for a lot of folks in the industry and for the FDA. They have all said that. The next time it happens, it probably won't be Heparin. It will be somewhere else. I think we do know based on that case and others some of the things that we need to do now.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member emeritus, Mr. Dingell, for 5 minutes for questioning.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy and for the recognition. I will direct my questioning to Mr. Coukell. I would observe that I have great concern for the tremendous amount of pharmaceutical medicines and ingredients that are coming in from abroad. So I would like to address this with yes or no answers here.

An increasing number of drug manufacturers are turning to outsourcing for pharmaceutical ingredients and manufacturers. As you mentioned in your testimony, up to 80 percent of pharmaceutical ingredients and up to half of the finished pharmaceuticals are purchased from clients in India and China. FDA is currently required to inspect U.S. drug facilities every 2 years, but there is no required frequency for inspection of foreign facilities. Food and Drug says that they investigate foreign facilities about once every 9 years.

Is that sufficient or not?

Mr. COUKELL. It is not sufficient.

Mr. DINGELL. Now, until 2009 FDA did not have a dedicated staff for foreign inspections. Rather, employees qualified to do inspections would travel abroad. FDA now has a cadre of 15 inspectors dedicated to foreign facility inspections.

Has this current cadre been sufficient to increase inspection of foreign facilities to a sufficient level that we can be comfortable that our supply of these pharmaceuticals is safe?

Mr. COUKELL. They improved the local FDA's local knowledge and have done some additional inspections, but they are not enough.

Mr. DINGELL. Thank you. Now, beyond inspections, quality manufacturing is also critical to a safe drug supply. In 2009, FDA issued 34 warning letters regarding adherence to good manufacturing practices, nearly double what was issued in 2008, ensuring manufacturing quality gets more difficult as supply chains move overseas and are more outsourced.

Are today's GMPs sufficient to ensure manufacturing quality, yes or no?

Mr. COUKELL. No, sir.

Mr. DINGELL. As you have spoken to a number of stakeholders and experts about FDA's oversight of foreign drug manufacturing, what if any consensus exists for increasing foreign oversight and resources to support?

Mr. COUKELL. I can't answer that with one word, sir, but what I can tell you is we have been interested as we talked to stakeholders across the system, I have expected to have people say inspections aren't the answer. We didn't hear that. Inspections are part of an overall quality system. Some major sectors of the industry, including the generic manufacturers and the active ingredient makers, are on record as supporting fees to help fund additional inspections overseas, both for safety and to provide a level playing field for American manufacturers.

Mr. DINGELL. Thank you. One approach to ensuring manufacturing quality would be to require manufacturers to implement quality systems that detail management responsibilities, risk management practices, supply chain management, record keeping amongst other components.

Do you believe requiring manufacturers to have in place a quality system would improve the safety of our drug supply chain? Yes or no.

Mr. COUKELL. Yes, sir. Those are recommendations now, but we need everyone to do it.

Mr. DINGELL. Should such a requirement relate not only to finished manufactured pharmaceuticals, but also to components and raw materials?

Mr. COUKELL. Yes.

Mr. DINGELL. Transparency throughout the supply chain is of particular concern and a valid one given the Heparin incident, but Heparin is only one of the examples of our problems. Currently, FDA recommends but does not require that companies conduct an on-site audit of a supplier.

Do you believe requiring companies to perform on-site audits of suppliers before a purchase agreement is made would improve supply chain safety? Yes or no.

Mr. COUKELL. Our meeting heard that every supplier and subsupplier should be audited by somebody.

Mr. DINGELL. Now, how frequent should these audits be to assure their effectiveness?

Mr. COUKELL. I think that depends on the material and the level of risk.

Mr. DINGELL. Could you give us some kind of a horseback guess?

Mr. COUKELL. I think it is going to depend, sir. If is a long-established relationship and a simple synthesis, it would be quite different from a new relationship with somebody who is making a very complex molecule.

Mr. DINGELL. Now, FDA recommends but does not require quality agreements with suppliers. Do you believe requiring quality agreements with suppliers would improve supply chain safety? Yes or no.

Mr. COUKELL. Yes, sir, and I believe leading companies are already doing that.

Mr. DINGELL. Mr. Chairman, I apologize. I have a couple more. May I pursue my business to its end?

Mr. PITTS. You may proceed.

Mr. DINGELL. Thank you. You are most courteous.

More must also than done to ensure transparency and access to information for products being imported into the United States.

Do you believe requiring importers and customs brokers to register with the FDA would help to improve FDA's general oversight of global drug production as well as drug safety assessments at the border? Yes or no.

Mr. COUKELL. Yes.

Mr. DINGELL. It is clear then that increasing foreign inspections and improving transparency and quality throughout the supply chain are necessary components to increasing the safety of our drug supply, and that would also include raw materials and components as well as finished products. I would also add, Mr. Chairman, that H.R. 1483 would address the vulnerabilities that we have just outlined.

I thank you for your courtesy, and I thank our panel for their assistance to the committee.

Mr. PITTS. The chair thanks the gentleman.

Without objection, the chair recognizes Mr. Bilbray from California for 5 minutes for questions.

