FDA CHECKUP: DRUG DEVELOPMENT AND MANUFACTURING CHALLENGES

HEARING

BEFORE THE

SUBCOMMITTEE ON ENERGY POLICY, HEALTH CARE AND ENTITLEMENTS

OF THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

FIRST SESSION

DECEMBER 12, 2013

Serial No. 113–101

Printed for the use of the Committee on Oversight and Government Reform

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

U.S. GOVERNMENT PRINTING OFFICE

87–645 PDF WASHINGTON : 2014

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

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

DARRELL E. ISSA, California, *Chairman*

JOHN L. MICA, Florida
MICHAEL R. TURNER, Ohio
JOHN J. DUNCAN, JR., Tennessee
PATRICK T. MCHENRY, North Carolina
JIM JORDAN, Ohio
JASON CHAFFETZ, Utah
TIM WALBERG, Michigan
JAMES LANKFORD, Oklahoma
JUSTIN AMASH, Michigan
PAUL A. GOSAR, Arizona
PATRICK MEEHAN, Pennsylvania
SCOTT DESJARLAIS, Tennessee
TREY GOWDY, South Carolina
BLAKE FARENTHOLD, Texas
DOC HASTINGS, Washington
CYNTHIA M. LUMMIS, Wyoming
ROB WOODALL, Georgia
THOMAS MASSIE, Kentucky
DOUG COLLINS, Georgia
MARK MEADOWS, North Carolina
KERRY L. BENTIVOLIO, Michigan
RON DESANTIS, Florida

ELIJAH E. CUMMINGS, Maryland, *Ranking Minority Member*
CAROLYN B. MALONEY, New York
ELEANOR HOLMES NORTON, District of Columbia
JOHN F. TIERNEY, Massachusetts
WM. LACY CLAY, Missouri
STEPHEN F. LYNCH, Massachusetts
JIM COOPER, Tennessee
GERALD E. CONNOLLY, Virginia
JACKIE SPEIER, California
MATTHEW A. CARTWRIGHT, Pennsylvania
TAMMY DUCKWORTH, Illinois
ROBIN L. KELLY, Illinois
DANNY K. DAVIS, Illinois
PETER WELCH, Vermont
TONY CARDENAS, California
STEVEN A. HORSFORD, Nevada
MICHELLE LUJAN GRISHAM, New Mexico
Vacancy

LAWRENCE J. BRADY, *Staff Director*
JOHN D. CUADERES, *Deputy Staff Director*
STEPHEN CASTOR, *General Counsel*
LINDA A. GOOD, *Chief Clerk*
DAVID RAPALLO, *Minority Staff Director*

SUBCOMMITTEE ON ENERGY POLICY, HEALTH CARE AND ENTITLEMENTS

JAMES LANKFORD, Oklahoma, *Chairman*

PATRICK T. MCHENRY, North Carolina
PAUL GOSAR, Arizona
JIM JORDAN, Ohio
JASON CHAFFETZ, Utah
TIM WALBERG, Michigan
PATRICK MEEHAN, Pennsylvania
SCOTT DESJARLAIS, Tennessee
BLAKE FARENTHOLD, Texas
DOC HASTINGS, Washington
ROB WOODALL, Georgia
THOMAS MASSIE, Kentucky

JACKIE SPEIER, California, *Ranking Minority Member*
ELEANOR HOLMES NORTON, District of Columbia
JIM COOPER, Tennessee
MATTHEW CARTWRIGHT, Pennsylvania
TAMMY DUCKWORTH, Illinois
DANNY K. DAVIS, Illinois
TONY CARDENAS, California
STEVEN A. HORSFORD, Nevada
MICHELLE LUJAN GRISHAM, New Mexico

CONTENTS

FDA CHECKUP: DRUG DEVELOPMENT AND MANUFACTURING CHALLENGES

Thursday, December 12, 2013

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON ENERGY POLICY, HEALTH CARE AND ENTITLEMENTS,
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM,
Washington, D.C.

The subcommittee met, pursuant to call, at 1:35 p.m., in Room 2154, Rayburn House Office Building, Hon. James Lankford [chairman of the subcommittee] presiding.

Present: Representatives Lankford, Gosar, Meehan, Speier, Duckworth, and Lujan Grisham.

Staff Present: Will L. Boyington, Press Assistant; Molly Boyl, Deputy General Counsel and Parliamentarian; Daniel Bucheli, Assistant Clerk; Katelyn E. Christ, Professional Staff Member; John Cuaderes, Deputy Staff Director; Linda Good, Chief Clerk; Emily Martin, Counsel; Sharon Meredith Utz, Professional Staff Member; Sarah Vance, Assistant Clerk; Jaron Bourke, Minority Director of Administration; Krista Boyd, Minority Deputy Director of Legislation/Counsel; Aryele Bradford, Minority Press Secretary; Courtney Cochran, Minority Press Secretary; Yvette Cravins, Minority Counsel; Adam Koshkin, Minority Research Assistant; Juan McCullum, Minority Clerk; and Daniel Roberts, Minority Staff Assistant/Legislative Correspondent.

Mr. LANKFORD. Committee will come to order. I would like to begin this hearing by stating the Oversight Committee mission statement. We exist to secure two fundamental principles. First, Americans have the right to know that the money Washington takes from them is well spent. And second, Americans deserve an efficient, effective government that works for them.

Our duty on the Oversight and Government Reform Committee is to protect these rights. Our solemn responsibility is to hold government accountable to taxpayers because taxpayers have the right to know what they get from their government, we will work tirelessly,in partnership with citizen watchdogs, to deliver the facts to the American people and bring genuine reform to the Federal bureaucracy. This is the mission of the Oversight and Government Reform Committee.

I am going to waive our opening statements today from the ranking member and myself because we have votes that are coming very soon and I want to make sure that we get the opening statements from our guests that are here on the first panel. It looks like those votes will be called fairly shortly. When they are called, we'll

slip away, vote, and then we'll come back and we'll do questions from then and then obviously move on to our second panel.

But with that, I would like to recognize Ms. Speier. One of the panelists is from her district, actually. I want to give a chance for her to be able to recognize him.

Ms. SPEIER. Mr. Chairman, thank you, and I, too, will submit my opening statement for the record.

I do want to take great pleasure in introducing someone who I have known professionally for a number of years. He is the CEO of OncoMed Pharmaceuticals, and that's Paul Hastings, who is with us this afternoon. OncoMed is located in my district and is doing groundbreaking work on stem cell therapies that could provide important alternatives for the treatment of cancer. And Mr. Hastings is what you would refer to as a serial startup CEO and has done great work over many decades.

So, thank you, Mr. Chairman.

Mr. LANKFORD. All members will actually have 7 days to be able to submit opening statements for the record as well.

Let me introduce the other two panelists as well. We have two prolific writers that are here. Dr. Scott Gottlieb is the resident fellow at the American Enterprise Institute, and Mr. Peter Huber is a senior fellow at the Manhattan Institute, all done significant work and research in the area. If you are not familiar with our topic today, we are dealing with the FDA and the drug approval process.

And so glad to have all three of you here as experts in this conversation.

So, pursuant to committee rules, all witnesses are sworn in before they testify, so if you could please stand. Raise your right hand.

Do you solemnly swear or affirm the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Thank you. You may be seated.

Let the record reflect all the witnesses answered in the affirmative.

In order to allow time for discussion, I would ask you to keep your testimony, your oral testimony to about 5 minutes. You'll see the clock in front of you. All of you are veterans at this table before, and so we would ask you to do that oral statement, as you know full well. All of you have submitted a tremendous amount of written information as well. That will go into the permanent record also.

Mr. Gottlieb, be glad to be able to receive your opening statement.

WITNESS STATEMENTS

STATEMENT OF SCOTT GOTTLIEB

Dr. GOTTLIEB. Thanks a lot, Mr. Chairman, Ms. Ranking Member. Thank you for the opportunity to testify today before the committee. My name is Scott Gottlieb. I am a physician and resident fellow at the American Enterprise Institute. I previously worked at

FDA as the agency's deputy commissioner and at CMS as a senior adviser to the administrator.

I want to address the issues related to FDA's review and approval of novel treatments for serious diseases that aren't adequately addressed by available medicine. The FDA has been effectively implementing provisions included in the last reauthorization of the Prescription Drug User Fee Act related to breakthrough therapies. I believe these provisions are having a noticeable impact on FDA's willingness to embrace new approaches to expedite the development of these sorts of new treatments, but I still believe there is more that can be done.

The drug development process itself has become long and costly owing to regulation that serves to add to premarket burdens, but often without meaningfully improving the safety of drugs or what we know about their effectiveness, and we are not taking full advantage of what science has made available, not only in terms of new and more targeted therapies, but better ways for evaluating them.

The review staff at FDA is a dedicated and well-intentioned clinical group of people who are often leading experts in their respective fields, but they are also heavily influenced by outside voices, and it's often the critics talking the loudest. Years of complaints about FDA's oversight of drug safety, about the high cost of drugs relative to their perceived benefits at the time of initial market entry, and criticism about the science that FDA uses in its review processes from vocal academics who often have their own parochial views in these matters, all of these things have taken a toll on FDA's culture.

Over time, it is sanding down people's willingness to take the risk of adopting new approaches to the agency's work, even around areas of unmet medical needs that might not have anything to do with the concerns that incited the initial concerns.

The result is that a fear of uncertainty now pervades the review process. When it comes to drugs targeted to unmet medical needs, I believe it's a fear of uncertainty around efficacy that is having the most profound impact of how drugs are being developed. FDA staff is often unwilling to take risk when it comes to observations around drug efficacy. They require experiments that leave little doubt that the magnitude of the benefit observed in a trial is not a function of any statistical chance. In short, they want to conduct pristine experiments that leave little uncertainty about the results describing a drug's efficacy that they are precise and beyond any statistical doubt.

Here it's important to distinguish between the magnitude of the benefit being observed and the believability of that result. I am not talking here about FDA's concern that a drug must show a certain amount of benefit. Some threshold of measurable benefit is always necessary to provide a proper balance against known risks.

Rather, it's how FDA guarantees the believability of that observation of benefit that I believe is having the most significant delay on the development of new drugs. FDA requires longer, larger trials to get pristine statistical results. This makes their ultimate decision around the approval easier since evidence is clear, but it also adds to time and cost.

I believe there are ways to enable faster development of new drugs for unmet diseases and timelier access, while still ensuring that future patients will have appropriate information. We need to focus on reforms that will help the review culture at FDA evolve when it comes to these issues. I want to offer some suggestions that are aimed towards these ends.

First, we should consider changing how clinical effectiveness is defined in the setting of rare diseases. FDA insists that there is a single standard for establishing safety and effectiveness. I think the FDA needs clearer direction around when we as a society want it to exercise its existing discretion to streamline development programs. This doesn't mean that safety and effectiveness isn't firmly established for the drugs aimed at rare disorders. It only means that we are making a much more explicit acknowledgment of FDA's existing discretion to adjust trial requirements based on the circumstances.

Second, the breakthrough therapies pathway has been a successful legislative effort and its implementation by FDA has had a palpable impact on the review process. But a full-throated embrace of the spirit of this legislation requires a cultural change at FDA that is invariably slow to unfold. For these reasons, we might also consider changing the organizational structure of FDA to hasten the adoption of these provisions.

Specifically, rather than allow drugs aimed at very rare disorders to be reviewed alongside drugs targeted to more common maladies, we might consider carving out the novel breakthrough drugs into a separate group inside FDA, a sort of skunk works charged with implementing novel review requirements and regulatory science. Such a group might more readily embrace concepts that can change how we develop drugs, introducing greater efficiency, ideas like the use of adaptive trial designs, Bayesian statistical techniques, and wider use of molecular profiling and targeting of medicines.

These are not new concepts, but they are very slow to gain adoption. In an agency where reviewers are under constant political pressure and time constraints, they don't feel a lot of liberty to incorporate unfamiliar and new approaches, or take new risks in embracing concepts that are untried. So they stick with familiar constructs, even if these traditional approaches are unnecessarily costly and burdensome.

These are just a few ideas on how to advance FDA's science and make the process for the consideration of drugs aimed at vexing and unmet medical diseases more efficient. FDA has made great strides towards these ends through its recent implementation of breakthrough therapies. I would argue that to make further reforms, it would require measures that start to change the culture of FDA as it relates to these challenges. Thank you.

[Prepared statement of Dr. Gottlieb follows:]

Testimony before the Committee on Oversight and Government Reform
Subcommittee on Energy Policy, Health Care and Entitlements

United States House of Representatives

"FDA Checkup: Drug Development and Manufacturing Challenges"
December 12, 2013

Scott Gottlieb, MD
Resident Fellow
The American Enterprise Institute

Mr. Chairman, Mr. Ranking Member:

Thank you for the opportunity to testify today before the Committee on Oversight and Government Reform, Subcommittee on Energy Policy, Health Care and Entitlements.

My name is Scott Gottlieb. I am a physician and resident fellow at the American Enterprise Institute. I previously worked at the Food and Drug Administration as the agency's Deputy Commissioner and at the Centers for Medicare and Medicaid Services as a senior advisor to the Administrator during implementation of the Medicare Modernization Act.

I am on the policy advisory boards to the Society of Hospitalist Medicine and the Leukemia and Lymphoma Society; and a member of the advisory board to the National Coalition for Cancer Survivorship. I am presently a Clinical Assistant Professor at the New York University School of Medicine. I remain active in the capital markets related to healthcare, and I am closely engaged with a number of the life science and healthcare services companies through a variety of consulting relationships and board assignments. I am here today testifying in my capacity as a Resident Fellow at AEI, and as a physician.

I want to address today the issues related to FDA's review and approval of novel treatments for serious diseases that aren't adequately addressed by available medicine.

The FDA has been effectively implementing provisions included in the last reauthorization of the Prescription Drug User Fee Act related to "Breakthrough" therapies that target these kinds of conditions. I believe these provisions are having a noticeable impact on FDA's willingness to embrace new approaches to expedite the development of these sort of therapies, and to take a more balanced approach toward weighing risk and benefit in these settings.

But I still believe there is more that can be done. That the drug development process itself has become needlessly long and costly owing to regulation that serves to add to pre-market burdens without meaningfully improving the safety of drugs (or what we know about their effectiveness). And that we're not taking full advantage of what science has made available, not only in terms of new and more targeted therapies, but better ways for evaluating them.

First on what we have recently achieved: To date, it's my understanding that FDA has received 90 Breakthrough designation requests, the agency has designated 30 products, and has approved three drugs that were labeled breakthrough therapies. All of these have been products from FDA's drug center. FDA's Biologics Center has approved none of the 10 requests it has received, to date, seeking "Breakthrough" therapy designation.

In my view, the breakthrough therapies authority has had a tangible impact on the drug center. It has enabled a re-examination of how the center handles priority applications for novel and promising drugs aimed at unmet conditions. It has enabled senior management in the drug center to play a more hands on role in helping to shape the policy and regulatory requirements around very novel areas of drug development -- concepts like targeted

therapies, genetically targeted drugs, and drug and diagnostic combinations. It has reinvigorated provisions that have long been in place to allow FDA added flexibility to expedite the development and review of promising therapies. These provisions such as accelerated approval have been marginalized in recent years as FDA backed away from the spirit, if not the letter of the prior statutory language that created these pathways.

The "Breakthroughs" designation has allowed these old concepts to be dusted off.

But there is more that needs to be done when it comes to how FDA handles the development of drugs aimed at unmet needs. The fact is that a lot of the most significant FDA challenges aren't problems with regulation or statute. They are issues of culture.

The review staff at FDA is a dedicated and well-intentioned clinical group of people who are often leading experts in their respective fields. But they are also heavily influenced by outside voices – and it's often the critics that are talking the loudest.

Years of complaints about the agency's oversight of drug safety, about the high cost of drugs relative to their perceived benefits at the time of initial market entry, and criticism about the science that FDA uses it is review processes from vocal academics who often have their own, parochial views on these matters – all of these things have all taken a toll on the culture of FDA. Over time, it is sanding down people's willingness to take the risk of adopting new approaches to the agency's work, even around areas of unmet medical needs that might not have had anything to do with the concerns that incited the initial criticism.

The result is that a fear of uncertainty now pervades the review process. This fear is so pervasive that it impacts not only the assumptions FDA is willing to make about a new drug's safety, but also its efficacy. When it comes to drugs targeted to unmet medical needs, I believe it's a fear of uncertainty around efficacy that is having the most burdensome impact on how drugs are being developed. FDA staff is often unwilling to take any risk when it comes to their observations around drug efficacy. They require experiments that leave little or no doubt that the magnitude of the benefit being observed in a trial is not a function of any statistical chance, or of a problem with how the trial was constructed or conducted.

In short, they want to conduct pristine experiments that leave little doubt that the results describing a drug's efficacy are precise and beyond any statistical doubt.

Here it is important to distinguish between the magnitude of the benefit being observed, and the believability of that result. I am not talking here about FDA's concern that a drug must show a certain amount of benefit. Some threshold of measurable benefit is always necessary to provide a proper balance against known risks. Judging how much benefit can offset a given risk in a particular condition is a matter of judgment, and a policy call.

Rather, it's how FDA guarantees the believability of that observation of benefit that I believe is having the most significant delay on the development of new drugs.

To illustrate these issues for an article I published in the journal National Affairs, I turned to the recent history with the development and approval of drugs to treat a family of inherited

inborn errors of metabolism called mucopolyscaccharide (MPS) diseases. I want to return to this narrative here, and briefly expand on it, to illustrate my point.

These diseases are a large group of metabolic disorders caused by the absence or malfunctioning of certain enzymes (called lysosomal enzymes) that are needed to break down certain sugar molecules found in the blood, called glycosaminoglycans. Since the body is unable to properly break down these sugar molecules, they end up building up in vital organs – with painful, debilitating, and often deadly consequences.

Many of these diseases are extremely rare. Since all of them are inherited, they start to affect people when they are typically very young. These diseases often claim the lives of their victims early. These disorders comprise a group of more than 40 genetic conditions. Some of these different disorders are so rare, that they affect as just a few hundred patients worldwide.

As I noted in National Affairs, drugs that could function as replacements for the missing enzymes have been developed for a number of these diseases, demonstrating that if the enzyme could be effectively reproduced, and delivered to patients in a way that enabled it to get to the target organs, then it would deliver a benefit to patients. Through these approvals, the basis for understanding how a replacement enzyme could function as a treatment in one of these related disorders has been firmly established over a period of more than a decade.

Yet an unfortunate thing happened as each of these similar enzyme replacement drugs -- for one of these closely related diseases -- came before FDA. With each approval, the agency's requirements for the next drug got more demanding, not less, even though the theoretical basis for understanding how these enzyme replacements worked was being more firmly established. This was so, even though each of these diseases was distinct, meaning an enzyme replacement approved for one disease – although conceptually very similar to the enzyme approved for another disease – still wouldn't work on the related disorders.

In short, when it came to these drugs and these diseases, the FDA was not using its accumulating experience with the success of prior enzyme-replacement drugs to streamline its evolving process. Instead, it was making it more and more cumbersome.

As I noted in National Affairs, the first drug to treat one of these disorders was Ceredase, which was indicated for Gaucher disease, a genetic disorder that kills most affected children before the age of five. The FDA approved Ceredase in 1991 on the basis of a single, six-month study of 12 patients; when regulators saw that the livers and spleens of these patients were shrinking, the FDA took this as evidence that the replacement enzyme was having its intended clinical benefit. If the FDA had required statistically significant evidence that the drug enabled patients to function better or live longer, rather than settling for proof that it addressed the physical markers of the disease, the trial could have taken several years.

Drugs were developed for several more of these lysosomal storage disorders. With each approval, the requirements FDA imposed on the next drug grew more burdensome.

By the time a drug for another one of these diseases, Hunter Syndrome, came before the agency in 2003, FDA's standards had grown substantially. Even as the agency became more

aware of how these drugs functioned, and delivered their benefits, it used its accumulating knowledge not to streamline the development of the next drug, but make it more difficult.

In order to approve the drug for Hunter Syndrome, the FDA required the trial to involve 96 patients with Hunter syndrome — some 20% of all Americans afflicted with the disease. Moreover, for the first time in such a study of enzyme-replacement therapy, the FDA also insisted that patients be randomly assigned to receive either the experimental drug or an inert placebo. The course of Hunter syndrome follows a regular pattern in most afflicted children; the results for patients who got the experimental therapy could easily have been compared against readily available historical databases that track the normal course of the disease. As I noted in National Affairs, it's hard to see why a placebo was necessary in such circumstances, especially when the requirement for a placebo group meant that some of the kids involved wasted a full year of the most able portion of their short lives effectively going untreated.

FDA also required a "clinical" endpoint in this trial – a measure that the drug was improving the function of the children, and not just impacting a "surrogate" measure of benefit, like shrinking their enlarged organs. In this case the two measures FDA chose were the ability to walk and breath (through the use of a "walk test" and pulmonary function tests). These and several other requirements meant that the Elaprase trial took longer, and was costlier, than any previous trial involving similar drugs. Prior trials with drugs targeting one of these rare enzyme disorders had lasted six months or less. The Elaprase trial, by contrast, was designed to last at least a full year. And all that time, the parents, the doctors, and the children did not know if they were getting the new drug or the useless placebo.

Unfortunately, the agency's history with how it handled the review and approval of drugs for these MPS diseases is a familiar one. It's not that the clinicians who work on these reviews are unaware of the suffering caused by these and similar diseases. They want to see new, effective treatments delivered to patients. They are aware that clinical trials like the one demanded for Elaprase can impose extraordinary hardships on patients and their families.

But simply put, there is a tradeoff that has become too commonplace in how we develop drugs. This tradeoff is a view that, in the long run, society will benefit more from a regulatory process that demands the development of very precise information about a new drug's benefit up front, before the drug is approved, rather than a process that enables timelier access to these treatments.

There is a view that if precise information isn't developed prior to approval, it will never accrue to medicine. This is simple not true.

And there's a view that sacrificing timelier access to a new drug for today's patients, and imposing even significant hardships on patients in clinical trials in the present time, will benefit many more patients in the long run by forcing the creation of better information.

I don't believe this tradeoff is appropriate, or necessary. I believe there are ways to enable faster development of new drugs for unmet diseases, and timelier access, while still ensuring that future patients will have appropriate information on which to base decisions.

But FDA, left to its own discretion, will always have a preference for designing experiments that leave little doubt about the magnitude of a new drug's benefits, and therefore leave the agency with a relatively easy decision when it comes to its review process and its decision to approve or reject a new drug. These ideal experiments, however, come at a significant human cost, not just in terms of time, but also money. They create barriers to investment in new treatments. And they make the development process much longer than it needs to be.

It's this desire to reduce uncertainty about efficacy (as opposed to just a focus on drug safety) that I believe is the most significant issue in delaying access to new drugs targeted to unmet needs. In many cases, when it comes to the newer, more targeted drugs aimed at rare diseases, safety is not the most prominent question. The safety profiles of these treatments are fairly well understood. Most often, the regulatory issues turn on a question of efficacy, and the desire of FDA to make sure that it has firmly established, with statistical precision, the full magnitude of the observed benefits. When we are dealing with diseases that affect very few patients, this imperative for exactitude can demand enormous costs and hardships.

FDA points to its review times and often argues that there are no problems with how it is handling applications for the vast majority of drugs. The cancer division at FDA routinely publishes these results, with self-congratulatory commentary about the timeliness of their reviews. The agency does deserve some credit here. Once an application is submitted to FDA, especially for drugs aimed at unmet needs, they typically undergo a timely review. The cancer division has done some very fast reviews in recent years. But I believe these statistics are, in some ways, misleading. They don't reveal the whole story on what is unfolding.

Now surely if the review times were long, that would invite criticism. But at the same time, the fact that FDA can lay claim to review times that are, on average, commensurate with review times in Europe, ignores the most important aspects of enabling timely access to new therapies. It's everything that happens before an application is submitted to FDA for review that counts most. It is all the time taken developing the drug that really counts. FDA can make rapid review of applications because the development programs are so exhaustive that they yield clinical data that speaks for itself – the review decision is made readily apparent.

For this reason, the ease of FDA review is often inversely proportional to the cost of development. The biggest chunk of time between the discovery of a new compound in the laboratory, and its approval as a new drug, is not spent while the application is under review at FDA. It's spent while the compound is undergoing the traditional three phases of clinical trials to satisfy FDA's review requirements. The more data generated during this process (and the more statistical rigor demanded of that evidence) the easier the job that FDA has reviewing the final results. This creates a strong incentive for FDA to impose substantial requirements when it comes to how those trials are conducted. That's what is happening.

It's these requirements that are raising costs, expanding development timelines, and creating a significant barrier to the entry of new medicines. By most estimates, the total average development time for a new drug is 15 years, at a cost of more than $1 billion.

So how can we build on the success of the "Breakthrough" therapies pathway, to continue to improve the process for how FDA directs the development of drugs targeted to serious conditions, and goes about reviewing the results of these clinical trials?

We need to focus on reforms that will help the review culture at FDA evolve when it comes to these issues. I want to offer some suggestions that are aimed toward these ends.

First, we should consider changing how clinical effectiveness is defined in the setting of rare diseases. FDA insists that there is a single standard for establishing "safety and effectiveness." But the agency already maintains (and sometimes uses) enormous latitude in adapting its clinical requirements based on circumstances. I don't believe that simply giving FDA more flexibility to streamline its pre-market requirements in certain settings is going to appreciably change how the agency approaches these challenges. It has that flexibility right now.

Instead, I think the FDA needs much clearer direction around when we, as a society, want it to exercise that discretion. To these ends, the Europeans have a much more explicit pathway that allows the limited approval (for a five year period) of drugs that show activity against very vexing disorders, but have not firmly established the same level of statistical proof of benefit as required for more common medicines aimed at more routine conditions.

This doesn't mean that safety and effectiveness isn't firmly established for the drugs aimed at rarer disorders. It only means that we are making a much more explicit acknowledgement of a virtue that's already embedded in the discretion that FDA sometimes exercises – that the clinical trial requirements for demonstrating proof of benefit are not fixed, but adjust based on the circumstances. Vexing diseases like Gaucher's sometimes demands that FDA embrace a less certain standard for statistical conviction in order to expedite a new drug.

We might consider some statutory changes that could hasten this sort of change. For example, hardwiring into statute language that already exists in regulation that enables FDA to use a standard that relies on a single clinical trial or a surrogate measure of benefit when it comes to certain unmet diseases – changing language that says FDA "may" to FDA "shall."

Second, the breakthrough therapies pathway has been a successful legislative effort and its implementation by FDA has had a palpable impact on the review process. But a full-throated embrace of the spirit of this legislation requires a cultural change at FDA that is invariably slow to unfold. For these reasons, we might consider also changing the organizational structure of FDA to hasten the adoption of these kinds of provisions.

Specifically, rather than allow drugs aimed at very rare or serious disorders to be reviewed alongside drugs targeted to more common maladies (and more conventional development programs) we might consider carving out the novel drugs for more serious conditions into a separate group inside FDA – a sort of "skunk works" charged with implementing novel review requirements and regulatory science aimed at expediting the development of critical medicines. There are many new, and effective regulatory concepts that could streamline the development process, making it more efficient and perhaps more effective.

There's no reason FDA's review process has to be strictly organized only by clinical areas. Most of the consultants to the review process are already therapeutic generalists who work across multiple areas. A separate group charged with managing "Breakthrough" applications could maintain its own clinical experts, or borrow them on consult from the divisions.

What ideas might such a group more readily embrace?

Concepts that can change how we develop drugs, introducing greater efficiency – ideas like the use of adaptive trial designs, Bayesian statistical techniques (rather than the more traditional, frequentist approach to statistical design), and wider use of molecular profiling and targeting of medicines. These are not new concepts. But they are very slow to gain any level of adoption. In an agency where reviewers are under constant political pressure and time constraints, they don't feel a lot of liberty to incorporate unfamiliar and new approaches, or take new risks in embracing concepts that are untried. So they stick with familiar constructs, even if these traditional approaches are unnecessarily costly or burdensome.

A separate group that's appropriately staffed with people expert in these new methods could help advance not only the development of very important drugs, but also the science behind FDA's regulation. The counter argument to carving out these "Breakthrough" applications is that the existing review divisions need to be challenged with these new concepts. But it's going to continue to be hard for the existing review teams to both meet current deadlines and demands, while trying to take some measure of risk with new approaches. It's time to consider placing the task of exercising these new authorities like "Breakthroughs," and developing the science behind these new approaches, in a separate team inside FDA that's charged daily with thinking about how to do things differently.

These are just a few ideas on how to advance FDA's science, and make the process for the consideration of drugs aimed at vexing and unmet diseases more efficient. FDA has made great strides towards these ends through its recent implementation of the "Breakthrough" therapies pathway. I would argue that to make further and more significant reforms, it would require measures that start to change the culture of FDA as it relates to these challenges.

These goals can't be accomplished through statutory or regulatory language alone. Lasting change requires a change in FDA's mindset, and its tolerance for risk and uncertainty.

Mr. LANKFORD. Mr. Huber.

STATEMENT OF PETER HUBER

Mr. HUBER. Mr. Chairman, Madam Ranking Member, among Federal regulators, the FDA plays a uniquely strong role in regulating not just the product, but the development of the core science that allows the industry to design the products that do what we want them to do.

The science at stake here is not drug science. There is no such thing. It is drug patient science. It is how the drug's chemistry interacts with the patients. And drug designers can learn quite a bit by just studying biology, but at the end of the day, to get the science right, you do have to start prescribing the drug to patients and study what happens.

So before it licenses a drug, the FDA issues something called an investigational license that scripts how we set about systematically and scientifically developing drug patient science, and those scripts have simply not kept pace, in recent years particularly, with what the best scientific investigations can now do and should be doing.

The blinded, randomized trial protocols that the FDA still relies on overwhelmingly to this day were first used in 1938. They were expanded and formalized in the 1960s. They begin with conventional clinical definitions of the disease. The criteria used to select the patients to participate in the trials must be specified before the trial begins, or to a limited extent resolved in the very early phases of the trial when very few patients are involved. The doctors involved aren't allowed to systematically explore molecular factors that affect how one patient may respond well to a drug and another may respond badly to the same drug even if they are presenting the same clinical symptoms.

The only issues that these protocols address systematically are something called selection bias, which is a deliberate or inadvertent stacking of the data by doctors, or the placebo effect, which is wishful thinking by patients. The trials teach us next to nothing about how variations in patient chemistry affect responses to the drug.

The FDA's concerns about selection bias are legitimate, but modern molecular medicine hinges on the deliberate scientific selection of the right drug-patient molecular combinations. Patients suffering from the same clinically defined disease often present different clusters of molecular targets deep down. There is no such disease as breast cancer. There are at least 10 biochemically distinct breast cancers down there. We treat some with estrogen blockers and we treat others with estrogen itself. One of the estrogen blockers, its performance depends on liver genes, which determine whether the patient metabolizes that drug properly or not.

And I could go on and on. There are diseases that change rapidly on the fly. The chemistry of cancer cells changes at a wild pace as it progress. So do HIV infections. Many of these fast-changing diseases require multi drug regimens and cocktails. Side effects add still more relevant patient side variation in the chemistry.

A good trial of a good drug should culminate in prescription protocols that will make it possible for future doctors to prescribe the drug to the patients who present the molecular profiles that will

interact well with that drug. When we don't do that, there are two major consequences. The first one is little noted but deserves a lot more attention. During the trials themselves, we may quite often be doing real harm unnecessarily to significant numbers of the patients involved. A consensus report issued a few years ago by a coalition of cancer experts drawn from the industry, academia, and the FDA itself says the FDA still relies on, "traditional population-based models of clinical trials...that may form the antithesis of personalized medicine, and accordingly these trials expose large numbers of patients to drugs from which they may not benefit."

If you are saying that you are exposing large numbers of patients to cancer drugs from which they won't benefit, you are saying quite something, because these drugs are very often toxic and powerful drugs, and you really don't want to be prescribing them to the wrong patients for long.

The second consequence follows directly from the first. If we are testing drugs in many of the wrong patients, many drugs that we do in fact need, because they would benefit significant numbers of patients, will not make it through these trial protocols, because to perform well, a drug has to be prescribed well. We know how to design what are called adaptive trials. In brief, you gather a great deal of data tracking, genomes, and proteins and other biomarkers that may affect the trajectory of the disease and side effects and cause different patients to respond in different ways. Patients can be added or removed from trials or treatment regimens can be altered to improve our understanding of the drug-patient molecular science.

There are sophisticated statistical profile processes and algorithms that can handle this very complex data. Because the adapters learn and because the investigators learn and adapt as they go, the patients involved receive on average much better treatments. It really is high time to dispense with these old trial protocols and use the statistical methods of the future and the modern molecular tools that let us track and learn about all these factors.

Mr. LANKFORD. Thank you.

[Prepared statement of Mr. Huber follows:]

Precision Molecular Medicine versus the FDA

Statement of
Peter W. Huber
Senior Fellow
Manhattan Institute for Policy Research

Before
The Committee on Oversight and Government Reform
Subcommittee on Energy Policy, Health Care and Entitlements

December 12, 2013

Pharmacology isn't a science of one hand clapping. The patient's chemistry matters as much as the drug's. The FDA doesn't license drugs—it licenses specified drug-patient combinations: the license's implicit promise of future safety and efficacy applies only "under the conditions of use prescribed, recommended, or suggested in the labeling thereof." The agency spent forty years creating protocols for the development of empirical crowd-science medicine, and it has spent the last thirty wondering how to fit molecules into those protocols. The system is currently frozen in the headlights. It can't handle the complexity and torrents of data that now propel the advance of molecular medicine.

Modern drug designers develop drugs from the bottom up. They select a target molecule and design a molecule to modulate it. They use "structure based" drug design – show a molecular target to a sufficiently smart biochemist, or, increasingly a sufficiently smart super-computer, and he, she, or it can probably come up with an anti-molecule precisely matched to that specific target. Alternatively, designers use a lab animal's genetically engineered immune system to design antibodies perfectly matched to a receptor isolated from, say, the surface of a cancer cell. Recently, biochemists and doctors have begun directly manipulating the molecular code of the patient's own white blood cells to induce them to home in on a specific target on the patient's cancer cells.

The development of this precision molecular medicine begins with the study of human or (in the case of infectious diseases) microbial biology. But the only practical way to work out much of the drug-patient science is to study how the drug actually performs in patients. And the first opportunity to do that systematically is during drug licensing trials authorized and overseen by the FDA.

A good clinical trial of a good drug should culminate in prescription protocols that will make it possible for future doctors to prescribe the targeted drug to the right patients. The best prescription protocols will be based on patient molecular profiles that can be checked before treatment begins — the whole point, after all, is not to wait for clinical effects to reveal whether the drug was prescribed well. By and large, however, the FDA treats patient selection as a problem the drug company must solve either before the clinical trial begins or, to a limited extent, in its very early phases, which involve small numbers of patients. For the most part, FDA-approved trial protocols don't allow

the participating doctors to systematically explore the molecular factors that determine why a drug performs well in some patients and not others.

At best, this means that during the trials the new drug is often prescribed to many patients whom it fails to help, and to still more of the wrong patients thereafter, until enough post-licensing data accumulate to reveal how to prescribe the drug more precisely. At worst, drugs that could greatly benefit some patients don't get licensed because the trials test the drugs in too many of the wrong patients. Either way, testing a drug in many of the wrong patients wastes a great deal of time and money. At some point the cost of relying on a very inefficient process to try to solidify the science up front surpasses how much the drug is likely to earn years later in the market. We then have an economically incurable disease.

To unleash the full power of modern molecular medicine the FDA will have to adopt trial protocols that allow the integrated development of drug-patient molecular science. In the words of Dr. Raymond Woosley, former president and CEO of the Critical Path Institute, a nonprofit group established to promote collaboration among drug companies, academic researchers, and the FDA, "Randomized controlled trials are out of date, and it's time to use the tools of the future."

* * *

Blinded, randomized trial protocols were first used in 1938. They were designed to regulate ignorance, not knowledge—the dearth of molecular medical science, not the science itself, nor its efficient, orderly development. Typically, one group of patients gets the real thing, the other a placebo; when a reasonably good treatment is already available, the comparison may instead be drug versus drug. Doctors track clinical symptoms. At the end of the trial, the newly healthy and the still sick, the living and the dead, vote the drug up or down. The only issues that these protocols address systematically are the risks of deliberate or inadvertent manipulation of the data by doctors —"selection bias"— or wishful thinking by patients -- the "placebo effect."