Mr. BILBRAY. Thank you very much, Mr. Chairman. Thank you for a chance to ask questions. I want to thank the ranking member for being here, because I think that this is an issue that we can have a bipartisan effort on. From personal experience in working with the ranking member for probably a decade, about a decade-and-a-half I think it has been, we have had a bipartisan effort going on water quality issues. I think this is one of those things that the ranking member can join with the majority in actually addressing an issue that knows no party affiliation.

Mr. Hastings, one of the crises that I am seeing in my district with my bio-med research people is the fact that we have lost 50 percent of the venture capital for what we used to say in environmental issues would be the economic soup, the startup companies, the little guy who is the krill of the bio-system; in other words, where the ideas and the innovation comes from that the big guys eat up, adopt and then develop into it. We have lost 50 percent of that capital. It looks like we could lose 50 percent of that overseas if we don't do something.

One of the items that has been brought up to me is how do we infuse and get venture capital back into the field, and one of the items is the issue that we have over $2 trillion of American capital overseas. Do you think that it would help in trying to backfill that loss of 50 percent if the Federal Government looks at changing the repatriation laws here to hold harmless if they bring the money back for research and development?

Mr. HASTINGS. Resoundingly absolutely.

Mr. BILBRAY. Anybody else got a comment on that or concern with that?

Mr. LEFF. Yes, I agree it would absolutely help and it would bring capital back into this country and release additional investment and innovation. The observation I would make, though, is that would be a one-time benefit to the system. It wouldn't change the trajectory necessarily that we are on and the fundamental underlying reasons that capital is leaving investment and innovative life sciences companies.

Mr. BILBRAY. I appreciate that. I was a public safety guy. I am just a lifeguard that triaged people and got more votes than the

next guy. But we do have a patient that is hemorrhaging, needs an infusion, an infusion to survive, and I think this is one thing we may be able to ask both sides to work on.

Let me ask, Doctor, speaking of looking at systems, back in the nineties there was a bipartisan effort made that did things on the AIDS epidemic that we had not done for anybody else, extraordinary efforts. We broke the rules, changed the rules, forced the bureaucracy to respond, and I think history has proven that was a great success.

Sadly, it looks like we did this great success and walked away from it. In those days we had Act Up, we had Men's Gay Health Crisis Project, we had the Treatment Action Group putting pressure on us to change the system, and we actually allowed patients to be at the table. We allowed, and the doctor can go over it, whole different protocols for what was allowed to be counted as a positive action, and we basically broke the mold and tried innovative issues.

Is there any reason in the world why we should not go back and look at what was successful in addressing the AIDS crisis and apply it to the crisis we are finding right now? A good example is why would we allow an AIDS patient on a review body for AIDS, but would not allow a cancer patient to have the same right to be able to participate?

Doctor, I solicit your comment about how we can address that.

Ms. SIGAL. Thank you for the opportunity. I think the HIV model is a wonderful model. It started activism, and, most importantly, it has had an impact. It helped patients, it helped science, and it made a huge difference.

It is a complex scenario though, because there we had a fire marker. We had the CD 4. We had viral load. We knew what we were looking for. But it did start advocacy, and I would agree with you fully that patients have not only a role but a right to sit at the table. Ultimately these decisions impact them. They need knowledge, they need the ability to have the information, and they have the ability and should have the ability to be at the table when these decisions are made.

We, along with the National Health Council and others, are working on that and believe that we have opportunities in the reauthorization of the User Fee Act to have a more active patient voice. It is essential that they be at the table, because we do impact them.

Mr. BILBRAY. The one thing I saw work in the AIDS community was the degree of urgency was brought on to the bureaucracy, the sensitivity that they know had an impact, an adverse impact just by denying, that at least there was opportunity there.

What I am concerned about is the study that you did showed that if you take the long-range, there was an item. But my question is, recently though it looks like the European Community's review and our review are starting to close that gap since 2008. Do you have any way of explaining why though the trajectory looked real good on cancer drugs over the long term, recently it looks like we are converging or going to be crossing? In that study, did you identify why since 2008 it looks like the numbers are changing?

Ms. SIGAL. Actually we did go past, we did look at that. And in fact, since we have concluded our study, we have had three more

approvals which they still do not have in EMA. So in fact the trend of earlier approval, faster approval, is continuing.

The problem is the complexity of the science. The science is very, very, very hard. But this is not an issue of speed, this is an issue of quality, and I can tell you as an advocate myself we in the cancer community and other advocates of deadly diseases, childhood cancers, other cancers, are just as anxious as anyone to have these new drugs approved, because it will——

Mr. BILBRAY. Let me tell you as a father, I am in that category.

Mr. Chairman, I appreciate the time. I think one of the things both sides need to talk about is the conflict of interest regulations that historically have been with FDA and these review bodies, because now you are getting, especially in cancer, you are getting items coming forward that the discipline is so limited of anybody who can make an informed decision that you have to bring somebody in from outside and somebody who has a connection to basically development and certain research to be able to get the expertise to make an informed decision. I don't think any of these conflict of interest requirements that we put in in the past was meant to exclude people that were essential to making informed decisions. I hope both sides can look at modifying those rules.

Mr. PITTS. The chair thanks the gentleman. That concludes the first round of questioning. We will go to one follow-up on each side, if we have any. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. I appreciate the recognition.

Mr. Boutin, if I could along that line of the advisory panels and the conflict of interest exclusions, are the restrictions on who can serve on advisory panels hindering activities to bring new drugs to market?