But patients suffering from the same clinically defined disease often present different clusters of molecular targets deep down, and precision molecular medicine hinges on the deliberate, scientific selection of the right drug-patient molecular combinations.

There are, for example, at least ten biochemically distinct breast cancers. Some are treated with an estrogen blocker, others with estrogen itself. The performance of one of the blockers depends on a genetic variation that affects how well patients metabolize the drug in their liver. More generally, the biochemistry associated with some of the biggest killers changes on the fly: cancer cells and HIV virions, for example, mutate rapidly.

Even a disease associated with a single gene may come in many molecular variations. In 2005 the FDA withdrew its approval of one of two drugs that target a receptor (EGFR) associated with one form of lung cancer. But as one oncologist remarked, "there are at least 20 different mutations in the EGF receptors in human lung cancers, and we don't know if the same drug works as well for every mutation which is why we want as many EGFR inhibitor drugs available as possible for testing." A large genomic study of individuals thought to be particularly susceptible to heart attacks,

strokes, obesity and other major health problems recently found that each subject carried about 300 potential "drug target genes" with rare variants that would probably alter a protein's structure in ways likely to undermine health and affect how the protein would respond to drugs. Safety issues add a further layer of complexity. Side effects occur when a drug sideswipes an innocent molecular bystander. But every body presents a somewhat different array of bystanders.

Given what molecular medicine knows and can do today, tying the drug licensing process to high-level clinical symptoms and the statistical study of large groups of patients is inherently anti-scientific. It is a process that deliberately loses molecular details in the crowd, collapses biochemically complex phenomena into misleadingly simple, one-dimensional, yes/no verdicts, and will often reject good drugs that many patients need.

The best drug science today is anchored in mechanistic facts about how a drug interacts with various molecules that propel the disease or unwanted side effects. Without an understanding of those facts many drugs that we need won't perform well because we don't know how to prescribe them well. As Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, put it in 2004, "biomarkers are the foundation of evidence based medicine—who should be treated, how and with what.... Outcomes happen to people, not populations."

* * *

In September 2012 President Obama's Council of Advisors on Science and Technology (PCAST) released a report on "Propelling Innovation in Drug Discovery, Development, and Evaluation." The FDA's trial protocols, the report notes, "have only a very limited ability to explore multiple factors. Such factors importantly include individual responses to a drug, the effects of simultaneous multiple treatment interventions, and the diversity of biomarkers and disease sub-types." These protocols lead to clinical trials that are "expensive because they often must be extremely large or long to provide sufficient evidence about efficacy."

The report proposes several reforms that, if vigorously implemented, would go a long way toward aligning FDA regulation with the drug development tools and practice of modern molecular medicine.

To begin with, the FDA should use its existing accelerated approval rule as the foundation for reforming the trial protocols used for all drugs that address an unmet medical need in the treatment of a serious or life threatening illness. As the PCAST report notes, the rule has "allowed for the development of pioneering and lifesaving HIV/AIDS and cancer drugs over the past two decades."

In brief, when applying the rule the FDA makes a first call about the drug's efficacy much earlier, based on "surrogate end points," without waiting for higher level clinical effects to surface and persist for some (arbitrary) period of time. In the Gleevec-versus-leukemia trials launched in 2000, for example, doctors tracked the drug's performance by following blood counts and the number of cells bearing the mutant "Philadelphia" chromosome. The truncated front-end trials need not resolve concerns about how the drug's performance might be affected by many aspects of genetic or lifestyle diversity; "differences in response among subsets of the population," in FDA

parlance, may be addressed later. So, too, may open-ended questions about long term side effects. The manufacturer must still complete conventional trials, but does so after the drug is licensed—and thus does so in tandem with the wider use of the drug by unblinded physicians who can investigate why the drug works in some patients and not others. The FDA rescinds the license if things don't pan out.

The PCAST report also urges the FDA to "expand the scope of acceptable endpoints" used to grant accelerated approval. Specifically, the FDA should make wider use of "intermediate" endpoints—indications that a drug provides "some degree of clinical benefit to patients" even though the benefits fall "short of the desired, long[-]term meaningful clinical outcome from a treatment." The Agency should "signal to industry that this path for approval could be used for more types of drugs" and "specify what kinds of candidates and diseases would qualify."

This is a very important recommendation. To deal successfully with complex diseases that require multi-drug treatments, we will have to develop treatments piece by piece, each piece consisting of a drug and a solid understanding of how a cluster of biomarkers can affect that drug's performance. Demanding a front-end demonstration that each drug can, on its own, deliver long-term clinical benefits to most patients will only ensure that no treatment for the disease is ever developed. Evidence that the drug is interacting in a promising way with a molecular factor that plays a role in propelling a complex disease is the best we can expect from any single drug.

A drug, for example, may successfully suppress an HIV protease enzyme and thus lower viral loads, or bind successfully with an estrogen receptor and thus shrink or slow the growth of a breast cancer tumor, yet have no lasting effect on the progress of the disease because the viral particles and cancer cells mutate their way past any single-pronged attack. The drug should be licensed anyway. A successful attack on a biochemically nimble virus or cancer has to begin somewhere, and the place to begin is with a targeted drug that has demonstrated its ability to disrupt some aspect of the disease's chemistry in a way that has some promising effect, in some patients, at some point further along in the complex process that propels the disease. When, for example, the first HIV protease inhibitor established that it could do that job and thus lower viral loads, it was a drug that medicine clearly wanted to have on the shelf—even though it would take several more years to develop additional drugs and assemble cocktails that could suppress the virus almost completely and for a long time.

The PCAST report also recommends adoption of "Bayesian and adaptive protocols" and "other modern statistical designs" to handle the data-intensive trials and explore multiple causal factors simultaneously. In brief, adaptive trials gather a great deal of data, tracking genes, proteins, microbes, and other biomarkers that may affect the trajectory of the disease and cause different patients to respond differently to the same treatment regimens. The trial protocols evolve as the trial progresses and investigators improve their understanding of the drug-patient molecular science. These adaptive, multi-dimensional trial designs gather relevant information much more quickly and efficiently than do trials conducted under the FDA's conventional protocols. And because the investigators learn and adapt as they go, the patients involved receive, on average, better treatments.

Multi-dimensional Bayesian analyses require very complex numerical calculations. The FDA's own information processing technologies, the PCAST report

notes, are "outdated" and "woefully inadequate." But as Andy Grove, the pioneering founder and for many years CEO of Intel, noted in a *Science* magazine op-ed in late 2011, the digital revolution now makes possible clinical trials that enlist patients much more flexibly, to "provide insights into the factors that determine … how individuals or subgroups respond to the drug, … facilitate such comparisons at incredible speeds, … quickly highlight negative results,…[and] liberate drugs from the tyranny of the averages that characterize trial information today."

* * *

In light of what we now know about the molecular environments in which drugs operate, the unresolved question at the end of many failed clinical trials is what failed: the drug or the FDA-approved script. It's all too easy for a bad script to make a good drug look awful. For example, the script begins with a standard clinical definition of a disease that is in fact a cluster of many biochemically distinct diseases; a coalition of nine biochemical minorities, each with a slightly different form of the disease, vetoes the drug that would help the tenth. Or a biochemical majority vetoes the drug that would help a minority. Or every component of what would be an effective cocktail fails when each drug is tested alone. Or the good drug or cocktail fails because the disease's biochemistry changes quickly, but at different rates in different patients, and to remain effective, treatments have to be changed in tandem, but the clinical trial is set to continue for some fixed period that doesn't align with the dynamics of the disease in enough patients. Or side effects in a biochemical minority veto a drug or cocktail that works well for the majority.

By continuing to channel much of the development of drug science through trial protocols developed decades ago, the FDA now makes it increasingly likely that many drugs that we need and the associated drug-patient science will never get developed at all.

Mr. LANKFORD. Mr. Hastings.

STATEMENT OF PAUL HASTINGS

Mr. HASTINGS. Thank you, Chairman Lankford.

Mr. LANKFORD. Mr. Hastings, do you mind turning your microphone on there? Thank you.

Mr. HASTINGS. Sorry about that.

Chairman Lankford and Ranking Member Speier, members of the committee, My name is Paul Hastings, chairman and CEO of OncoMed Pharmaceuticals, headquartered in Redwood City, California. I also serve as chairman of the BIO Emerging Companies Section Governing Board, which represents the small entrepreneurial and emerging biotechnology companies that often do not yet have a product on the market, and we are the majority of BIOs over 1,000 members.

I personally have 27 years of experience in biotechnology and the pharmaceutical industry. My current company, OncoMed Pharmaceuticals, is working at the cutting edge of oncology research, focused on antibodies that target a specific set of cells within tumors known as tumor initiating cells. These cells drive the growth and metathesis of the tumor of the spread, and they can differentiate into various cell types within the tumor. Currently we have five products in clinical development, all discovered at OncoMed, and over 13 completed or ongoing clinical trials, with more than 280 patients receiving our investigational agents.

We continue to pursue the discovery of additional disruptive and novel antitumor initiating product candidates. The U.S. biotechnology industry is working on treatments and therapies that have the potential to deliver new solutions to our most pressing healthcare needs and is a key element of an innovation-driven economy. We've come a long way in turning incurable disease to treatable disease, increasing the ability of patients to maintain independent lives. With the number of people over 65 increasing, improving the quality of life and ability for patients to maintain independence is a national imperative. Hundreds of companies like mine are working on these solutions with over 400 clinical trials currently underway focused on developing the next generation of medicines for over 200 diseases.

This is also an industry poised to be a major contributor to a 21st century innovation-driven economy in the United States. However, we continue to face intense competition from other countries, as well as increasing R&D costs, regulatory challenges, and a contracted funding environment.

This year, working with the FDA, we have seen positive signs that the biotechnology industry is recovering not only from some of the regulatory hurdles, but also from the economic crisis. Thirty-nine biotech companies have gone public this year, including my own, marking the most active IPO market in a decade. Additionally, in 2012 the FDA approved 39 new molecular entities, the most approvals we have seen in 16 years.

Now, while this is good news, the financial and regulatory environment continues to pose significant challenges to innovation and drug and biologic developers like ourselves. For example, first-time private financings, not public financings, but private financings,

venture capital financings, the lifeblood of the innovation biotechnology industry, these first-time financings for new companies are actually at the lowest we've seen since 1995. And while we've seen an increase in the number of approvals, we have also seen a steep increase in research and develop cost, much of which is associated with increased requirements and costs to run clinical trials.

FDASIA contains several provisions designed in cooperation with industry and the FDA specifically to provide FDA with the resources and processes that encourage the utilization of modern tools and approaches, such as adaptive clinical trial design, and allow for more interactive scientific dialogue between the FDA, the industry, and patients. Some of the most exciting provisions in FDASIA now include an expanded accelerated approval pathway designed to improve on the historical success this program has had with developing game-changing medicines to treat HIV and AIDS and other cancers, as well as other diseases, and expand its utilization in other disease areas, and a new breakthrough therapy designation designed to get the most promising medicines to patients much more efficiently.

However, while FDASIA included an agreement by the industry to significantly increase user fee funding for the FDA to help support FDA's drug review activities and enable them and these new programs, sequestration has diverted a portion of these industry fees to an escrow account that has no practical purpose for the FDA, industry, or patients. This has severely hindered FDA's ability to fully implement critical provisions of FDASIA that would improve our ability to more effectively develop and deliver innovative medicines to patients. This is the equivalent of our paying our utility bills and then being told we can't access power, lights, or heat.

BIO would like to thank Congress for proposing a 2-year delay in sequestration of user fees in the proposed budget agreement but urges Congress to rectify this irrational and counterintuitive situation by passing the FDA Safety Over Sequestration Act of 2013, sponsored by Representatives Leonard Lance and Anna Eshoo, with broad bipartisan support.

While many new measures have been embraced and encouraged by Dr. Hamburg, Dr. Woodcock, and their colleagues and management at the FDA, it's yet to be seen if the regulatory flexibility afforded by FDASIA is being fully embraced at and across the FDA reviewer level to advance the development of new therapies for unmet medical needs. Releasing user fees from sequestration, successful implementation of FDASIA, and enabling our colleagues at the FDA could significantly improve the ability of our industry to more effectively develop new medicines and get them to patients who need them.

These actions could also help stimulate investment in early stage companies that are working on the next generation of medical discoveries and breakthroughs. The Biotechnology Industry Organization is committed to working with FDA and Congress to ensure these goals are achieved. Thank you for this opportunity, and I look forward to your questions.

Mr. LANKFORD. Thank you.

[Prepared statement of Mr. Hastings follows:]

TESTIMONY OF PAUL J. HASTINGS, CHAIRMAN & CEO,
ONCOMED PHARMACEUTICALS

ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON OVERSIGHT & GOVERNMENT REFORM
SUBCOMMITTEE ON ENERGY POLICY, HEALTH CARE & ENTITLEMENTS

DECEMBER 12, 2013

"FDA CHECK-UP: DRUG DEVELOPMENT AND MANUFACTURING CHALLENGES"

Chairman Lankford and Ranking Member Speier, Members of the Committee, my name is Paul Hastings, Chairman and Chief Executive Officer of OncoMed Pharmaceuticals headquartered in Redwood City, CA. I also serve as Chairman of the Biotechnology Industry Organization (BIO) Emerging Companies Section Governing Board, which represents the smaller, emerging biotechnology companies that often do not yet have a product on the market.

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations – the majority of which are small and emerging companies, with 90% having fewer than 100 employees. BIO members are involved in the research and development of innovative health care, agricultural, industrial, and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better health care, enhanced agriculture, and a cleaner and safer environment.

I have over 27 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: tumor initiating cells, which drive the growth of the 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 these 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 the 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. We currently have five products in clinical development in 13 completed or ongoing clinical

trials, with hundreds of patients having received our experimental therapies, and we are pursuing the discovery of additional novel anti-tumor initiating product candidates.

I would like to thank the Committee for holding this timely and important Congressional hearing. The U.S. biotechnology industry is working on treatments and therapies that have the potential to deliver new solutions to our most pressing health care needs and is a key element of an innovation-driven economy.

I. UNLEASHING THE PROMISE OF BIOTECHNOLOGY TO IMPROVE HUMAN HEALTH

Currently, there are nearly 1,000 biotech drugs and vaccines under development for more than 100 diseases.[1] By harnessing the power of molecular biology and genomics, we have come a long way in turning incurable diseases into treatable diseases, increasing the ability of patients to maintain independent lives, and generally improving the quality of life for many patients suffering from chronic and life-threatening diseases. Improving quality of life, decreasing hospitalizations, and allowing patients to live longer and more independent lives is not only a public health goal – it is a national imperative.

Approximately 60% of individuals between the ages of 50 and 64 have at least one chronic disease and the Baby Boomer population is projected to double the number of individuals that are 65 or older to 71.5 million by 2030.[2] In fact, chronic medical conditions account for more than 75% of total health care spending.[3] If we consider that the projected cost to care for a single chronic disease, Alzheimer's, is projected to increase from $203 billion in 2013 to $1.2 trillion per year in 2050, and that developing a treatment that would delay the onset of Alzheimer's by just five years would reduce that projected increase in cost by $447 billion – it is clear that we need to promote and implement policies that enable the effective development and approval of innovative treatments and therapies.[4, 5]

In addition to the primary mission of developing and providing new medicines and improving the lives of patients, the biopharmaceutical industry is and will be an important sector in a 21st century innovation-driven U.S. economy. In 2011, the U.S. biopharmaceutical sector directly and indirectly supported approximately 3.4 million U.S. jobs and accounted for $789 billion in economic output.[6] However, this is an industry that continues to face intense competition from other countries, as well as increasing research and development costs, regulatory challenges, and a contracted funding environment. While outside the scope of this particular hearing, it is vital to the success of the industry that our nation's policies protect the intellectual property of these

[1] "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Analysis Group January 2013 http://phrma.org/sites/default/files/pdf/2013innovationinthebiopharmaceuticalpipeline-analysisgroupfinal.pdf
[2] CNN Library, "Baby Boomer Generation Fast Facts," November 6, 2013, http://www.cnn.com/2013/11/06/us/baby-boomer-generation-fast-facts/
[3] National Center for Chronic Disease Prevention and Health Promotion, Center for Disease Control, "The Power of Prevention," 2009, http://www.cdc.gov/chronicdisease/pdf/2009-power-of-prevention.pdf
[4] http://www.alz.org/alzheimers_disease_facts_and_figures.asp#quickFacts
[5] http://www.alz.org/documents_custom/trajectory.pdf
[6] Battelle/PhRMA, The Economic Impact of the U.S. Biopharmaceutical Industry, July 2013. http://phrma.org/sites/default/files/pdf/The-Economic-Impact-of-the-US-Biopharmaceutical-Industry.pdf

companies, as any weakening of those protections will have a deleterious impact on the ability to attract the necessary and long-term investment required to research, develop, and ultimately make new medicines available to the public. We also ask Congress to support funding for NIH, which supports the basic research that industry depends on to discover and develop drugs that will benefit the public.

II. BIOTECHNOLOGY INDUSTRY: SIGNS OF RECOVERY, BUT CHALLENGES REMAIN

This year we have seen positive signs that the biotechnology industry is recovering from the economic crisis of 2007 and 2008. There have been 39 biopharmaceutical companies that have gone public this year, including my own company, OncoMed, marking the most active IPO market in a decade.[7] Additionally, in 2012 the FDA approved 39 new molecular entities, the most approvals we had seen in 16 years and up from 35 approvals in 2011.[8,9] CDER has approved 25 new molecular entities so far this year.[10] This number is still higher than the average of 24 drugs per year we saw from 2003-2011.[11] While this is good news, the financial and regulatory environment continues to pose significant challenges to innovative drug and biologic developers.