Mr. BOUTIN. Yes. I think there is a real challenge. Right now, the FDA is charged with looking at multiple regulatory and legal requirements for conflict of interest, and the standards within each are not necessarily inconsistent, they are different. As a result, the FDA has had to look at how do we apply them all together.

In the previous reauthorization of the prescription drug user fee, there was an additional requirement that compelled FDA to limit its use of waivers, and as a result they took a look at how they would apply the conflict of interest rules. In their new look, they acknowledge that they are being more strident in addressing the conflicts, and as a result what you are seeing is it harder to fill the advisory committees, and currently about 25 percent of the advisory committees are vacant, and as a result there is delays in having the advisory committees meet and the FDA has acknowledged that it has led to delays in the approval of new treatments.

So from our perspective, we need to look at this carefully. Conflict of interest rules are important and we recognize they provide credibility and transparency to the process, and nobody is suggesting they should just be done away with. However, we have to balance the need for transparency and managing of conflict of interest with the need to ensure that we get treatments to people who need them.

Mr. BURGESS. That was a subject of a lot of discussion when we marked up this bill in 2007 and recognizing that for some products.

Pediatric antineoplastic plasma medications, the universe of people that understands these is probably very small, and it is probably very difficult to find someone who has not worked in some way on the development of that product at some point along the line. This was really where we painted ourselves into a corner.

Mr. Chairman, I hope we will be serious about fixing this. And your thoughts on things that we might do to relax or keep the appropriate focus where it needs to be but at the same time allow these advisory panels the ability to form and do their work, I think that is going to be critically important when we reauthorize.

Thank you.

Mr. PITTS. The chair thanks the gentleman.

I don't see any other questions. That concludes today's hearing. I remind members they have 10 business days to submit questions for the record. I ask that the witnesses all agree to respond promptly to these questions.

With thanks to the witnesses, this subcommittee is adjourned.

[Whereupon, at 1:20 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable John D. Dingell
House of Representatives
Washington, D.C. 20515-2215

FEB 08 2012

Dear Mr. Dingell:

Thank you for your questions to the Food and Drug Administration (FDA or the Agency), during two of the Committee on Energy and Commerce, Subcommittee on Health's, PDUFA hearings: July 7, 2011, "PDUFA V: Medical Innovation, Jobs and Patients," at which Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research (CDER) testified, and February 1, 2012, "Reauthorization of PDUFA: What it Means for Jobs, Innovation, and Patients," at which Dr. Margaret Hamburg, Commissioner of Food and Drugs, testified. During these hearings, you requested additional information for the hearing record related to the 2008 contamination of the U.S. supply of heparin and its relationship to new authorities to secure pharmaceutical supply chain safety. This letter responds to that request.

The 2008 heparin contamination crisis is a case study in the vulnerabilities of the global supply chain. Heparin is a widely used injectable anticoagulant, derived from the mucosal tissue of pigs. In early 2008, contaminated heparin from China was associated with an increase in deaths in the United States. Whatever was contaminating this imported heparin could not be identified by the tests used at the time. After launching a far-ranging investigation, FDA scientists, working closely with academia and industry, developed a test methodology that identified a previously unknown contaminant in Chinese-manufactured heparin. The contaminated heparin contained oversulfated chondroitin sulfate (OSCS), an intentionally added adulterant. An outbreak of blue ear pig disease had killed off a large portion of China's pig population, creating an incentive for criminals to seek an alternative that mimicked the chemical makeup of heparin, but tragically, proved dangerous to consumers.

FDA publicly referred to the heparin contamination crisis as a "wake-up call." It was an alert not only for FDA, but also for U.S. citizens, industry, and lawmakers about our dependence on a globalized drug supply and the key vulnerabilities in our drug supply chain. FDA has taken a number of significant steps to safeguard the U.S. supply of this medically necessary drug. The Agency invested considerable resources to inspect heparin manufacturing and testing facilities related to the supply of heparin in the United States. Additionally, the United States Pharmacopoeia, a standards-setting organization upon which FDA relies, now calls for the testing of heparin to detect the presence of OSCS, the contaminant that sickened patients in 2008. FDA has also implemented heparin-specific import surveillance, including an import alert and multiple warning letters, to ensure that adulterated heparin does not enter our borders.

But our efforts have not stopped there. The heparin crisis was a crime of opportunity, and we need to minimize these opportunities. We are committed to putting preventive measures in place that will protect American consumers from adulteration of all imported drugs. We combine risk-based approaches with sound scientific evidence to protect the public from adulterated and unsafe drugs. The Agency takes several factors into account in determining whether a particular drug ingredient may be at risk for adulteration. For example, when a drug ingredient depends on raw materials that are particularly expensive, criminals may have extra incentive to find a cheaper alternative to the expensive ingredient. If the cheaper alternative can mimic the chemical activity of the product and thereby go undetected by standard testing, as was the case in the heparin and melamine incidents, the risk of adulteration is higher. To date, FDA has systematically ranked more than 1,000 active pharmaceutical ingredients (API) in order of their respective risk of adulteration, based on a multi-factorial, risk-based model we developed. A subset of these higher-risk ingredients is targeted for additional sampling and special testing at the border. In addition, FDA is working to reduce the risk that counterfeit or adulterated drug products reach consumers in the U.S. market by developing standards for a track-and-trace system that would enable the identification of these products and facilitate efforts to recall them.