In 2012 we saw a 15% decrease from 2011 in venture capital dollars invested in the biotechnology industry.[12] The majority of this decrease was seen in first-time financings, which were the lowest they have been since 1995.[13] This is a trend that has continued in 2013. In the first three quarters of 2013, first-time venture deals in biotechnology were the lowest they have been in 17 years.[14] And while the number of first-time financings increased in the third quarter of this year, the overall dollar value decreased 56%.[15] This means that start-up companies, working on the next generation of medicines, are competing for a limited amount of funds from fewer venture capital firms, as well as non-venture funding mechanisms from angel investors, venture philanthropies, and non-traditional equity deals.

The regulatory environment has improved in recent years, but there continues to be a need to improve the efficiency, timeliness, and consistency of the U.S. drug development and evaluation enterprise. The number of drug approvals has increased, yet so too have the research and development costs. According to a 2013 study from Deloitte and Thompson Reuters, which analyzed the 12 largest life science companies' R&D spend,

---

[7] FierceBiotech, "UPDATED: Fresh burst of biotech IPO pitches launches a busy Q4 season," October 21, 2013, http://www.fiercebiotech.com/special-reports/biotech-ipo-frenzy-headed-crack

[8] http://www.ey.com/Publication/vwLUAssets/Beyond_borders/$FILE/Beyond_borders.pdf

[9] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276413.htm

[10] http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm

[11] http://www.fda.gov/downloads/drugs/developmentapprovalprocess/druginnovation/ucm337830.pdf

[12] MoneyTree Report PWC/NVCA Full-year 2012, https://www.pwcmoneytree.com/MTPublic/ns/moneytree/filesource/exhibits/Q4%202012_Full%20Year%202012_MoneyTree_Summary_Report.pdf

[13] MoneyTree Report PWC/NVCA Full-year 2012, https://www.pwcmoneytree.com/MTPublic/ns/moneytree/filesource/exhibits/Q4%202012_Full%20Year%202012_MoneyTree_Summary_Report.pdf

[14] FierceBiotech, "As VC falters, early-stage biotechs look elsewhere for cash," October 21, 2013 http://www.fiercebiotech.com/story/vc-falters-early-stage-biotechs-look-elsewhere-cash/2013-10-21

[15] FierceBiotech, "As VC falters, early-stage biotechs look elsewhere for cash," October 21, 2013 http://www.fiercebiotech.com/story/vc-falters-early-stage-biotechs-look-elsewhere-cash/2013-10-21

the cost of developing a single drug from discovery to the market increased 18% from $1.1 billion in 2010 to $1.3 billion in 2013.[16] The average annual R&D spend for a biopharmaceutical company (both small and large) in 2012 was $54 million, up from $48 million in 2010.[17]

The rising costs of drug development and the resulting decrease in R&D efficiency are complex, multi-faceted problems, but increased cost, complexity, and duration of clinical trials are widely accepted to be critical contributing factors.[18] A study conducted by the Manhattan Institute found that as much as 90% of the development costs for many drugs ultimately approved by the FDA were incurred during Phase III clinical trials.[19]

Additionally, the duration of the clinical phase of approvals for biopharmaceuticals has steadily increased from an average of 4.6 years in the early 1990s to 7.1 years in 2005-2009.[20] Concomitant with the increase in clinical trial duration are the rising protocol complexities and requirements. In fact, by the early 2000s the average clinical trial required enrollment of 2-3 times more patients than comparable trials in the previous decade.[21] Median unique procedures per protocol increased from 105.9 in 2000-2003 to 166 in 2008-2011, an increase of more than 57% in an 11-year window.[22]

And lastly, almost 60% of all clinical trial protocols are amended at some point during the trial, taking more than 60 days to identify and correct, with one-third of those amendments being avoidable.[23]

III. ADVANCING A REGULATORY ENVIRONMENT THAT FOSTERS BIOMEDICAL INNOVATION

While developing medicines that treat serious and life-threatening diseases is a complicated and high-risk endeavor, the importance of increasing the efficiency and effectiveness of the research and development process is clear. To that end, the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) focused on enabling FDA to be an agency that advances innovation by implementing review processes designed to promote the effective review of innovative products in a timely manner and that promotes a consistent, science-based decision-making process reflective of patient needs. It is yet to be seen if the regulatory flexibility afforded by FDASIA is being fully embraced at the FDA reviewer level to advance the development of new therapies for

[16] Deloitte, Thompson Reuters, "Measuring the Return From Pharmaceutical Innovation 2013," http://www.deloitte.com/assets/Dcom-UnitedKingdom/Local%20Assets/Documents/Industries/Manufacturing/uk-manufacturing-measuring-the-return-from-pharmaceutical-innovation-2013v1.pdf

[17] John Carroll, "Biotech R&D spending roars ahead as Big Pharma grimly holds the line," FierceBiotech, 12 September 2013, http://www.fiercebiotech.com/story/biotech-rd-spending-roars-ahead-big-pharma-grimly-holds-line/2013-09-12

[18] See, Scannell JW, Blanckley A, Boldon H, and Warrington B, "Diagnosing the decline in pharmaceutical R&D efficiency," Nature Reviews: Drug Discovery 11, 191-200 (2012) See also, Ruffolo RR, "Why has R&D productivity declined in the pharmaceutical industry?" Expert Opin. Drug Disc 1(2).99-102 (2006).

[19] Avik R, "The Stifling Cost of Lengthy Clinical Drug Trials," Manhattan Institute, 2012, http://www.manhattan-institute.org/pdf/fda_05.pdf.

[20] Allison M, "Reinventing clinical trials," Nature Biotechnology 30(1) 41-49 (2012).

[21] Vogelson CT, "We are the world?" Modern Drug Discovery 4(6) 36-38, 40, 42 (2001).

[22] Allison M, "Reinventing clinical trials," Nature Biotechnology 30(1) 41-49 (2012).

[23] Tufts Center for the Study of Drug Development, "Majority of Clinical Trial Protocols are Amended, But One-Third of Those Changes Are Avoidable," September 13, 2011, http://csdd.tufts.edu/news/complete_story/pr_ir_sep-oct_2011.

unmet medical needs. and significant challenges must be overcome in order to fully implement FDASIA in the spirit Congress intended.

A. Eliminate the Sequestration of Industry User Fees

Under FDASIA, which also reauthorized the Prescription Drug User Fee Act (PDUFA V), industry agreed to significant increases in user fee funding for the FDA to help support FDA's drug review activities and advance regulatory science. However, as a result of budget sequestration, a portion of the user fees paid by private industry are being diverted and held in an "escrow" account that has no practical purpose for FDA, industry, or patients. This has severely hindered FDA's ability to add the capacity and infrastructure necessary to implement FDASIA and meet its commitments under PDUFA V. To make matters worse, the $82 million in user fee funding that was sequestered in FY 2013 cannot be released to FDA without forcing corresponding cuts elsewhere in the FDA budget.

BIO urges Congress to rectify this counter-productive situation by passing the Food and Drug Administration Safety Over Sequestration (SOS) Act of 2013 (H.R. 2725), sponsored by Representatives Leonard Lance (R-NJ) and Anna Eshoo (D-CA) with broad bipartisan support. In addition to clarifying that sequestration should not apply to industry-paid user fees, we encourage Congress to continue to support FDA through the annual appropriations process.

B. Expedite Drug Development for Serious and Life-Threatening Diseases

FDASIA also encourages FDA to expedite the development of modern medicines for serious and life-threatening conditions by expanding the existing Accelerated Approval pathway and enacting a new Breakthrough Therapy Designation process.

The Accelerated Approval pathway has historically been very successful in accelerating the development, review, and availability of innovative medicines to treat HIV/AIDS and cancer. Congress recognized that modern drug development has changed substantially since the initial implementation of Accelerated Approval in 1992 and that the pathway should be expanded to additional diseases and better leverage recent scientific improvements. Specifically, the Congressional findings included in FDASIA provided a detailed description of what Congress intends to achieve by expanding Accelerated Approval, and what it expects FDA to accomplish when applying these expanded authorities:

> *"FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in shorter clinical trials for*

the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for approval of drugs."

In August of 2013, FDA released *Draft Guidance for Industry on Expedited Programs for Serious Conditions—Drugs and Biologics*. While this guidance is helpful in explaining the characteristics and features of FDA's four expedited approval pathways, greater clarity in several areas is still needed. In particular, FDA should establish a systematic framework and evidentiary criteria for discussing Accelerated Approval and endpoint selection earlier in drug development, which would foster predictability and stimulate greater Sponsor confidence in the process. Additionally, the guidance inadequately addresses the unique issues associated with rare diseases under Accelerated Approval, which should be the focus of future guidance. BIO is closely evaluating the modernization of the program to track how it is being utilized in additional therapeutic areas by leveraging novel surrogate and intermediate clinical endpoints.

The new Breakthrough Therapy designation program is one of the most publicly discussed provisions of FDASIA. The criteria for this designation require that the drug may be a substantial improvement over existing therapies, based on preliminary clinical evidence from one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The benefit of this program is increased interactions with FDA in order to expedite the development and review process. As of December 10, 2013, the FDA website listed a total of 121 requests for a Breakthrough designation with 34 requests granted, 61 requests denied, and three breakthrough-designated products approved.[24] A majority of the designations thus far have been for products in the Phase III stage of development.[25]

While clearly the Breakthrough Therapy program has been successful in generating interest and granting several requests, BIO is in the process of tracking the success of this program and analyzing specifically how this program is expediting the development and review of these drugs, such as increased interactions with senior FDA staff and utilization of modern tools and approaches such as adaptive clinical trials to clinical development.

Additionally, it is important that non-clinical aspects of drug development also be expedited to keep pace with an accelerated clinical program. For example, we have urged FDA to adopt a risk-based, life-cycle approach to the review of Chemistry, Manufacturing, and Controls (CMC) data and inspectional activities. Additionally, for Breakthrough Therapies and expedited program products with companion diagnostics, Center for Devices and Radiological Health (CDRH) senior staff should be involved in cross-disciplinary engagement during drug development.

C. Advance Scientific Dialogue and Interactive FDA-Sponsor Communication

[24] Friends of Cancer Research, http://www.focr.org/breakthrough-therapies.
[25] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.htm

There were several provisions in PDUFA V and FDASIA designed to improve the opportunities for biopharmaceutical companies, patients, and FDA to engage in timely, scientific dialogue in order to facilitate efficient and effective drug development programs. For example, a centerpiece of PDUFA V is a new review program for New Molecular Entities intended to reduce unnecessary delays in the review process by improving FDA-Sponsor communication and transparency.

To improve communication during the drug development phase, PDUFA V also created an Enhanced Communications Liaison Office tasked with two primary objectives: facilitate general, and, in some cases, specific interactions with Sponsors and FDA review teams; and develop training for CDER staff and communication of best practices to the Sponsor community. Unfortunately, due to sequestration, FDA has been unable to fully staff this office and thus is likely limited in its ability to conduct training and communication of best practices. As it is a new program, BIO will be working with the FDA to educate the biotechnology community about this new office.

BIO recently completed a survey of BIO member companies focusing on communications between FDA and companies during the drug development process. We are in the process of completing our analysis and will be releasing our findings to the public in the coming weeks. In general, we found that companies believe that communications with FDA have improved since 2007. However, when we asked more specific questions based on type of application (NME vs. BLA), type of review (Priority, Fast Track, Accelerated Approval, Breakthrough Therapy), type of communication (formal vs. informal), and, most importantly, the review division, the level of satisfaction with communications varied significantly. Additionally, while conditions have been improving and culture shifting happening, a significant amount of companies cited miscommunication with FDA as a major factor in delays of one or more products in the past.

D. Incorporate Patient Perspectives when Balancing Benefits and Risks

FDASIA and PDUFA V also take unprecedented steps to incorporate the patient voice into FDA regulatory decisions. By definition, all prescription drug products offer both therapeutic benefits and potential adverse events. The FDA drug review process must be grounded in a careful evaluation and balance of these benefits and risks made in the broader context of disease severity, patient perspectives, and the body of available scientific evidence. Therefore, it is essential for the public to understand that safety is not an absolute; rather, the acceptability of the safety of a drug is assessed in the context of whether its benefits outweigh its risks.

FDA is taking several important steps under PDUFA V to incorporate greater patient involvement, transparency, and consistency in this benefit-risk assessment. The Patient-Focused Drug Development initiative will carefully assess patient perspectives in 20 therapeutic areas to better understand the patient community's views on the severity of the underlying condition, current treatment options, potential benefits, and anticipated risks. This information will help to inform FDA's proposed *Structured Approach to*

Benefit-Risk Assessment in Drug Regulatory Decision Making, a grid-style framework released in May that will be integrated into FDA's approval decisions over the course of PDUFA V. BIO supports FDA's continuing efforts to enhance the clarity of this complex and critical process of benefit-risk assessment, both internally and for the public, throughout the lifecycle of drug evaluation, and will continue to work with FDA on this important issue.

Additionally, there are provisions in PDUFA V designed to increase patient participation in medical product discussions and better enable FDA to engage with external experts on the development and review of targeted therapies and drugs designed to treat rare diseases. BIO will be tracking these activities to determine if they are being successfully implemented.

IV. CONCLUSION

Ours is an industry that is working to provide better medicines that can improve the lives of patients and bring new solutions to our country's critical health care needs. There have been many positive indicators over the past two years demonstrating that the biotechnology industry is rebounding, but significant challenges on both the financial and regulatory fronts remain. The key provisions of PDUFA V and FDASIA discussed in this testimony, if implemented successfully, could significantly improve the efficiency and effectiveness of the clinical development of innovative drugs by increasing scientific dialogue and enabling the utilization of modern tools and approaches to drug development. BIO is committed to working with FDA and Congress to ensure these goals are achieved.

Mr. LANKFORD. I recognize myself for the first round of questions, and we will go through the questions as we can, and we're still not called for votes yet. You'll hear the bells and the lights and everything else go off when that happens, and we'll have a little bit of time to be able to move from there.

Let me ask a couple of quick questions on this. I think I am going to work in reverse.

Mr. Hastings, you talk about the venture capital being the lowest it's been since 1995 on that. Do you have a gut feeling on why that is, why is the venture capital suddenly drying up when we have a record number of IPOs happening?

Mr. HASTINGS. It's a cycle. So, while now the public markets are doing well, the venture capitalists who have fueled all these early stage companies, had fueled them for so many years before the IPO market was open, that they drained themselves of a lot of their resources. They weren't able to provide the returns to their investors.

So when the public markets opened up and the public investors embraced the public markets, everybody on the public side did really well, but there's a lot of catchup that's being done now by the venture capitalists. So they now look like they haven't provided their returns over the course of the 10 or so years prior to the public market opening up that their investors required, so those same investors invest in the public markets as well.

Mr. LANKFORD. Okay. So, what's your gut on how quickly that turns around? You've tracked this for a while, it sounds like.

Yes, I track this constantly. It's going to take a few years. So once the public markets continue to reward the venture capitalists for delivering these companies. So now, by the way, all those private investors, all the investors that are in OncoMed Pharmaceuticals on the private side, they won't be able to cash out until the lockup period is over, and even then they have to see the company do well on the public markets in order for them to get their exit. All that takes a little bit of time, probably a couple of years before people start reinvesting now in the early stage venture financing.

Mr. LANKFORD. Mr. Huber and Dr. Gottlieb, they are both recommending different ways of doing some of the trials and processes and things, and I want to be able to get to both of those in a moment.

Mr. Hastings, though, what is the most expensive part or the most difficult or cumbersome part of the clinical trial or the R&D or approval process—you can broaden that as broad as you need to make it—of getting the actual drug through the research to development. What is the pricey, cumbersome part of that?

Mr. HASTINGS. I'll give you one example. There are many places along the development cascade where it gets expensive. In the early stages, for young companies, it gets expensive even in the Phase I or Phase II portion of the trial, particularly in Phase I when there is a lot of communication back and forth with regard to safety of the drug. And one of the areas that we've been working on is this informal communication where rather than having a letter-writing campaign back and forth, there is more dialogue between the reviewer and the company. Saving a month on that communication process could save a small company, and there has

been a lot of effort from both the FDA and the industry to work on that together. That's been an example of something that's improved dramatically.

Mr. LANKFORD. Okay.

Mr. Huber, let me ask you a quick question on it as well. The statement is interesting to me, the molecular profiles. How would that work for them, and expand that somewhat is what I'm saying, as far as the FDA, because that's obviously a completely different paradigm than what they are currently doing on it. So how would that function in real life for them.

Mr. HUBER. I was having dinner last night with a prominent oncologist from MD Anderson in Houston, and he said the real clinical trials begin after the drug is licensed. Now, I will emphasize, first of all, that cancer a very distinctive disease. It's wildly dynamic. The cells are constantly mutating. And by the time a tumor grows at all, you don't have one disease in there. You have a whole bunch. That's what makes it so hard to attack it and why so often drug cocktails are used and so on.

But in any event, the fact is that oncology has been the beneficiary of the accelerated approval quite often as one of two diseases. The other are HIV infections have gotten this. And the main advantage of accelerated approval in my book is that it releases oncologists to practice and to work out what the patient needs step by step. The answer is you begin prescribing drugs. These are targeted drugs increasingly that target one molecular receptor. And you can track very early on with modern diagnostic tools what's going, not up at the clinical level, which takes quite a lot longer to surface, but much deeper down inside the patient's body. I mean, it can be things that are not that much deeper down, like tumor shrinkage or so on, but you can also be looking at densities of cancer cells being shed from the tumor and circulating in the patient's blood. The FDA calls these surrogate end points or intermediate end points.

And you get feedback much faster. If you begin getting that, you can early on begin saying, look, we begin seeing different patterns of response. And it gets eye glazing when you talk about the statistics, but the fact is the statisticians know how to handle multidimensional trials where you're exploring multiple factors as you go. We have mechanistic understandings of why certain receptors should be accelerating the progress of the disease, or if you inhibit them, slowing it down. You study these things and you adapt.

I could give you one vivid example, if you will allow me. Memorial Sloan-Kettering in New York some years ago launched a trial using a kidney cancer drug to treat bladder cancer. It was an abysmal failure. Almost everybody that was treated with this drug did not respond well. However, one 73-year old woman responded extraordinarily well. In fact, 2 years later she is completely cancer free.

Now, in the past, and certainly if this were all within the confines of one trial, you'd ignore that. I mean, one patient does not license a drug. Memorial Sloan-Kettering doctors went in and they searched for the biomarkers associated with cancer, they explain this, they couldn't find one. They then did a whole tumor sequence. They just looked for everything that was in this one patient's

tumor and they found the receptor that was being targeted by the kidney cancer drug. One patient in that group. It turns out about 8 percent of bladder cancers have this receptor. And so then they launched a new trial.

That is a slow motion adaptive trial. You learn something and then you change. You can do that internal to a single trial if you are working hard at it, but you have to do things that the FDA doesn't allow. You actually have to be saying these are the people who are being treated with the drug. Let's look at what's the details. I mean, if you have toxicity problems and metabolism problems, same thing, we've got biomarkers for livers that metabolize things well or badly. You can look for them, and you can then converge on treatment protocols that work better.

Mr. LANKFORD. Okay. We will follow up with FDA in the days ahead. Let me yield to Ms. Speier for her questions. They have called votes now. We have around 11 minutes or so on the vote count. I think what we will do is take Ms. Speier's questions, then we'll take a quick recess. We'll have three different votes that are happening, and then we'll come back and we'll go at you with some more questions. Okay with that? So we get a quick break.

Ms. Speier.

Ms. SPEIER. Mr. Chairman, thank you.

And thank you all for your testimony.

The sequestration has really cut the limbs off of NIH funding to the tune of about $1.2 billion a year. From your perspectives, each of you, I want to know how that affects your ability to do your science.

Mr. HASTINGS. Well, that's a wide open question. So to me it goes all the way back to what and how we want to be perceived as a Nation, right? If we're not getting behind STEM education from kindergarten through grade 12, all the way up through our university system and the NIH and getting behind innovation, it's not then going to leave the technology transfer offices of our universities or the halls of the NIH and come with a license to an entrepreneur who then can develop that drug.

So it's a little hard to pinpoint exactly what sequestration does with the NIH in terms of what it might bring to our industry other than to say it's huge, very broadly. You can't really look at any one drug that came out recently and say that wouldn't have happened under sequestration. I can't think of one off the top of my head. But that's the kind of thing that comes out, the thought process, the focus on innovation. And without that and without those jobs for those people to do those things, they are going to go to other places.

Dr. GOTTLIEB. I'm less focused on NIH, just to pick up on what Mr. Hastings said about FDA. I think the sequestration has been problematic for the FDA insofar as what I see, and I wrote an article about this. A lot of the sequestered funds were funds that would have been targeted towards the areas of new regulatory policymaking, the things that were embedded in PDUFA, in particular, where FDA was going to advance or try to advance some of the scientific principles that we're talking about here today.

There were unfilled positions at the time that the sequester was imposed that will continue to probably go unfilled, but a large

chunk of the money that was taken out was taken out of the programs of new regulatory policymaking.

Ms. SPEIER. Dr. Gottlieb, you suggest that there is a certain amount of risk that we should just be willing to accept, and I'd like to know what you think that percentage of risk should be in terms of the FDA process.

Dr. GOTTLIEB. Yeah, I'm not sure you can, you know, articulate it in terms of a percentage. There is obviously a certain level of palpable risk we are always willing to tolerate, and it adjusts based on what the clinical circumstances are. And if you are facing a grave disorder and you don't have other options, you're willing to embrace quite a bit of risk.

I cited in my written testimony the case of mucopolyscaccharide diseases, diseases that are inborn, there's a metabolism where children are born, these are largely fatal diseases, they are terribly debilitating. I think families who have children with those disorders would be willing to embrace a large degree of uncertainty around a new drug, but in many circumstances say they are not able to because the clinical trial requirements are getting more difficult.

Remember, I'm talking here about, in particular, risk around the benefit, not the safety. I'm talking about situations where the magnitude of the benefit that's observed in a clinical trial can't be firmly established because the statistical rigor hasn't reached a high enough degree of, you know, suredness, if you will. So you see a certain magnitude of benefit and you have to probability address that and say, well, since it wasn't a large trial and there were these flaws in the trial, we can be 70 percent certain that it's going to deliver that 40 percent benefit. That's the situation.

Ms. SPEIER. But my understanding is that—and I've actually accessed compassionate use for the FDA for a number of constituents from time to time—my understanding has been that they have been very willing to allow the drugs to be used for compassionate use, which typically you would say in a case of a young child would be embraced. So do you find that at all being restricted in its availability?

Dr. GOTTLIEB. No. I think FDA has been very flexible when it comes to individual patient INDs, but keep in mind there is two challenges there. One is that only certain physicians are going to be able to navigate that process in collaboration with their patients. It takes a certain level of sophistication and resources to work through that process. And that's not a criticism of FDA. It's just a hard process. So it is putting at a disadvantage a whole lot of patients who will never have access to that.

The other thing is that if that's what we're dependent upon to make therapeutics available in these kinds of, you know, sort of grave situations, situations where there's a real unmet need, the framework, the sort of framework on the industry side won't be in place to make the drug broadly available. In today's environment, especially with a lot of biopharmaceuticals, the manufacturing isn't available until the time of approval.

Ms. SPEIER. All right. Thank you.

Dr GOTTLIEB. And so we are dependent upon that approval.

Ms. SPEIER. I am going to try to get one more question to Mr. Hastings.

Dr GOTTLIEB. All right.

Ms. SPEIER. Mr. Hastings, if there is one thing that you would recommend that we do to assist the emerging BIO companies to be successful in their interactions with the FDA, what would that be?

Mr. HASTINGS. Enable the FDA, through some of the policies that we've put forth, some of the breakthrough therapeutic areas, which would allow us to, with appropriate risk, also see the reward for these patients. So taking some of the risk that Dr. Gottlieb was just talking about. There are certain diseases, like cancer, there are other diseases, chronic diseases, chronic inflammatory diseases where patients recognize some of the risks associated with therapies. And so enabling some of these breakthrough areas where we can get drugs approved quickly, safely to patients faster is the way to go, and there's a number of those initiatives that I outlined in my testimony.

Ms. SPEIER. Thank you. My time is up.

Mr. LANKFORD. Actually all of our time is up for this point. I would like to take a recess for about 20 minutes. We have three votes in the series. Each one of the votes is about 5 minutes apiece in between. We'll go over and do the votes, we'll come right back, and then we'll jump right back into pummeling you with some more questions if that's all right with you. So let's take a short recess.

[recess.]

Mr. LANKFORD. The committee will come back to order. I apologize for the delay on that one. We should not have votes again until about 4:30 or so, so that will be in the middle of the time period that we will have our FDA witness, so we will still have her on the stand at least until 10 I would assume tonight. Thanks for the delay on that. I would like to recognize Dr. Gosar for the next line of questioning.

Mr. GOSAR. Thank you very much. Mr. Hastings, how much would you say the typical biopharmaceutical company spends annually on drug research and development?

Mr. HASTINGS. It depends on the size of the company. But an innovative company, our company has 90 employees, roughly $55 million to $60 million a year. You could spend, companies with 400 or 500 employees with multiple drugs in the clinic, you could spend $1 billion a year in R&D.

Mr. GOSAR. And has that gone up over the years?

Mr. HASTINGS. Yes.

Mr. GOSAR. And what are driving those factors of raising those costs, R&D costs?

Mr. HASTINGS. So in certain instances, it is what trial designs have turned into, the numbers of patients one needs to go into clinical trials, the amount of time it takes to file an I&D and get your first patient treated on a therapy, to enrolling patients in Phase I, II, and III clinical trials, not only in the U.S., but also globally. So it is a very large undertaking to do, even randomized Phase II clinical trials today. I call the randomized Phase II clinical trials today the old randomized Phase III trials of the past. They are roughly the same size as Phase III's used to be.

Mr. GOSAR. Got you. Mr. Huber, in his written remarks Mr. Hastings cites a 2012 Manhattan Institute study that found as

much as 90 percent of the development cost for many drugs approved by the FDA are incurred during Phase III clinical trials. Are you aware of this study?

Mr. HUBER. I do definitely remember seeing it, but those numbers are not of my origin and I cannot speak further about them.

Mr. GOSAR. So what would be your thoughts on those findings?

Mr. HUBER. Clinical trials and certainly the time value of money are a very large component of the cost of getting a drug to market. I could not be any more specific than that.

Mr. GOSAR. Got you. I am going to stay with you, Mr. Huber. How would you define a good clinical trial?

Mr. HUBER. A good clinical trial is one that if the drug is good, ends up with enough guidance on prescription protocols that future doctors with high confidence prescribe the drug in ways that are likely to do more good than harm. Likewise, I might add one that rejects drugs that aren't going to be able to meet that criterion.

Mr. GOSAR. So do you think that randomized control trials are out-of-date?

Mr. HUBER. Well, yes, I think they are. Yes. Yes is the answer. Not—I mean, there are some exceptions to every general statement, but, yes, they are not making full use of the tools we should be using.

Mr. GOSAR. So what steps would you use to update those?

Mr. HUBER. Well, President Obama's Council of Scientific Advisors on Science and Technology issued a report last year that I cite in my written testimony. It is a pretty good starting point. I think things should go further. Others will be testifying before you today saying they have already gone further, and if they are, terrific, and the faster they move, the better.

I do know that we should have been heading down this road a decade ago and high officials with excellent qualifications who I greatly admire who were sketching out what needs to be done to develop multi-dimensional data on how drugs operate. If it is happening, it sure is happening slowly.

Mr. GOSAR. Very slowly. Dr. Gottlieb, can you define the clinical end point that the FDA requires in its trials?

Dr. GOTTLIEB. Well, clinical end point is an end point. You know, the simple way to define it is it is something that can be experienced by a patient, so some kind of measure of clinical improvement that is going to be of benefit that the patient can appreciate. So the ability to breath better, a reduction in pain, certainly living longer, changes in morbidity and mortality, as opposed to a surrogate end point, which is an interim measure that presumably could correlate with a clinical outcome but isn't something that is perceivable by the patient. It is a marker.

Mr. GOSAR. Would you enhance that or enlarge that from your personal experience?

Dr. GOTTLIEB. Enhance the use of surrogate measures? Certainly. I mean, FDA, I think, over a period of time, made wider use of surrogate measures, particularly in oncology, things like tumor shrinkage. I think the agency's experience with that was mixed insofar as some of the surrogates that they relied on didn't necessarily correlate with clinical benefit when they did the larger

studies, and so it left somewhat of an unhappy experience, and the agency became more skeptical of using surrogates generally.

So I think where I would try to advance this is in trying to create some kind of pathway to better validate these surrogates more quickly. There is a lot of surrogates that make a whole lot of clinical sense, there is good theoretical reasons why they should correlate with a clinical benefit, but FDA is unwilling to rely on them or reluctant to rely on them because nobody has demonstrated that, and it is very hard to demonstrate that until you actually do the very long trial in the context of a drug, and by then you have sort of, you know, put a drug through an enormous clinical development program.

Mr. GOSAR. Do you see any interim type of facility or group that could actually mitigate that?

Dr. GOTTLIEB. Well, you know, people always talk about having independent entities like the NIH invest in trials just for the purposes of validating surrogates. You know, I think the FDA has flexibility, has a lot of authorities that it could use to, you know, take some risk around the uncertainty that pervades these surrogate measures to allow drug trials to go forward.

You know, one of the examples that I cited recently was polycystic kidney disease where it is a genetic disease. You inherit it over the course of a lifetime. You develop cysts in your kidneys and eventually your kidneys fail and you go on to end stage renal disease. The question is could a reduction in the accumulation of these cysts be a valid surrogate for a clinical trial?

FDA has been reluctant to accept cyst reduction or reduction in the propagation of cysts as a valid surrogate in the past, although it makes a whole lot of theoretical sense that if you can reduce the accumulation of these cysts, obviously it is going to, you know, prolong the length that your kidneys function.

These are the kinds of things I think we need to look for these opportunities where there are these surrogates that make a whole lot of clinical sense and theoretical sense and either take the risk of allowing the trials to go forward on the basis of them or find a way to validate them more quickly.

Mr. GOSAR. You kind of breached my next question. How important is it for the FDA to use its accumulating experience when conducting clinical trials as outlined in your written remarks?

Dr. GOTTLIEB. Right. And I cite the example of mucopolysaccharide diseases where if you look at—this is a sort of cluster of related disorders, but they are each treated by distinct drugs. Very rare. Some of them only have hundreds of afflicted patients. If you look at the initial drug that was approved in this broader class, it was approved on the basis of, I think, about a 20-patient open label non-randomized study, probably as least rigorous as you can conceive of. And then there were subsequent approvals for a number of other drugs and with each approval, the theoretical basis for understanding why a replacement enzyme would work in one of these diseases was more firmly established, yet with each subsequent approval, the clinical trial requirements got harder and not less. And you can't argue that it was a function of the fact that there was available therapy because there wasn't.

Each disease was distinct, so the subsequent therapies were only going to treat one of these diseases.

I think those are situations where when the agency has knowledge that it is accumulating in a clinical setting like that, it needs to find a way to make wider use of that so that it can lower barriers to entry as it gains more knowledge in an area and not raise them.

Mr. GOSAR. Got you. Thank you, Chairman.

Mr. LANKFORD. Ms. Duckworth.

Ms. DUCKWORTH. Thank you, Mr. Chairman.

Mr. Hastings, thank you for appearing here today and offering your testimony. I want to touch on a few points you highlighted where you speak to FDA's regulatory environment has improved in recent years, but you noted that there are additional ways to improve efficiency, timeliness and consistency of drug evaluation. I am specifically interested in how the FDA communicates with you and your members.

I understand that according to your internal survey, the majority of your member companies believe that communications with FDA, while it has improved, it has really been affected by sequestration, especially recently. Have your members, Mr. Hastings, expressed disappointment that the Industry Liaison Office that was anticipated by PDUFA V has yet to be fully staffed because of sequestration?

Mr. HASTINGS. So, yes. The Office of Enhanced Communication, I am paraphrasing it, was an attempt to create an office whereby folks could call in if there were communications issues. But one of the things I was just sharing with Dr. Woodcock earlier is that the whole intention of the enhanced communication provision we had in PDUFA was for a cultural shift to occur inside the agency such that we actually wouldn't need that office to communicate with our reviewers.

What has interestingly happened and could be a side effect of sequestration, there is only one person in that office that I know of right now versus the five or six that were going to be there, but some of the communication between reviewers and companies has gotten better. And when you look at the survey, in areas like oncology, which is the area that we are studying, that communication has gotten markedly better. So rather than writing letters back and forth and taking 30 days each time a letter gets written to have the other person have the opportunity to respond, a simple phone call takes place. So a cultural shift has been very beneficial.

The issue that we have right now is we would like to that very positive example and make it extend across all the division and all the reviewers so that each company, no matter what therapeutic area they are, is benefiting from that same enhanced communication. Now, would that office, the Office of Enhanced Communications, had it been staffed up without sequestration, would that have helped? It probably would have in some of those other areas.

So I think the main beef we have about sequestration, again, is that these are fees that we are paying on top of what we pay in taxes and everything else, and we are paying those fees in order to enable. And like I mentioned, it is a little bit like paying your electric bill and then being told you can't have power.

Ms. DUCKWORTH. No, the power is there. You are just not allowed to access it.

Mr. HASTINGS. Right. But I think—and we have been working on this for many, many years now, enhanced communications, and we are seeing some good progress. So I don't want to pin this all on, well, it is that one office that is going to solve this issue. It is more a reviewer cultural issue. And I will say for the Office of Oncology, there is an openness to communication. Now, again, what is going to help them communicate more openly with us is that they are effectively staffed, they are effectively funded, so they actually have time to pick up the phone and have a conversation with us.

Ms. DUCKWORTH. So I am just a teeny bit confused. So you said that office should be staffed at—should have four or five people right now only has one because FDA can't staff it up due to sequestration. But you are saying just that one person is more responsive. Or are you saying because they are not there you are just talking directly to the reviewer and not going through the office?

Mr. HASTINGS. What I am saying is it is great to have that office and that office is going to be helpful, but the whole concept was to have open communication with reviewers which are not in that office.

Ms. DUCKWORTH. Okay. But that is happening now and that has improved?

Mr. HASTINGS. Right. So the mere fact that we are paying attention to the issue on both sides has made the issue better, right?

Ms. DUCKWORTH. Right.

Mr. HASTINGS. And so the fact that—it would be great for the office to be staffed because I think in general being staffed appropriately is going to help, but equally important as that office are individual reviewers in individual divisions having good communications with sponsor companies.

Ms. DUCKWORTH. Are there any fears that if that office staffs up completely, there will be another layer of bureaucracy and that the communications directly with the reviewers will stop because people will feel like they have to go through that office?

Mr. HASTINGS. No.

Ms. DUCKWORTH. No fears of that?

Mr. HASTINGS. Absolutely not. No. I mean, companies don't work that way. You have a relationship with your reviewer and you have communication with that reviewer. If a hiccup should occur, there are a number of ways one can help to remedy that, including talking to that office about ways to enhance the communication.

Ms. DUCKWORTH. Great. Thank you very much. I yield back, Mr. Chairman.

Mr. LANKFORD. Thank you. Mr. Meehan.

Mr. MEEHAN. Thank you, Mr. Chairman, and I want to thank this very distinguished panel for taking your time and giving us your expertise in this area. I represent an area in which there are a higher degree than normal of businesses associated with bio and technology and others and have actually tried to work with some of my constituents as we have negotiated the process of dealing with the agencies, and I also worked as a prosecutor acting on behalf of the agencies at certain times.

So I have seen it from both sides. But if I was to look from 500 feet, there is just a tremendous frustration with the inability to have people make decisions, and I am not sure that I understand exactly why that is. What I see, frequently, is the process being used as a mechanism to avoid decisionmaking. And I can appreciate that if a wrong decision is made, there can be implications. But the very process we have is designed to somehow negotiate that fine area.

My experience, in a number of cases, was the concern of clients, when I say clients, I mean constituents, who were afraid to be too aggressive in dealing with the FDA for the very fear that what would happen is now we will be further pushed back in their efforts. And every time a new order is made for a new trial, you are implicating potentially millions of dollars and longer periods of time. So why does it take so much time to make decisions?

And I will conclude my questions with what I would find would be these 30-day periods, Mr. Hastings, you are talking about the communication, no communications would take place. There would be substantial amounts of information put together by very qualified people, the best in the business, in the form of making the case. And on the 29th day, they would get another letter asking for more information. So it was almost like every time the clock would reach the moment, something else would be put into place, the time would toll and there would be more requests, until ultimately you got to a point there was a decision-maker and somebody would say you know, what you are right, and a few times we broke through. But I am struggling with this problem. And I want to see both sides. But you are out there too. What do you see? What is the solution?