Through the creation of a new directorate focused on global operations and policy other activities at the Agency, we have made addressing the challenges of globalization a top priority. To support this effort, FDA can benefit from new legislative authorities that are, at a minimum, commensurate with those of its major global counterparts.

In general, new regulatory authorities, many of which are contained in H.R. 1438, the "Drug Safety Enhancement Act of 2011," may help ensure that industry takes principal responsibility for the security and integrity of its supply chains and the quality control systems it uses to produce drugs for the American people. In an era of globalization, new authorities can help to level the playing field between domestic and foreign manufacturers, ensure product safety, and provide FDA with the information it needs to protect consumers. Those authorities may include:

Leveling the Playing Field

- Refusal of product admission to the United States, if inspection of the manufacturing facility is delayed, limited, or denied – this authority is critical to providing a strong incentive for foreign facilities to allow FDA to perform inspections and to permit FDA to exclude from domestic commerce products whose foreign manufacturers or facilities try to avoid subjecting themselves to the same requirements as domestic manufacturers and facilities. This authority is not currently explicit in FDA's law for any product other than foods.

- Require information upon importation – the Agency can refuse entry of an import that appears from examination of samples or otherwise to be adulterated or misbranded, but FDA lacks authority to require certification or other assurance of compliance with applicable standards or requirements as a condition of importation, consistent with FDA's standards and requirements for the domestic drug supply. This is the opposite of the approach taken by many other countries that place the burden on the importer or product owner to prove that its drug is compliant with country requirements.
- Quality management systems – FDA currently works with industry to ensure that individual companies have effective quality management systems in place; however, additional statutory authority could place greater responsibility on manufacturers to account for the quality and provenance of the materials that go into their products. This would level the playing field between the companies that work diligently on their quality management systems to provide high quality products, and those that do not.
- While FDA does not seek to interfere with regulatory authorities outside the United States, having express authority to address threats to U.S. consumers, whenever and wherever they may arise is critical.

Increasing Drug Safety

- Mandatory recall authority – while in most instances firms eventually agree to voluntarily recall drugs that FDA believes pose a risk, FDA lacks the authority to compel such recalls and critical time can be lost in negotiations between FDA and a firm, leaving the public exposed to potentially serious health risks. The Agency currently has mandatory recall authority for medical devices, infant formula, and now many other foods, but not for drugs.
- Administrative destruction at the border – absent this streamlined authority, FDA is often forced to return violative products to their senders because the current process for destruction requires a hearing, which is time-consuming and costly. Foreign drugs can then find their way back to U.S. ports of entry several times, posing a potential threat to consumers and wasting critical resources that could be better spent identifying new threats. This authority would level the playing field for those who produce compliant products, whether located in the United States or abroad.
- Administrative detention – while FDA has the authority to administratively detain illegal foods and medical devices in U.S. commerce, it does not have a similar authority for drugs. Currently, we cannot immediately detain dangerous drug products when we find them. Absent this immediate tool, consumers can be exposed to unnecessary risks.
- Enhanced criminal and civil penalties for foreign and domestic suppliers – statutory changes could help to deter would-be criminals from targeting drug products, and bring FDA's penalties in line with those for other serious federal health and safety violations.

Increasing Information

- Modernization of drug registration and listing – revising these statutory provisions may improve the timeliness, completeness, and accuracy of FDA's current registration and listing information, making sure FDA has accurate and up-to-date information about foreign and domestic parties involved in medical product manufacture.
- Notification to FDA – this authority would permit FDA to require foreign and domestic companies to provide complete information on threats such as counterfeiting, theft, non-compliance with regulatory standards, mislabeling or misbranding, or other threats to the security of the drug supply chain. Among other things, this would allow FDA to better spot emerging risks and trends across companies and then inform industry or take other proactive, preventive steps.
- Unique facility identifier – the absence of a system of unique drug facility identifiers, such as a D-U-N-S number, submitted to FDA both as a condition of registration and import, makes it difficult for FDA to properly follow threats up the supply chain and makes it more difficult to get different systems, including at different agencies, to properly cross-reference.
- Authority to share certain non-public information with other regulatory agencies and foreign governments – this authority would allow FDA to share certain information that could lead to timely identification, prevention, and resolution of emerging threats. Our ability to form global coalitions of regulators will be hampered if we cannot share critical information with our trusted partners.
- Track and trace – requiring a cost-effective track-and-trace system for all drug products throughout the supply chain would improve the security and integrity of the drug supply and ensure transparency and accountability of product manufacturing and distribution, whether the product is manufactured domestically or internationally.

In our increasingly complex and globalized world, these additional authorities represent important tools to help support efforts to protect the safety of imports and the health of our citizens.

Thank you, again, for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

Jeanne Ireland
Assistant Commissioner
for Legislation

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

NOV 17 2011

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the July 7, 2011, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "PDUFA V: Medical Innovation, Jobs and Patients." We are providing responses for the record to questions posed by certain Members of the Subcommittee in your letters of August 5, 2011, and September 14, 2011. This is a partial response.

If you have further questions, please let us know.

Sincerely,

Jeanne Ireland

Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosure

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Mike Rogers

1. **You stated several times that FDA is meeting all of the performance goals set forth by PDUFA IV. Can you provide the Committee with the data you are using to support your claims?**

As of March 31, 2011, for applications received in FY 2010, FDA is meeting its PDUFA review performance goals for both priority applications and for standard applications, with five percent of priority applications and 25 percent of standard applications still pending FDA review—all within their PDUFA goals.[1] FDA has been, on aggregate, meeting these review performance goals for priority and standard applications submitted from the fourth quarter of 2009 to the present.

We are enclosing a copy of our FY 2010 Performance Report to the President and Congress for the Prescription Drug User Fee Act (PDUFA), which contains additional supporting data.

2. **You stated the FDA currently has the highest rate ever of first cycle approvals. Is that for priority review applications? If so, can you please provide the approval timelines for standard review applications?**

The statement that FDA currently has the highest rate ever of first-cycle approvals is based on the approval rate for combined standard and priority review New Molecular Entities (NMEs) and New Biologic Entities (NBEs) filed with the Center for Drug Evaluation and Research (CDER) in FY 2010. For FY 2010 (the most recent year for which all new NME marketing applications have reached a first regulatory action), CDER approved 56 percent of the 27 filed NME/NBE applications on the first regulatory review cycle—the highest approval/action rate since the enactment of PDUFA. More specifically, 7 of 10 (70 percent) priority NMEs and 8 of 17 (47 percent) of standard NMEs were approved on the first-review cycle.

It is still too early to determine final FY 2011 first-cycle performance; however, as of September 30, 2011, FDA has acted on seven FY 2011 NME/NBE applications (all priority-review designation) and has approved all seven (100 percent) on the first-review cycle.

3. **Why do you believe there has been a sudden acceleration of drug shortages over the last 2-3 years? Prior to 2006, shortages were much more stable and manageable. In your view, what has changed - either in the approval process,**

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[1] For more information on PDUFA performance, see the 2010 report to Congress: *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf*. Please note that the data as of March 31, 2011, may differ from the figures in the Performance Report, which reflect the data as of September 30, 2010.

manufacturing process or in the market - that has caused this alarming development?

Drug shortages occur for a variety of reasons, including a manufacturer's inability to obtain raw materials; manufacturing problems, such as drug quality problems that lead to stops or delays in the production of a drug; and business decisions made by a manufacturer to discontinue a drug.

In 2010, there were a record number of shortages and in 2011, FDA has continued to see an increasing number of shortages, especially those involving older sterile injectable drugs. In 2010, 74 percent of the shortages involved sterile injectables, of which approximately 54 percent were due to quality problems at the manufacturing facility. Some of these quality problems included particulate material in the drugs, microbial contamination, and impurities. Although quality and manufacturing problems were a major reason for these shortages, there has not been a significant increase in domestic enforcement actions (seizures or injunctions) for sterile injectables in recent years.

Older sterile injectable drugs are sometimes discontinued by companies in favor of newer, more profitable agents. Furthermore, consolidation in the generic pharmaceutical industry has led to fewer firms making older sterile injectable drugs. These drugs are also vulnerable to shortage because of the small number of manufacturers and limited production capacity at the firms, combined with the economic factors related to these older drugs, the long production lead times, and complexity of the manufacturing process for injectable drugs.

FDA does everything possible within its regulatory authority to address drug shortages. This involves working with manufacturers to resolve quality issues, expediting FDA's process for drug applications under review to help get products to the market as soon as possible, helping manufacturers identify new sources of raw material, identifying alternative producers of finished products, and at times, utilizing regulatory discretion for the temporary importation of medically necessary drugs in shortage after FDA evaluates the drug manufactured for a foreign market and the facilities in which it is manufactured.

The Agency can not require companies to continue manufacturing medications that are in short supply. Moreover, the statutory requirement in section 506C of the Act to notify FDA in the event of a discontinuation in manufacturing has limited application.

4. **A June 14 statement from the Obesity Care Continuum, representing obesity patients and providers nationwide, said: "the FDA is being 'benefit-blind' causing an overly risk averse position...this will likely further discourage any research and development in the area of obesity ever again." Can you respond to these concerns?**

FDA is committed to working with pharmaceutical companies to bring new obesity drugs with favorable benefit-risk profiles to the market, but obesity has been a difficult area in which to develop drugs with favorable benefit-to-risk profiles. Two obesity drugs and one dietary supplement have been withdrawn from the market because they increased blood pressure and, in the case of the two obesity drugs, were documented to increase the

incidence of stroke and/or heart attacks. FDA took another class of obesity drugs off the market because they increased the risk for heart valve disease, and in some cases, resulted in patients needing to have open-heart surgery to replace their damaged valves. An additional drug to treat obesity that was recently approved by the European Medicines Agency (EMA), but not by FDA, was later withdrawn from the European market due to an increased risk of suicide. We must make sure that any new products to treat obesity are safe, while taking into account the public health impact of obesity.

FDA is planning a scientific meeting to discuss obesity drugs and cardiovascular safety, and we are also planning to attend stakeholder meetings involving pharmaceutical companies, patient advocacy groups and obesity experts to discuss development of obesity drugs. We expect these meetings to be very helpful to industry in developing drug products to treat obesity.

As FDA evaluates new drugs for the treatment of obesity, we will carefully consider the role of Risk Evaluation and Mitigation Strategies (REMS) and required post-marketing studies to ensure that the benefits of the drug outweigh its risks.