Dr. Gottlieb, your written testimony speaks to, I think what you said was a failure for people to—you know the language—the fear of uncertainty pervading. So you understand my questions. Maybe you could each in order respond to my concerns and tell me what you think.

Dr. GOTTLIEB. Well, I think generally there is a lack of appreciation for the time and cost of capital inside FDA, and it is probably not something you would expect them to be very cognizant of. But there is a significant time—cost to time when you are running a development program, even more so than getting advice back from the FDA that you have to run a bigger clinical trial. That can be funded and financed if you are a biotech company, but the time itself is a lot of lost capital.

And the cycling has always been a problem. The multiple cycles has always been a problem. In FDA, there has been over time various efforts to try to address multiple cycle reviews but it is a significant problem.

I would argue the process isn't just used to avoid decisions. I think the process is used to try to tee up easy decisions. From my perspective, the reviewers in the early development stages of a drug program have a lot of autonomy or a fair measure of autonomy to prescribe what they think the clinical trial requirements should be to the companies. And when the companies get advice back from the medical reviewer they are very reluctant to challenge it in many cases. They follow it.

So if you are a medical reviewer and you know you are going to be ultimately responsible for making an approval decision or a decision to reject the drug, what you want is very clear evidence to make that decision. And so if you have discretion, you could prescribe a very rigorous clinical trial that is going to lead you to a place where you are ultimately are going to have very clear evidence. But there is a significant cost to that.

So I think the process is used to try to make easier decision-making and that is what—and that is what ends up delaying the development programs.

Mr. MEEHAN. Let me ask the other panelists to respond to sort of the sentiments that I expressed. Mr. Huber.

Mr. HUBER. Well, I would like to try answering from a slightly different perspective. In 1981, or 1982 it was, that HIV surfaced as AIDS, people hadn't yet identified the virus, it was a real sense of panic. I arrived in Washington right around that time and there was a palpable sense of, gee, something really terrible is happening once people realized what is going on.

In the late '80s as AZT emerged and through the 1990s, the FDA was remarkably agile and willing to bend its rules. It carved—the accelerated approval rule was spawned during that time. They began doing treatment INDs during that period, basically a parallel track of actually prescribing the drugs through hospitals and clinics and so on to make what was available, and there wasn't that much available, broadly available.

It is astonishing what was accomplished during that period of a substantial number of drugs to treat the secondary effects of HIV, the AIDS-related disorders, and then a whole series of HIV drugs. We needed a whole bunch because the virus is so nimble you have to attack it from multiple points to subdue it. And also a number of cancer drugs were also the beneficiaries during that decade.

And I think anybody who looks retrospectively at this believes that—you know, medicine was really advancing very well. We accomplished fantastic stuff. There was—despite talk of the biases of one side or the other, there was really quite a bipartisan coalition to do this, and we beat what was thought to be and what was, in fact, an extraordinarily difficult virus.

You know, it is possible to make decisions fast in this city when people are really sufficiently united and scared. And the President's own, the PCAST report I mentioned earlier, by all accounts the accelerated approval process overall, which does what it says, it is a conditional approval, but it does approve drugs much faster, has had—I think very few people think it has done anything other than more good than harm, okay? You can move these things quickly if you want to and you can get, I won't say invariably good results, but many more good results than bad ones.

Mr. MEEHAN. Thank you. Mr. Hastings.

Mr. HASTINGS. I would like to first speak to the fear of retribution comment you made earlier. If I was fearful of retribution, I wouldn't be sitting here, I have to say.

Mr. MEEHAN. Was it a fair comment? Do you think others may feel that way?

Mr. HASTINGS. I think it is. I think it is. I just want to say I think it is a very individual thing, but I do believe with good dia-

logue and adults in the room, decisions can get made. And I will tell you that in my experience, now having been doing this for a number of years, what we need to do in Washington now is become 25 percent of our jobs as CEOs of biotechnology companies, and that engagement, when you have that engagement and there is good dialogue, good things can come out of that.

Now, I will just give you an example from my company and I will juxtapose that to an example from a colleague of mine. One of the benefits of being the chairman of the Emerging Company Section of the Biotech Industry Organization is I am with a roomful of CEOs as big as this room every quarter.

So we had a situation not too long ago where there was a 30-day period and on the 30th day we got an answer and it was yes, where you might get an answer and it could be no. So if the answer is no, invariably they are going to ask for more information if they want you to turn it around to a yes.

But what we are seeing, what I was seeing recently was that particular case took 30 days. I have had situations where it has happened sooner, okay? But 30 days I got a yes. Great. Now I have a colleague who didn't get an answer in 30 days in another division. So I think that inconsistency needs to be dealt with. But I also think that part of that inconsistency has to do with the volume of work people have and the proper staffing and the proper funding of the agency, and, again, going back to user fees, making sure that user fees are being spent to actually enable the FDA.

So I do think there is variability. I think the retribution thing, there are mechanisms now within the FDA that if there is a person who is behaving in a way which is professionally inappropriate, that you can go and get that issue solved. And I don't know how many folks may have mentioned to you the fear of retribution if you had asked them what did you do about that, but that is what I often do. And sometimes there are—you know, they are not aware of the mechanism or they don't partake in the mechanism and then all of a sudden this becomes a big problem.

Mr. MEEHAN. I think they often make cost benefit analysis of the things.

Mr. HASTINGS. Could be. Could be.

Mr. MEEHAN. I don't want to overstep my time, so I appreciate the time you gave me, Mr. Chairman.

Mr. LANKFORD. Thank you. To the panel, let me recognize Ms. Speier again.

Ms. SPEIER. Thank you, Mr. Chairman. I just want to thank our panelists for participating today under what are difficult circumstances at the end of the year with everything else being equal.

I do want to make a point though as they have presented. I think that we here in Congress have to take a certain amount of blame for the period of time, and I don't believe it is right now, but the period of time when the FDA started to hold back, because the first thing that would happen when there was a bad outcome with a drug is that the FDA was hauled up here by us and scrutinized and beaten up and pummeled about their process and how could this have happened? And I think the result was that these FDA representatives would go back and say, all right, then, you know,

we will just put the brakes on many of these approvals. So we have got to take some responsibility I think for what has happened.

I think more recently, and I think it has been testified to today, there has been a loosening of the process within the FDA and strategies employed that show that there are new pathways that are working, maybe not in every area, but certainly in some that show promise. And I guess the silver lining in the sequestration is that if it gets to the point where people actually get on the phone and talk to each other, that is really a good sign. So maybe we can enlist more of that in the future.

Mr. LANKFORD. And the good news of that comment for me, Ms. Speier, is that Mr. Meehan and I, we were not here earlier during that time in Congress, so we can—I am grateful for your time here. Thank you for what you have contributed both in written form and oral form. We will continue to tap on your research in the days ahead, both in what is being written and the insight you can bring. So I appreciate you very much. We will take a short recess in order to reset the panel and to have our second panel.

We now welcome our second panel of witnesses. Dr. Janet Woodcock is the Director of the Center For Drug Evaluation and Research of the Food and Drug Administration. I am very glad you are here and that you sat in obviously on the first panel as well, and I look forward to just some of the conversation about that.

Pursuant to committee rules, we do swear in all of our witnesses before they testify, so if you would please rise and raise your right hand. (Sworn.)

Mr. LANKFORD. Let the record reflect that the witness answered in the affirmative. Since you are the sole witness on this panel, we typically do a 5 minute time period on the clock. You are welcome to do that. We are going to receive your written testimony which will be part of the permanent record. We will be glad to be able to receive your oral testimony now. We won't be as attentive to the clock, and we will follow up with questions from there. Thank you.

STATEMENTS OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Thank you. Mr. Chairman, Ranking Member Speier and distinguished members of the committee, I am Janet Woodcock. I am head of the Center For Drug Evaluation and Research at FDA. This hearing explores current challenges in drug development and manufacturing. And given the critical role that medicines play in the health of our population, these, I think, are very important and timely issues.

One challenge that the other panelists already alluded to is the escalating costs and time required to develop new therapies. This problem was identified in FDA's report on the critical path identified in 2004, but has only really gotten more serious since that time.

The root cause, in my opinion, probably in contradistinction to some of the panelists can be boiled down to two major factors. The first is most investigational drugs that are taken into clinical trials are not successful. Perhaps 10 percent of the drugs get to the market. And about half of the drugs that are taken into Phase III trials

don't work or are too toxic and are dropped at that point, which is a very expensive point.

This extremely expensive failure rate has been difficult to address, although companies have been trying to address this in the last decade. And also over this decade, we have been working with academia and the industry to try and improve drug development tools, including biomarkers and other tools, that could help raise the success rate over this 10 percent mark. Until this happens, there are huge opportunity costs generated by this large scale of clinical failure.

Now, the second factor is the hugely escalating cost of clinical trials, which have already been alluded to. Clinical development programs are plagued with multiple problems, including slow or no accrual at some sites, ever-increasing per patient cost, patient shortages and lack of data standards. The traditional clinical development program is inefficient and does not utilize most up-to-date technologies. Patient access is limited because only sites at major medical centers enroll patients typically.

FDA has been working on these problems. We have been working in the clinical trial transformation initiative, which is a consortium we have with Duke University and multiple other stakeholders. We have been working on data standards. And we have been working very intensively with groups that are doing new trials, such as the I–Spy trial which is an adaptive trial that is being done in breast cancer, and a new master protocol for lung cancer. And both of these trials are innovative because they study multiple different drugs in the same trial, and thus enable a lot of savings of setting up one trial after another for each investigational drug, and I am happy to discuss any of this with you.

Also we have been talking about the use of telemedicine to better reach patients who live outside of major medical centers.

Now, a second issue and challenge relates to modernizing drug manufacturing. The United States is no longer the world leader in drug manufacturing, like many other manufacturing sectors that we have lost. We rely on foreign sources around the world for drugs critical to the health of U.S. citizens. The trend of moving drug manufacturing offshore is continuing. However, we now may have a chance to reverse this trend.

Modern manufacturing methods that have only recently become technically feasible allow for continuous manufacturing from drug synthesis to the final drug form such as tablets or capsules. So you put in the raw chemicals at one end and you can get out pills at the other end. Such manufacturing requires much smaller but high-tech facilities staffed by a highly-educated workforce. There is also a trend toward using disposable manufacturing for the biologics, which again provides much savings. Environmental burdens for both of these are greatly diminished, and this was one of the barriers to continuing to building pharmaceutical plants in the United States.

I believe the U.S. Should do whatever is needed to incentivize this type of manufacturing sector growth in the United States, both because we need better security of our drug supply, and because it would provide a manufacturing sector that would be very valuable.

The FDA has been encouraging and collaborating on this for about a decade, but I think there is now a unique opportunity.

So there are multiple areas in which drug development continues to be a big challenge in also manufacturing and maintaining the drug supply, and I would be happy to discuss all of this with the committee.

[Prepared statement of Dr. 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

BEFORE THE

SUBCOMMITTEE ON ENERGY POLICY, HEALTH CARE AND ENTITLEMENTS

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

FDA CHECK UP: DRUG DEVELOPMENT AND MANUFACTURING CHALLENGES

DECEMBER 12, 2013

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Ranking Member Speier, 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 important issue of modernizing the manufacturing of pharmaceuticals.

The United States, through its investment in biomedical research, has become a world leader in drug discovery and development, but it is no longer in the forefront of drug manufacturing. Historically, the production of medicines for the U.S. population has been domestically-based. However, in recent decades, drug manufacturing has gradually moved out of the United States. It is currently estimated that 40 percent of the finished drugs taken by U.S. patients and 80 percent of the active ingredients come from sources overseas, including some of the drugs in shortage as noted below. While there are multiple reasons for this shift, common underlying factors include the fact that most traditional drug production processes require a large footprint, often have environmental liabilities, and can utilize a low-cost labor force.

Use of foreign-sourced materials creates vulnerabilities in the U.S. drug supply. The Department of Commerce's Office of Technology Evaluation, in its 2011 report entitled "Reliance on Foreign Sourcing in the Healthcare and Public Health (HPH) Sector: Pharmaceuticals, Medical Devices and Surgical Equipment," identified a high degree of foreign sourcing and dependency for critical components, materials, and finished products in the pharmaceutical sector. For example, most of the U.S. heparin supply comes from non-U.S. sources. When contaminated heparin, sourced from China, was found in the United States, FDA had to urgently devise several

tests to detect the contaminant and screen out contaminated product, because heparin is a critical drug for U.S. patients, and there was no adequate alternative source.

FDA also has had to intervene to prevent shortages resulting from problems with non-U.S.-based suppliers. For example, shortages have resulted when raw material manufacturers discontinue an ingredient for business reasons. In these circumstances, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. Shortages can occur when transport and shipping delays occur due to severe weather and other unforeseen events. In recent years, flight cancellations and potential shipping difficulties could have been caused by the Iceland volcano, the tsunami in Japan, or a threatened cargo ship strike. Examples of critical drugs currently or recently in shortage with an active ingredient and/or finished goods sourced primarily from overseas include propofol, heparin, and Tamiflu. Our reliance on foreign-sourced materials continues to create ongoing vulnerabilities.

Advances in pharmaceutical manufacturing technology in the last decade provide new opportunities to address this situation and to reinvigorate the pharmaceutical manufacturing sector in the United States. FDA has been working to stimulate development of novel manufacturing technologies in collaboration with academic and industry experts. The new technologies enable forms of "continuous manufacturing," wherein the finished drug product is produced in a continuous stream, as opposed to traditional methods that involve a series of so-called "unit operations," such as milling, mixing, granulation, and so forth. In examples of advanced novel manufacturing, production is continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage form. This type of manufacturing is on the verge of entering commercial production. There are a multitude of advantages of this type of production, when done well. Product quality can be precisely controlled. Production scale-up

issues, which frequently bedevil drug development, will likely be much less of an issue. Increases in capacity can be handled in a straightforward manner. A range of strengths or doses may be prepared more easily, which may be important for personalized medicine. However, other key advantages do not relate to the specific drug product being made. For example, continuous manufacturing plants require a smaller footprint and can be located closer to markets, thus reducing the need for transcontinental shipping of components.

FDA has been working for over a decade to stimulate modernization of drug manufacturing; however, the Agency's efforts alone cannot reinvigorate the pharmaceutical manufacturing sector in the United States. Other essential actions include support for academic research in this area and opportunities for collaboration, possibly through public-private partnerships or consortia. In parallel with FDA's initiatives, we have seen a resurgence in academic research supporting modern pharmaceutical manufacturing. FDA works cooperatively with many of these academic groups to help advance the science of pharmaceutical manufacturing. For example, Cooperative Research and Development Agreements (CRADA) have been established with several academic groups to enhance understanding of concepts of manufacturing science. Utilizing a CRADA, one or more FDA laboratories may work with one or more non-Federal parties to conduct specified research or development efforts. FDA participates in a number of collaborative research projects being conducted by the Product Quality Research Institute and the National Institute for Pharmaceutical Technology and Education. However, these efforts are relatively small in scale, given the impact and criticality of the drug supply.

The future of drug manufacturing lies in high-technology, computer-controlled production facilities that can rapidly respond to changes in demand and are capable of seamlessly producing a variety of dosages and even dosage forms. This future can unfold within the United States, or

it may take place elsewhere, forcing U.S. patients to continue to rely on drugs produced on other continents.

The following discussion describes FDA's efforts to stimulate modernization of drug manufacturing.

What is FDA doing to encourage modern manufacturing?

In August 2002, FDA announced a significant new initiative, Pharmaceutical current Good Manufacturing Practice (cGMP) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This initiative had a number of objectives, including encouraging early adoption of new technological advances in the pharmaceutical industry, facilitating industry application of modern quality management techniques, implementing risk-based approaches, and ensuring that regulatory policies and decisions are based on state-of-the-art pharmaceutical science. In 2004, FDA issued a final report on the initiative, highlighting the Agency's commitment to restructuring its oversight of pharmaceutical quality systems.

In 2006, FDA issued a final guidance, "Quality Systems Approach to Pharmaceutical cGMP Regulations." This guidance not only provides information to help in implementing quality systems and risk management approaches, but also provides the framework for integrating these approaches into existing programs with the goal of encouraging industry to adopt modern and innovative manufacturing technologies. Additionally, in 2011, we released a final version of the process validation guidance, which modernized recommendations and expectations of how pharmaceutical manufacturers should ensure a state of control of their commercial manufacturing processes over the life cycle of the product.

Additionally, collaboration with international health and regulatory organizations has been a vital part of the modernization efforts. FDA has participated in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use (ICH) to help with the development of pharmaceutical quality systems based on an integrated approach to risk management and pharmaceutical science. These ICH guidances have become the international foundation for Quality by Design (QbD) and modern pharmaceutical manufacturing approaches. FDA is also participating in various expert working groups within ICH to develop guidelines to help ensure that drug regulatory processes are more efficient and uniform in the three regulatory regions.

Implementation of a Question-based Review (QbR) process has occurred in CDER's Office of Generic Drugs. QbR, a general framework for the assessment of the chemistry, manufacturing, and controls information submitted in abbreviated new drug applications (ANDA), incorporates the most important scientific and regulatory review questions that focus on critical pharmaceutical attributes essential for ensuring generic product quality. The QbR serves a dual purpose. First, it provides a guide to reviewers in preparing consistent and comprehensive evaluations of whether a product is of high quality and in the determination of the level of risk associated with the manufacture and design of the product. Second, it provides industry with transparency about the logic that reviewers invoke in their reviews. CDER is currently exploring the expansion of the QbR approach beyond generic drugs.

FDA's inspection and compliance focus has also changed in recent years. In addition to the publication of our 2006 quality systems guidance, we have enhanced our inspectorate capability and increased familiarity with the quality systems model. Some of these inspections have found

operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized.

What is Quality by Design (QbD)?