5. **Dr. Woodcock, earlier this year Gene Green and I wrote the Drug Enforcement Administration about a situation that we find troubling. It has come to our attention that DEA scheduling of certain FDA-approved products, pursuant to the Controlled Substances Act, appears to be somewhat inconsistent, with timelines varying widely. While we agree that DEA scheduling actions play an important, and necessary role in preventing diversion and abuse of controlled substances, we also believe unnecessary delays in this process result in barriers to patient access to life-saving and/or life improving medical therapies. To better understand this situation, we asked how the scheduling process works inside DEA, and in their response, DEA noted "one important initial and critical event that affects the time to complete drug scheduling is the rapidity with which the Department of Health and Human Services provides its scientific and medical evaluation and scheduling recommendation to the DEA." We've looked into recent timelines, and it seems that in some instances, HHS/FDA send their recommendations to DEA prior to FDA approval. In other instances, the HHS/FDA recommendation is not sent until months after FDA approval. Could you please describe FDA's role in this process in greater detail? Additionally, to what do you attribute the reasonably widely varying timelines for making scheduling recommendations, relative to the product's FDA approval date?**

FDA's role in scheduling drug substances under the Controlled Substance Act (CSA) is to perform a scientific and medical evaluation of drugs based on eight factors and findings established in the CSA and to provide, through the Secretary of the Department of Health and Human Services (HHS), a recommendation to the Attorney General as to whether a drug should be controlled and, if so, in what Schedule (I, II, III, IV or V).

The required findings relate to considerations, such as whether the drug or other substance has a currently accepted medical use in treatment in the United States, whether there is a

lack of relative safety for use under medical supervision, and the extent to which the drug has a potential for abuse and to which the use of the drug or other substance may lead to physical or psychological dependence.

Proceedings to add, delete, or change the schedule of a drug or other substance may be initiated by HHS, the Drug Enforcement Administration (DEA), or by petition from any interested party, such as a drug manufacturer, medical society, pharmacy association, public interest group, state and local government, or an individual citizen.

Typically, FDA does not begin its medical and scientific evaluation until it receives a formal request from DEA. FDA may also initiate such an evaluation during the drug development process. Such an evaluation typically begins during the investigational stages of drug development or when an application to market a new drug is received by FDA and the Agency determines that the substance may be a candidate for scheduling under the CSA.

Scheduling Process for New Drugs

The CSA requires the HHS Secretary, and by delegation, FDA, to notify the Attorney General through the DEA at the time a New Drug Application (NDA) is submitted for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system and it appears that the drug has an abuse potential.

Throughout the drug development process, FDA evaluates preclinical, clinical, and epidemiological data to determine whether a drug under review requires abuse liability studies, scheduling under the CSA, or additional measures such as those related to risk management, if needed, directed to reducing abuse, misuse, and overdose.

Some of the Agency's analyses relating to the abuse potential of a drug, such as analysis related to risk management, is completed within the PDUFA timeline. FDA review constitutes the assessment of the abuse potential of a drug, which is based upon the comprehensive evaluation of the chemical, pharmacological, pharmacokinetics, and clinical data (including human abuse studies, clinical trial data relative to abuse, and epidemiological data, if available).

For a new drug substance, final drug scheduling by DEA follows the NDA approval date, so that the drug can meet all of the required findings for scheduling in Schedules II through V. Drugs in Schedules II through V must have accepted medical use in treatment in the United States, which often means an approved NDA. Nevertheless, the abuse potential assessment can be finalized before NDA approval by FDA, if the medical and scientific evaluation that forms the basis for the scheduling recommendation by HHS has been completed. In this circumstance, HHS has been able to forward its scheduling recommendations to DEA prior to NDA approval and, therefore, to enable DEA to have sufficient time to complete its role in the scheduling process and to expedite publishing a *Notice of Proposed Rulemaking* (NPRM) in the *Federal Register*. Final scheduling by DEA requires that the NDA be approved.

Once a scheduling recommendation has been transmitted by HHS to DEA, the recommendation remains confidential until published by DEA in the *Federal Register*. That rulemaking process may involve other federal agencies and requires public notice through an NPRM, which may result in receipt of public comments, objections, and hearing requests, prior to DEA issuing a Final Order.

Factors Affecting Timelines for FDA's Scheduling Recommendations

It is important to understand that NDA review and drug scheduling are two independent review processes regulated by two different laws. NDA review and approval are under the FD&C Act and timelines for review are established by PDUFA, while the process for drug scheduling is under the CSA. Even though these two processes are independent from a regulatory perspective, FDA strives to coordinate the CSA scheduling of a drug as closely as possible with that drug's approval for marketing.

There are many factors influencing the time it takes for HHS to develop a final scheduling recommendation. The steps necessary to develop a scheduling recommendation need to be performed in a certain order. A delay in any step of the process can adversely affect the timeliness of scheduling relative to the NDA action date.

Some of the factors that can potentially affect the timeliness of the drug scheduling process include:

1. Timeliness, quality, and completeness of data submitted by the drug company (Sponsor) to support drug scheduling determination by FDA
2. Completion of all primary reviews for the new drug product (medical/pharmacology, clinical pharmacology, chemistry, and scientific issues)
3. Review and clearances by multiple federal agencies (legal/regulatory issues)
4. New or precedent-setting medical and legal issues requiring regulatory policy development

To expedite the scheduling process and to guide Sponsors on the type of studies needed to characterize the abuse potential of a drug, FDA published in January 2010 draft guidance entitled *Guidance for Industry: Assessment of the Abuse Potential of Drugs, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf*. In addition, FDA communicates to Sponsors the importance of an early interaction and high-quality submissions to support efficient scheduling.