QbD offers an opportunity to reduce manufacturing costs while ensuring that consumers receive high-quality drug products. The focus of QbD is to build quality into a product using a thorough understanding of the risks of the product and process, and controlling those risks. QbD starts in development, and adaptation continues throughout the manufacturing life cycle if a firm has a strong quality management system. QbD utilizes a systematic approach to product design and development. It involves identifying what characteristics are important from the patient's perspective, identifying necessary material attributes and manufacturing parameters to achieve the quality characteristics, and then designing manufacturing controls and developing methods to assess process capability and make improvements. Instead of being in a reactive mode and taking corrective actions once failures occur, QbD causes manufacturers to focus on developing process understanding and supporting proactive actions to avoid failures through vigilant lifecycle quality risk management. It can enhance development capability, speed, manufacturing robustness, as well as the manufacturer's ability to identify the root cause of manufacturing failures. In certain cases, QbD can also help a manufacturer make post-approval changes and scale-up operations.

QbD and quality systems are beginning to gain ground in the pharmaceutical sector. A recent survey of pharmaceutical companies conducted by the International Society of Pharmaceutical Engineers Process Analytical Technology Community of Practice of United Kingdom/

Ireland (PAT COP UK/IR) indicated that significant cost benefits resulted from QbD-developed products. Benefits such as improved product quality and process robustness, increased process capability, and greater speed and reliability to market were also cited. This same organization found in another survey that inadequate manufacturing capability is a frequent cause of critical drug supply shortfalls, and cited lyophilization (freeze-drying) and sterile manufacturing as two areas in need of improvement.

From FDA's observations of industry, QbD in development is quickly becoming the standard way of doing business for small molecule innovator drugs. Biotech companies and generic companies are also shifting toward QbD for development, but at a slower pace. While QbD is catching on in development, manufacturers have been reluctant to modernize manufacturing methods by taking advantage of advances in modern facility and process design, such as replacing manually-intensive processes with automation, using closed systems, integrating process analytical technologies into operations for better process control, and adopting continuous manufacturing platforms. These technologies would help achieve improved manufacturing reliability, increased robustness, and lowered costs. Consequently, only part of the potential benefit of QbD and robust quality systems is currently being captured by much of the pharmaceutical sector. Increased efforts to better manage facility and process risks by making life cycle improvements are underway in the industry, and some transformative thinking at FDA has helped to promote this gradual evolution.

CDER's Office of New Drug Quality Assessment has conducted two pilot programs for implementing QbD. The first, announced in 2005 and now complete, allowed the Agency and industry to explore the scientific and regulatory aspects of QbD. The data from this pilot were incorporated in resulting ICH guidance documents. The second pilot, which started in 2011 and

is still ongoing, provides for collaboration with our European regulatory colleagues in review of applications that follow the QbD approach.

CDER's Office of Biotech Products has held similar piloting efforts. Its QbD pilot, which began in 2008 and is now closed to new applicants, is exploring the extension of QbD concepts to protein drugs. Additionally, we have also collaborated with our international colleagues to discuss QbD approaches in review.

What results could we expect to see from adoption of QbD?

Full implementation of QbD and modernization of manufacturing by the pharmaceutical industry in development through manufacturing is expected to provide lasting benefits to industry, regulators and patients. For industry, we expect the long-term benefits to include lower production costs which result from more efficient manufacturing, decreased failure rates, and lowered inventory costs. For regulators, we expect that application of science- and risk-based approaches will increase our work efficiency, so we can focus our efforts on higher risk products and processes. But most of all, we expect that application of QbD and modernizing manufacturing will benefit patients with higher assurance of product quality, greater availability, and a resulting decrease in drug shortages and recalls.

While this may require some investment for manufacturers who need to improve the infrastructure, the benefits of more dependable operations strongly aligns with the business goals of process predictability (e.g., Right First Time) and product dependability. Reduced variability will lead to reduced rejected goods, higher supply dependability, fewer defects, and overall better productivity and profitability. Modernizing drug manufacturing represents a great opportunity to

lower costs and develop more flexible manufacturing processes while continuing to ensure that the public receives high quality drug products. In addition, the public health will also be well served as modernization can help reduce the root causes of drug shortages, and industry's cost savings can be reinvested into developing new products to serve public health needs.

CONCLUSION

In summary, FDA has been working diligently for over a decade, in collaboration with the pharmaceutical industry, to improve drug manufacturing. Building on this foundation, and utilizing new technologies, groundbreaking new manufacturing methods are within reach. These new ways of making drugs could, with the proper strategies, revitalize pharmaceutical manufacturing in the United States.

Mr. LANKFORD. Thank you. Let's run through a few questions. We will take 5 minutes at a time and then come back and do a second round of conversation as well.

The sequestration issue has come up multiple times in this, the sequestration of the user fees itself. These are paid by the companies to be able to expedite this. You and I have spoken on this before as well. What has been done at this point from FDA? Has there been communication with OMB to have a discussion about this? Because that is a user fee, and there is a lot of bipartisan frustration with OMB to say why has that been sequestered as well. That was different from the start. Tell me about the communications that is happening right now between the FDA and OMB?

Dr. WOODCOCK. Well, I believe the administration certainly has communicated within itself. This was a ruling by OMB that according to how the budget was structured, that the user fees would be subject to sequestration, and that was done at the time the original sequestration was put into effect.

Now, I realize Members of Congress have written to OMB about this and there has been multiple discussions, but it seems to be that it is felt that some type of overt action by Congress might be necessary to change this situation.

Mr. LANKFORD. Has there been communication between FDA directly to OMB to talk about that, or is there just the assumption that that conversation was at OMB?

Dr. WOODCOCK. No, I am sure that OMB—I personally haven't had those conversations, but I believe those conversations have been—OMB is quite aware of this situation.

Mr. LANKFORD. Oh, yes. Several comments have also come up on the President's recommendations—the recommendations. There are several of them again that have been itemized as we have gone through the earlier panel as well. One of them, recommendation number three; expand the use and practice of FDA's existing authorities for accelerated approval and confirmatory evidence. The FDA should make full use of accelerated approval for all drugs meeting the statutory standard of addressing an unmet need for a serious or life-threatening disease and demonstrating an impact on clinical end points other than survival or irreversible morbidity, or on a surrogate end point likely to predict clinical benefit.

How is that coming in the conversation? I know you all already looked at this as well. Where is that?

Dr. WOODCOCK. Yes. Well, some of that was substantiated in FDASIA that was passed last year. So we have issued a guidance on our expedited programs that further defines what unmet medical need is to make a standard definition of that. We certainly have talked about and are working on the issue of clinical endpoints short of clinical benefits, but likely predict clinical benefit. And we have full intent of applying accelerated approval to any area of unmet medical need. And I believe our breakthrough drug program that also was put in FDASIA demonstrates that we are very interested in this. Many of those have had potential clinical benefits based on surrogates and so forth.

Mr. LANKFORD. So the guidance is being written currently on that. Tell me the timeframe on this as far as when this moves from conversation and we are drafting to done.

Dr. WOODCOCK. The draft guidance is out for comment and we should issue a final guidance soon.

Mr. LANKFORD. Soon being tomorrow? Soon being six months?

Dr. WOODCOCK. Within months I would expect.

Mr. LANKFORD. Okay. Great. And then this ongoing conversation that has happened earlier that you are extremely aware of as well, this balance between safety and efficacy, access from patients coming in, whether it be the compassionate use that Ms. Speier had mentioned before or other methods to get patients that are terminal access to drugs faster, or even the information about the clinical trials out.

So let me do two different sets of questions on that. One is the compassionate use and getting the information to doctors about how to go through that process and connecting and what the steps would be. So that is an information part of it. And the second part of it is the clinicaltrials.gov site, the information there, the access to that, helping more patients get involved in the trial process so they can be in the structure which not only helps them but helps others as well. Where are we on those two issues?

Dr. WOODCOCK. Well, clinicaltrials.gov is intended to—is run by the National Library of Medicine and is intended to, among other things, alert patients or caregivers to where a trial might be opening up that they might be eligible for.

Mr. LANKFORD. Do you consider that site up-to-date and the information accurate?

Dr. WOODCOCK. I think the site is up-to-date on the existence of the trials. There has been a lot of controversy about the results section of that and whether that is up-to-date. But if you are talking about patients being able to enter into the trials, except for Phase I trials were not included, so there may be some Phase I trials. But those are dose escalation, early safety trials.

Mr. LANKFORD. It has all the beauty of Craigslist when you go there as far as the site itself and its functionality, but the access to some of the results and the information is part of what my consideration is. How do we make sure that people not only get good accurate information there, but there is the possibility of they know about this early enough to get involved, and that physicians have access to that information. They know it is very, very timely.

Dr. WOODCOCK. Well, I think that would be a matter of more publicity about the site through various patient groups, through other professional organizations that treat those given diseases, so that the information is disseminated out in that manner.

Mr. LANKFORD. Does FDA have a good relationship with those patient advocacy groups? Is there an ongoing communication there?

Dr. WOODCOCK. I have recently set up in the Center for Drugs a new group office for patient advocacy relations and professional relations, so we plan to be building that capacity within the Center For Drugs.

Mr. LANKFORD. Okay. That would be very helpful, not only to patients, but also to physicians as well.

Dr. WOODCOCK. Agreed.

Mr. LANKFORD. And I want more information on that. I am going to try to honor time on this and recognize Ms. Speier.

Ms. SPEIER. Mr. Chairman, thank you.

Dr. Woodcock, thank you for your decades and decades of service to our country and to the health of our country.

Mr. Huber had mentioned in his testimony that the FDA clinical trials process is not suitable for new biologic and molecular medicines, and it essentially results in economically incurable diseases. How is the FDA responding to these new medical technologies?

Dr. WOODCOCK. Well, I had a conversation with Mr. Huber. I don't agree with his analysis. We have been in the forefront of pushing molecular medicine since 2000. FDA, I can offer this for the record, recently put out a booklet on all the things we are doing on personalized medicine. But for example, I think in 2003 I accepted the first award from the Personalized Medicine Coalition really on behalf of the center for our work, the first award they had ever given, for our work in driving personalized medicine along.

And why would we do that? Because personalized medicine allows—because you try to eliminate people who don't respond, you increase the size of the treatment effect so that you actually see how well a drug works in people and has a chance in working. Then on the safety side, you can eliminate people in advance who are at risk so the drugs can become safer by screening out people who are at high risk of side effects.

So from our point of view, and I think from the patient's point of view, personalized medicine can only be a positive. We have, in fact, been criticized by some in the community for pushing it too hard. So I believe we really—and I believe it is paying off now. It is paying off with the targeted therapies. A lot of the breakthrough drugs are targeted therapies, and I think that we are going to see increasingly targeted medicines over the next decade.

Ms. SPEIER. I appreciate that clarification. Now, Mr. Gottlieb also stated that he saw one of the greatest challenges for the FDA in terms of innovation was the culture, and he believed that there is significant influence exerted by outside groups upon the FDA clinical group. I would like to give you the opportunity to respond to that.

Dr. WOODCOCK. Well, I certainly read Dr. Gottlieb's testimony. I have had conversations with him about this. And, of course, FDA has considerable flexibility in applying the safety and efficacy standards, and we basically use a sliding scale. So for a headache, a drug has to be pretty safe because no one wants to risk their life to cure their headache, right? On the other hand, for serious and life threatening diseases where there isn't any alternative, there is a lot of tolerance of risk, and there is also greater tolerance of uncertainty about the effects, which is what Dr. Gottlieb was talking about. And as I understand his comment, it is very similar to what you said, which is that a lot of the criticisms over the years about drug safety issues have, in his mind, led to conservatism, even in the area where a lot of flexibility is indicated.

Ms. SPEIER. So give us some good news, because I think there is some good news coming out of FDA, and particularly your area. So tell us from your perspective some of the good news.

Dr. WOODCOCK. Well, I think from my point of view the good news is that the industry, we are really seeing, I think, a renaissance in the industry. We are approving a lot of drugs now that

are first in class or that are treating untreatable diseases, or that are advances in therapy and they are treating bad diseases better.

The breakthrough program that was put in place by Congress last year, we have had over 100, I believe, requests and we have granted 34. And those designations that we give are where we think the drug is really a game changer in that disease, and if we grant that designation, we offer to really do a full court press on that drug and do everything we can to get it developed basically in the most, I call it parsimonious manner possible. In other words, what is the shortest path between where the drug is now, what we know about it, and what we need to know to get it on the market in the hands of doctors and patients. And I think there is a lot of enthusiasm, both internally and externally, about this breakthrough drug program and the promise of these drugs.

Ms. SPEIER. Okay. Let's talk about manufacturing for a moment. It is pretty stunning, and I think if the American people knew that 40 percent of the drugs that we take are manufactured outside of the country, and 80 percent of the ingredients are manufactured outside of the country, they would be pretty appalled because there is just consternation about the supervision and oversight that goes on overseas.

So tell us, and to your point, when there are shortages and there are tsunamis and there are other conditions that prevent us from accessing the drugs that our population needs, we are really left with a very difficult position to be in. So, how do we create more opportunities for manufacturing, or what is it going to take?

I mean, I am thrilled that Apple computer has decided to bring jobs back to America. I might actually buy more Apple products now. But that was a ways in coming, and part of it is because we are now seeing transportation costs are more expensive. There are lots of reason why on the bottom line they are doing that. How can we create incentives for manufacturers to be manufacturing in the United States?

Dr. WOODCOCK. Well, that is a very good question, and because I am not an economist, I am not like probably the best person to consult. What I am going to say is that FDA is trying to provide encouragement for advanced manufacturing, wherever it might be, because it is going to be safer, it is going to be reliable, it is going to enable personalized medicine because it is going to be much more agile than the kind of manufacturing that we have right now.

But I do believe that it should be considered—incentives should be considered and States should consider this as perhaps an industry they would want to put in place incentives to bring back into the State, because I believe this will be a viable sector for a very long time, making drugs.

But the technology, I am here to say that the technology has reached a point where this is reality; where we can see these plants can be built, they can decrease our vulnerability in the sense that we are relying on foreign sites of supply that may have many different things that might happen that mean a drug might become unavailable in the United States, and yet it is also a very good, I think, source of jobs.

Ms. SPEIER. Thank you. My time has expired.

Mr. LANKFORD. Mr. Meehan.

Mr. MEEHAN. Thank you, Mr. Chairman.

Dr. Woodcock, I want to thank you too for your long distinguished career working in this area, and congratulations for your recognition. It is nice to receive an award. That is one of the few benefits of public service, that you don't get the compensation sometimes in other ways.

But I want to step off of the questioning that my good friend and colleague from California was asking you because you made a comment about the industry now expanding in Europe and other places and not here. But why do you think that is?

Dr. WOODCOCK. My understanding is it is primarily they are setting up plants in India, China and many other parts of the developing world. And I don't know, as I said, I am not an economic expert, but the analyses that have been published about this say that it is the environmental regulations, certain tax advantages, a lower cost labor force and the usual kind of factors that we see with manufacturing moving offshore from here.

However, the new manufacturing methods require a high-tech labor force. They will have low environmental impact. It will be much diminished, all right? And it will require not a very large footprint of size of a factory to operate. So it is more like the kind of innovative high-tech industries that we really do see coming back to the United States or we would like to retain in the U.S.

Mr. MEEHAN. What do we do? I mean, I accept the analysis. I don't have a better analysis of it, and I suspect and do believe that it includes all among those, including tax policies and other things. But I do hear as well the time that it takes from somebody who has effectively a start-up concept to have it moved through Europe and approved and put into, you know—the chain of treatment, so-to-speak, is much shorter than what we deal with in the United States. And you talked about time and cost being an expanded aspect of FDA, or at least the process here which FDA participates in here. And since we can hopefully deal with those other issues as well at some point in time, tax policy and those sorts of things, what can we do to do a better job of enabling the FDA to be timely in their response, or are you doing it correct? I am moved by your point that only 10 percent of the drugs actually get approved, that there are good reasons why it is appropriate to make sure we don't put bad products out. But what is the difference between what Europe is doing and here? Why can they do it faster than we can?

Dr. WOODCOCK. Which part do you say they are doing faster?

Mr. MEEHAN. Well, it is my understanding, and maybe correct me if I am wrong, that there is an ability to take a start-up idea and move it through the clinical trials and get it to a point where it can be approved and put into commerce quicker than is done here, and that that is one of the driving forces, is the tremendous cost associated and the time delay. That if you can manufacture—get the drug approved and begin to manufacture and get it in, once it starts to work, it will find its way back here to the United States. But we have lost jobs and the other kinds of things that are associated with the development of the industry.

Dr. WOODCOCK. Well, we keep figures on what we call the new molecular entities, the novel drugs, right, and where they are approved first in the world. And consistently over the past, at least

5 years, we have led the world in approvals of first on the market and we are above Europe. We are not in any competition with Europe, but we are about 50, 60 percent compared to all other markets, and then each sector, Japan, Europe, has a smaller percentage up to 100 percent. Last year I think we were at 60 percent of all new molecular entities. I can get you that figure. So I am not sure. That used to be, before the user fee program PDUFA, FDA approved drugs much later than in Europe. But that hasn't been true for some time.

Now, as far as manufacturing, we have more or less the same manufacturing regulations as the Europeans. So if a plant can be got up quicker in Europe, it would do with other permitting and, you know, other regulations related probably. But generally the manufacturing is going to India, China, other places, Brazil.

Mr. MEEHAN. Okay. My time has expired, Mr. Chairman. I look forward to a round of follow-up questions.

Mr. LANKFORD. And we will. And, Dr. Woodcock, if you don't mind, we are just going to open the microphones and just have an ongoing conversation, so there may be multiple of us instead of a structured time period. That has been our habit I would say here once we get into the second round. So we will start throwing questions at you back and forth.

You had mentioned first about the approval process faster here for some of the types—faster than Europe or Japan, and that has changed over the last several years. Is that still true for all types or are there certain types where Europe and Japan are still approving drugs faster than we are?

Dr. WOODCOCK. Well, since I am under oath, my impression is that we—because of the user fee program we have deadlines. We approve most of the drugs on the first cycle, all right? So it is submitted in. The companies have really figured out what they need to give to us to get an approval and we have timelines for when. And I think my impression is for all the types of new drug applications, we are ahead of other countries.

Mr. LANKFORD. Okay. Your ideas to bring down the cost, as I walked through the several issues of this particular hearing and got a chance to explore where FDA is moving on this and what is happening, the cost of drugs is significant, and every one of those companies say it is because of the cost of actually the trials process and everything else. So your idea is that you have seen to bring down the cost of that. I also want to ask you several other questions. But can we spend a little time on that?