If sufficient information exists to make and support a drug-scheduling recommendation, the FDA procedure, though complex, is not excessively long or delayed and closely parallels the PDUFA timeline.

Once the HHS recommendation is with DEA, FDA is removed from the process and does not have a formal role in scheduling other than to respond to DEA questions on issues that may need to be clarified..

6. What is the vacancy rate on FDA advisory committees? Have there been situations in which experts have been disqualified from serving on advisory committees because they have served as an investigator in a clinical trial for an unrelated product?

Congress enacted new conflict-of-interest provisions for FDA Advisory Committees in September 2007, with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA). FDA guidance addressing advisory committee member screening for potential conflict of interest is consistent with the legislation and helps ensure the integrity of the advisory committee process. FDAAA requires that the Agency review the financial interests of a potential advisory committee member along with his/her expertise before appointment, so as to minimize the need for a waiver of conflict of interest for future participation. Because a member may advise on many topics during his/her tenure, FDA has flexibility to appoint advisors with some financial interests related to FDA-regulated products. FDA's principal review for conflict of interest is done for each meeting topic only, after a member has been appointed and the particular meeting topic(s) has been identified.

Since FDAAA's enactment, FDA has actively focused on reducing advisory committee vacancies. Whereas vacancy rates were 32 to 35 percent in 2007 and 2008, as of May 2011, FDA has reduced vacancies to 20 percent (of 608 positions, 121 positions are vacant). FDA continues to increase its outreach to scientific and professional organizations, consumer and community-based organizations, and minority groups to further reduce the number of vacancies. While vacancies are being reduced, FDA is sensitive to the growing need for subject experts and the complexities of finding and screening these experts in a timely manner.

FDA carefully analyzes all financial interests reported by advisors. Service as an investigator in a clinical trial for a product unrelated to the topic and potential discussions and outcomes of the advisory committee meeting is not in itself a disqualifying interest.

7. Shortly after the passage of FDAAA, the FDA declared that it would not be able to meet its review goals for new medicines, because the Agency needed to implement REMS and other new authorities. Have REMS implementation and other new authorities contributed to these delays? If so, how?

The Agency experienced an increase in review times of applications filed in FY 2008, coinciding with the implementation of FDAAA. The law included a number of provisions that affected the human drug review process, including provisions that authorized FDA to require Risk Evaluation and Mitigation Strategies (REMS) (section 901 of FDAAA[2]), established pediatric research requirements (section 401 of FDAAA[3]), increased use of Advisory Committee Meetings (section 918 of FDAAA[4]), and established new requirements

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[2] Section 505-1 of the FD&C Act
[3] Section 505B of the FD&C Act
[4] Section 505(s) of the FD&C Act

regarding advisory committee members' conflicts of interest (section 701 of FDAAA[5]), as well as establishing other new requirements.

Implementing these new provisions significantly affected FDA's ability to consistently meet review timelines. In addition, NDAs and Biologics License Applications (BLA) filed in FY 2008 represented a 14 percent increase compared to applications filed in FY 2007. This increase in the volume of work in FY 2008, coupled with new FDAAA provisions affecting the review process, resulted in decreased on-time percentages for both standard and priority reviews. As workload levels dropped in FY 2010, on-time performance has improved substantially. FDA has been, on aggregate, meeting our review performance goals for applications submitted from the fourth quarter of 2009 to the present.

8. **FDA has devoted significant resources to improve its transparency by using the Internet and social media to deliver public health messages. The Agency has repeatedly promised since 2009 to release guidance to medical product companies so that they can use the same tools the FDA is using. When will the FDA release comprehensive guidance on the appropriate use of the Internet and social media?**

We agree that developing guidance on the appropriate use of the Internet and social media is important and we have committed this area as one of our highest priorities. It is difficult to provide a time frame for the issuance of our guidances due to the complexity and extensive work and review process in developing meaningful guidances. Our goal is to focus on concepts that have long-term applicability, such as accountability, ownership, responsibility and regulatory requirements, rather than on any particular social media tool or technology platform, so that our guidances will not become quickly outdated as the tools and technology evolve. In addition, we are taking into consideration the input from within and outside FDA, including testimony and comments from the Part 15 hearing held on November 12-13, 2009, "Promotion of FDA-regulated Medical Products Using the Internet and Social Media Tools," and will issue draft guidances as expeditiously as possible.

We are currently prioritizing policy and guidance development for promotion of FDA-regulated medical products using the Internet and social media tools. Taking into consideration the input from within and outside FDA, including testimony and comments from the Part 15 hearing, we have identified the issues that are important to address. We are developing multiple draft guidances to address these topics to benefit industry and the public. We follow "Good Guidance Practices" (GGPs), which ensure that FDA's stakeholders are provided well-vetted guidances, articulating FDA's current thinking on a topic and that these draft guidances are meaningful and well thought out when they are issued for public comment.

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[5] Section 712 of the FD&C Act

The Honorable Bob Latta

1. **Has any FDA-approved pharmaceutical treatment for obesity been pulled from the market because of an increased risk of stroke?**

Phenylpropanolamine (PPA), sold as an over-the-counter weight-loss drug, was removed from the market because it was associated with an increased risk of stroke. Meridia (sibutramine), sold as a prescription weight-loss drug, was removed from the market after FDA asked the manufacturer to voluntarily withdraw it from the U.S. market on October 8, 2010, because it was associated with an increased risk of stroke and heart attack. On February 11, 2004, FDA issued a final regulation declaring that dietary supplements containing ephedrine alkaloids (ephedra), used by many people in an attempt to lose weight, were adulterated under the FD&C Act. This regulatory action "banning" dietary supplements containing ephedra was taken in large part because ephedra was shown to increase blood pressure. Increased blood pressure is associated with heightened risk for serious adverse cardiovascular events such as stroke and heart attack.

2. **Meridia was pulled from the market because of increased risk of myocardial infarction in a high cardiovascular risk population- the majority of patients in that study (SCOUT TRIAL) were given the drug in the trial outside the FDA approved prescribing indications. Why was the drug "voluntarily" pulled from the market? Was there pressure for the company to remove it?**

The SCOUT trial demonstrated that sibutramine increased the risk of heart attack and stroke in a population of overweight and obese individuals with or at risk for cardiovascular disease. Following a thorough review of the SCOUT trial data, as well as all other relevant information on the efficacy and safety of sibutramine, and discussion of these data with an Agency advisory committee, FDA determined that sibutramine's risks outweighed its benefits. This determination was conveyed to the company and FDA asked that it voluntarily withdraw sibutramine from the market. The company agreed to FDA's request.

3. **You stated that "one of the problems that we're identifying is many of the weight loss drugs increase blood pressure." Can you list those obesity drugs that the FDA has identified that increase blood pressure?**

PPA, sibutramine, and ephedra were all shown to increase blood pressure and were removed from the market. The investigational weight-loss drug Contrave (naltrexone SR/bupropion SR) has been shown to increase blood pressure relative to placebo.

4. **Is it true that all three of the new drug applications for obesity that were reviewed by the FDA last year satisfied the Agency's 2007 Draft "Guidance for Industry: Developing Products for Weight Management?"**

The 2007 draft guidance states: *"In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:*

- *The difference in mean weight loss between active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*
- *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant*

The weight-loss data submitted in the original NDAs for Contrave, Qnexa (phentermine/topiramate), and Lorqess (lorcaserin hydrochloride) satisfied at least one of the above efficacy criteria. However, the weight-loss efficacy or benefit of a drug must be weighed against its potential risks or harms in determining whether the drug's benefits outweigh its risks. During review of these NDAs, significant safety concerns were raised. Contrave is associated with increases in blood pressure, raising concern about risk for stroke and heart attacks; Qnexa may increase the risk for birth defects; and Lorqess was associated with increased numbers of breast and brain tumors in studies in rats. Based on the data submitted in the Contrave, Qnexa, and Lorqess NDAs, FDA determined that the potential risks of these drugs outweighed their potential benefits. FDA continues to work with the sponsors of these NDAs to help them more fully characterize their drug's benefit-risk profiles.

The Honorable Henry Waxman

1. **During the hearing, the following exchange occurred:**

   Dr. Cassidy: You mean, there is a union agreement which is keeping us from being able to inspect foreign manufacturers?

   Dr. Woodcock: Partly. That's my understanding.

   I would like clarification on your statement. It is my understanding that the collective bargaining agreement between FDA and the National Treasury Employees Union, which represents FDA employees, sets up a system to determine the order in which employees are selected to be sent on foreign inspections, starting with the dedicated foreign inspection cadre and then followed by volunteers and after that, other employees. Is there anything further in that agreement that actually prevents FDA from sending an employee abroad if such staffing is necessary to ensure the safety and effectiveness of imports?

FDA highly values the dedication and professionalism of our employees who work in the field of public health protection. FDA is able to conduct successful inspections because it has effective investigators who have both substantive knowledge and good judgment. It is through this talented workforce that FDA is able to protect the public health.

FDA has the ability to shift resources from domestic to foreign inspections and we have committed to making the shift to achieve the Agency's goal of addressing the risks posed by the global supply chain. We have used a number of strategies to increase the number of foreign inspections. Where there are barriers or obstacles, we are aggressively figuring out ways to overcome them.

We have established a dedicated foreign cadre in this country to conduct pharmaceutical inspections abroad. We have also stationed investigators and other staff abroad. We have opened offices in several locations abroad, including India, China, Latin America, and Europe.

Our current Collective Bargaining Agreement (CBA) with our union partner, the National Treasury Employees Union (NTEU), incorporates a Memorandum of Understanding that outlines a process we agree to use when assigning foreign inspections to investigators in the United States who are not a part of the dedicated cadre.

Conducting foreign inspections entails more resources than domestic inspections, more planning, cooperation by the foreign firm, and cooperation by the foreign country. We must and will take steps to reduce costs to the extent possible, work with our foreign partners, and use all of our tools to ensure the cooperation of foreign firms.

3. **Does the collective bargaining agreement limit FDA's ability to inspect beyond the restraints on the agency due to limited budgetary resources?**

Under the CBA, FDA and the Union agree that fulfilling the public health mission comes first. As we consider every option to adjust to the increasingly globalized marketplace, we will continue, as we always have, to sit down with our Union partners to improve any processes that hinder our obligations to serve the public.

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