Dr. WOODCOCK. Certainly. To bring down the costs, we have been working on this for at least a decade, and recently, my idea of having these standing trials where many drugs could be tested in the same trial and you just keep running them through instead of setting up a new trial for every drug, which is extremely expensive and time-consuming. And the goal then would be to reach out to the community and enroll patients all through the United States, not limit it to major medical centers, so more patients have the opportunity. It decreases the time taken to recruit patients.

Mr. LANKFORD. Who has done that at this point? How many have done that? Is that a pilot issue that you are working with or how would companies know they can try that?

Dr. WOODCOCK. It has to be done by consortia, and the I–Spy trial, the I–Spy 2 trial was the pioneer in this, okay.

Ms. SPEIER. Where was that done?

Dr. WOODCOCK. It was led out of UCSF through the foundation for NIH as a consortium, all right. So many companies, the FDA, NIH, everybody would be a part of that, set up that trial. It is a screening trial, and they screen breast cancer drugs with a biomarker to the point about personalized medicine. So they take high risk breast cancer patients and they are trying to improve the treatment so they can screen many drugs, and I won't go into how that is designed.

And then another one is now being set up by the National Cancer Institute, the FNIH, and FDA is participating in this, for lung cancer, where many patients can be recruited and they already have five drugs, and all investigational drugs, that they will be testing using biomarkers in that trial. So those are prototypes. But it is not widely adopted yet.

Mr. LANKFORD. But that is obviously in an area where you are having a lot of patients and a lot of opportunity. You mentioned breast cancer. Lung cancer. Unfortunately, we have a lot of people in that. What can be done in some of the other drug processes where we don't have as many people?

Dr. WOODCOCK. Well, in rare diseases, I think certain groups like the Cystic Fibrosis Foundation have led the way. We recently approved a drug for cystic fibrosis, and that is a rare disease to start with, but it only treats 7 percent of those patients. But that Cystic Fibrosis Foundation already had the patients genotyped so we were able to identify—the company who was developing the drug was able to identify which patients that drug might work in and rapidly test them. So that drug is approved and on the market for cystic fibrosis.

Mr. LANKFORD. So what kind of time period and cost did that change for that? That went from 12 years, 10 years I would assume is a typical process?

Dr. WOODCOCK. Yes. I think it was remarkably shortened, but I can't tell you how short that was. They did randomized trial, because this is a very novel approach, and they were able to show in a 48-week trial that they really improved markers for cystic fibrosis, lung function, and the children gained weight.

So another idea that we have also is we have been discussing, and I know you all have been discussing with the community is a way to speed the introduction of antibiotics for drug resistant organisms. And that is a different idea that has been discussed, which is putting some kind of mark or logo or having Congress speak to a special mechanism that we would have a very limited drug development program, get those drugs into the hands of doctors, who are serious drug resistant organism infections, and have some kind of notation or mark on those drugs so that the doctors knew they had been developed by a very limited program and that good antibiotic stewardship should be used with them.

Mr. LANKFORD. Okay. Only antibiotics in that program, though.

Dr. WOODCOCK. It's been discussed wider, and I think that's a matter for ongoing discussion. But that would be one way to do it. Because the need is very great. The CDC said, I think, last year,

I believe, they said 23,000 people died from infections with drug resistant organisms, and we are behind that epidemic. As you have said, it takes a while to develop a drug, even if we shorten the time, and so we don't have time, you know, anymore. We're running out of time to get a handle on this epidemic.

Mr. LANKFORD. Okay. So clarify that for me because you said "we're working on" several times there. Is this a process that is set, that you've done guidelines for, that's done, or again, what is the timeframe on this? Is this done tomorrow? Is this done 6 months, 6 years from now?

Dr. WOODCOCK. What we've been discussing is that Congress would speak on this and tell us to establish a program.

Mr. LANKFORD. You do not have the statutory authority to do that right now you feel?

Dr. WOODCOCK. It would require regulations.

Mr. LANKFORD. But if we did statute, you would have to promulgate regulations off that statute as well.

Dr. WOODCOCK. I'm not a lawyer. Being under oath, I want to give you an exact answer. But I think we could probably do it with the statute. We might have to do guidance to help companies figure out how to do the programs, but I believe that we could probably implement something if we're directed to in a statute directly.

Mr. LANKFORD. Okay. I'll just make sure.

Congresswoman Speier.

Ms. SPEIER. Dr. Woodcock, the experience that Gilead just had where it had their hepatitis C drug approved with the recommendation by FDA to do additional trials, I believe, with a different cohort, maybe you could just explain. Because it was unusual but it showed flexibility within FDA, and Gilead was thrilled with the opportunity to kind of move that process quickly.

Dr. WOODCOCK. Uh-huh.

Ms. SPEIER. And I think it would be good for all of us to understand it.

Dr. WOODCOCK. I would have to get back to you on that because I don't know the details of it, but I will say that you asked for good news, I think the new generation of drugs for hepatitis that we are going to see is really good news because we have a lot of patients in this country who develop liver failure from hepatitis or develop liver cancer, and we believe the new generation of drugs may well be curative of hepatitis C, and that's really big news.

Ms. SPEIER. And it's big news on a lot of levels because they become disability insurance recipients and Medicaid recipients and Medicare recipients, and that is a very costly procedure that they then go through in terms of dialysis and the like. So that's good.

Let me ask you this. You said that only 10 percent of the drugs that are considered actually get approved because there's a failure in Phase III. Can you explain that to us? Is there some way we can find that out sooner so there's not as much money invested by the drug companies?

Dr. WOODCOCK. That's the $64,000 question. All right. What happens is there's attrition all the way through the drug development process. The attrition, before you get into people, so you do animal studies or something and you find toxicity, that's not that expensive. But once you start doing trials, losing a drug somewhere dur-

ing the clinical development program is very expensive, and the longer you go and study the drug, the more sunk costs you have in that drug.

And so in Phase I there is attrition often for toxicity. In Phase II there may be attrition because a drug doesn't work. But remarkably, in Phase III, at least several years ago, the last time this was studied, there's about 50 percent of attrition is in Phase III when you've spent a huge amount, maybe, you know, upwards of a billion dollars on developing the drug, and you find out it doesn't work. Some of the drugs in Phase III don't have any effect compared to placebo.

Ms. SPEIER. But is that because for the first time they are being used or human beings? They are being used on human beings in Phase II, are they not?

Dr. WOODCOCK. Uh-huh.

Ms. SPEIER. So what is happening?

Dr. WOODCOCK. It's hard. For some diseases you can't tell in Phase II. All you're doing in Phase II is trying to get the dose right, maybe using a biomarker to try and figure out, you know, are you affecting the disease? But the disease may be a longer-term disease or it may take a while, and so you have to do a Phase III trial to see whether or not it actually works or not, and then you're very sadly disappointed.

For example, we just had a couple trials in Alzheimer's disease, you know, that did not affect Alzheimer's disease, and that is a bitter disappointment because we need treatments for Alzheimer's disease, but it's hard to tell in earlier trials whether or not you're affecting dementia.

Mr. LANKFORD. I'm jumping on this as well.

Ms. SPEIER. Sure.

Mr. LANKFORD. Going back to a statement, Doctor, that Mr. Huber made earlier where he talked about the drug that was set up for kidneys and they were using it for bladders and it was not successful on anyone but one, and it was flawless on that one.

Dr. WOODCOCK. Uh-huh.

Mr. LANKFORD. Is that the type of thing that we're finding or we're finding it's effective on some so we're looking for the molecular markers for that group and why you had, you know, 500 people in the study and it worked great on 12 and not on the rest, and so now you're studying it, or you're blanket saying this doesn't work for everyone?

Dr. WOODCOCK. It really varies by the disease. In Alzheimer's we have don't really have any good molecular markers yet. That's what those biomarkers are working on. So those studies are what you call empirical. In other words, they are trial and error. And that's a lot of the problem with drug development, it's still trial and error.

But in cancer, because we did the war on cancer that you all funded, and we have a tremendous amount of information about what makes that cancer a cancer. And as Mr. Huber was saying, it's molecular changes, genetic changes in the tumor that do that, and some of them are driving the cancerous behavior. And if we can target that and turn it off, then the cancer subsides to some extent. And so that's a new way of developing a drug where you

actually understand the mechanism and you can target that mechanism.

And so, in cancer, we used to talk about breast cancer and colon cancer, but now we really talk about what is the driver, what mutation is driving that tumorous behavior and how can we turn that off. So that's been a revolution, and I think that's going to get better and better, but we need to focus on curing cancer.

Mr. LANKFORD. Right. No, the point I'm trying to drive at, though, is in a large-scale study, it's a Phase III, you have a lot of people that are involved in it. What do you do if you have a small group in there that it is successful for, that it is effective, but statistically, across the size of the group, it's not? Is that something the drug company goes back and goes back to the drawing board and tries to determine that, or is it something FDA is involved in? What happens?

Dr. WOODCOCK. Usually companies will submit subgroup analyses and they would give them a hypothesis, well, maybe it works in this group, okay, we don't know why, but maybe it works in this group. And they would have to do more trials. Why? Okay, well, in a famous example, Richard Peto, who's a statistician in the UK, did a subset analysis of a trial, and he showed that people with the astrological sign Virgo, okay, did much better than all the other people. And, you know, people say we should approve the drug based on these subset analyses, but the actual fact is you can do many of them and there's always going to be one that the drug appears to work, and we see this all the time. That doesn't necessarily mean it actually does work, just like the astrological sign Virgo is not a predictor of better cardiovascular outcomes.

So, yes, if there is a convincing molecular marker, though, okay, that's a hard scientific thing, not some kind of fishing expedition, then we might have a different approach.

Ms. SPEIER. Could we talk about your staffing. Is all of your staffing—I should know this and don't—subject to user fees or is there a percentage that is not subject to user fees?

Dr. WOODCOCK. We have S&E funding that is subject to sequestration. We have PDUFA funding, and we have GDUFA, the generic drug user fee program has just set up funding, and funding for biosimilars drug user fee. The S&E is maybe about 30 percent of our funding.

Ms. SPEIER. S&E is?

Dr. WOODCOCK. The appropriated taxpayer's dollars.

Ms. SPEIER. It's about 30 percent.

Dr. WOODCOCK. Uh-huh.

Ms. SPEIER. So what has that meant in terms of sequestration. I mean, how many jobs are no longer being——

Dr. WOODCOCK. I wish I could remember these figures, but it's been a pretty significant hit that we've taken. Now, we're able to hire under GDUFA anyway, but what you've been talking about here about the interaction of companies, innovator companies with the review divisions, has been hampered because those review divisions did not get the hires they expected under the new PDUFA program because of the sequester.

Mr. LANKFORD. The generic group, you're still able to hire. That money was not sequestered?

Dr. WOODCOCK. I'm very confused about this. I know that we had so many hires that we had to make, that we certainly are able to hire under GDUFA. I don't understand. We could get back to you on the impact of the sequester.

Mr. LANKFORD. Yeah, the question is whether user fees sequestered for the generic are not sequestered for the generic, do you know? You've made some hires there. I just didn't know if that's a function of the user fees.

Dr. WOODCOCK. I think the answer is yes and no. I think the first year weren't maybe because it was a new program. That's why I'm confused.

Mr. LANKFORD. Okay.

Dr. WOODCOCK. And then it will be, but we can——

Mr. LANKFORD. Can we follow up on that? Because obviously it has been this ongoing conversation should the user fees have been sequestered at all. Okay.

Dr. WOODCOCK. Yeah, okay. Uh-huh.

Mr. LANKFORD. Pat, did you have anything you wanted to add? Jump in any time.

Mr. MEEHAN. Well, I don't want to jump in while you're on a roll. And I kind of laughed to myself when you were hesitant to answer the question because you said, I'm not a lawyer. I was just with a guy who said, he saw the high priced lawyer and he asked him, he said, I've got two quick questions. If I give you a thousand dollars, can I ask you? And the guy said, absolutely, what's your second question? So a bit of levity to help us. As a recovering lawyer, I have to take chances.

The sort of the dialogue I exchanged with Dr. Gottlieb, among others, was not just anecdotal, dealing with the concerns about the timeliness of responsiveness, and you didn't really have a chance to talk to it.

Dr. WOODCOCK. Uh-huh.

Mr. MEEHAN. And I think it has sometimes to do with the ease with which it is just to ask one more question and send it back. What can be done to assure that those who are managing their portfolios, particularly in light of the fact that PDUFA, MDUFA, have been put in place to ameliorate just this issue, that we are getting timely and responsive communication? And maybe it is just as, you know, Mr. Hastings identified, better communication all along. But I'm talking from knowledge of specifics where there would be communication, and in effect, send me what you have, 28 days, no response, 29th day, the whole new raft of questions. So how as an agency can you oversee to assure that those who are managing their portfolios are doing it effectively?

Dr. WOODCOCK. Well, it is a complicated question. These interactions are governed by agreements that are made under PDUFA, many of them, all right, and we track something like 25,000 transactions, right, every year. Don't quote me on this. Something like that, or I can't give you the exact number, right, but it is a very large number of transactions that occur, because we track not only all the filings for the marketing applications, but we have type A, B, and C meetings, we track how timely the meeting minutes are to get back on these meetings, how timely scheduling of the meet-

ings are, et cetera, et cetera. So it's very micromanaged, but again, that's the process. It's not the content.

And I will say, in my opinion, if you pay too much attention to process, you often give short shrift to content, and to me that seems to underlie your question, too.

Mr. MEEHAN. It did. I mean, I think that was the example, that once they got somebody else to step in and took the time to evaluate it, they realized the information was there and it was sufficiently explained.

But I just appreciate the process, but I do think it's this balance of when people feel comfortable to make decisions. And I do adopt my colleagues' concerns that obviously people have come and been lambasted for having made the wrong decision, and it creates an environment in which people say, well, no decision is easier on me, so they don't do it. How do we have to work together to assure that that happens?

I just have a couple of follow-up questions. The President's Council on Science and Technology put together their innovation package, and they had eight recommendations. I'm looking forward to going into greater detail into that. But you've been through it. What do you think, what stood out with you, to you, in that report, and what do you think we can work with you on to help do a better job of getting, you know, more effective cures to the market?

Dr. WOODCOCK. Well, I think some of the things that Congress has already sort of instantiated in FDASIA around accelerated approval already alluded to have been helpful in having us pay more attention to our expedited programs. The other thing that struck me about the proposals in the PCAST report called for more translational science, because it's hard for us to make decisions, you know, if the science isn't there.

Mr. MEEHAN. What do you mean by translational science?

Dr. WOODCOCK. Well, you know, there's basic science you can say, well, this pathway inside of a cell does this and that and the other thing, and then there is translational science which said this biomarker really is predictive of a good outcome. The more data a company or we have on that, the more confident everyone feels that we can, you know, put our money down on that, right. But if we have no data or say the rare diseases you're talk about, we don't have any data on the natural history of the rare disease, what people do is get a bunch of experts together and say, in my opinion, the disease progresses in this manner.

Now, that's been a problem not just for us, for the companies, because it turns out the disease does not progress in that manner and therefore their study they designed, you know, didn't work. It wasn't long enough, or, you know, it didn't measure the right things or whatever. And so that's translational science, is the science that supports actually studying the drug in people and actually enables you to study the drug effectively and quickly.

So PCAST called for formation of a consortium where everyone would work together to enable this translational science and move it along, and I think that would be very helpful. I also think this other mechanism I already talked about for antibiotics would also be helpful in dealing with some part of that epidemic.

Mr. LANKFORD. Can now jump in as well? Help me understand again why you think you need a statute for the antibiotics in the new process, why you don't feel like you already have statutory authority to do that, based on so many other areas, with the breakthrough, with the accelerated process, with all those things that are already in place, why do you need another statute for that?

Dr. WOODCOCK. I think we have statutory authority or we could claim we did and do a regulation. That would take many years, in my experience nowadays.

Mr. LANKFORD. Have you noticed how long it takes to get a bill through Congress?

Dr. WOODCOCK. Well, I just have great faith in you.

Mr. LANKFORD. That makes one.

My concern is, as deadlocked as we are in so many different areas, my preference, and I'm not going to speak for all of us, would be you get started on what you feel like you have statutory authority for now and so we can have something in process.

Dr. WOODCOCK. Right.

Mr. LANKFORD. We have a responsibility to get our stuff done as well, but that has not gone as smoothly as it should and that we are capable of, obviously. And I would hate for FDA to sit back for 2 or 3 years and wait on us to get something done, and then once it's done, you have to promulgate rules based on that, and then we're even farther behind.

Dr. WOODCOCK. We had a public meeting on this, which is often a prelude to rulemaking. We have certainly been in discussions with companies that are interested in utilizing this pathway.

Mr. LANKFORD. Okay. I do not want you to try to feel like I'm saying to you, though, leave statutory authority. If you do not have statutory authority, obviously don't go outside of statutory authority. But if you have it and you feel like you already have it, validate it, and I would encourage you to get moving on it.

Dr. WOODCOCK. Uh-huh.

Mr. LANKFORD. So, again, I'm not going to try and speak for all of us, but while we do have a responsibility, things have bogged down significantly here. Fairly obvious, I think.

Ms. SPEIER. I have a question. There was a period of time in the not-so-distant past when a number of companies had come to me with questions about their approval when they had two drugs that had been previously approved by the FDA. They were combining them for obesity and were having either a difficult time getting it approved or actually getting it denied, even though both of those drugs independently had already been approved by FDA.

Can you talk about that on the one hand, and also about where we are in terms of obesity drugs? Because we all know this is a huge issue in terms of American health.

Dr. WOODCOCK. Certainly. Well, when you——

Ms. SPEIER. And I need a quick fix.

Dr. WOODCOCK. We've had a lot of obesity drugs have to be pulled off the market for safety problems, and primarily they were cardiovascular safety problems. And so, I think the FDA is trying to exercise caution on new obesity drugs but recognize this is another epidemic that we're facing that needs some kind of new thinking as far as how to deal with it.

The sliding scale I talked to you about before. So if you have a drug that's indicated for seizures, say, that drug's benefit risk will be looked at in the light of what is epilepsy, what are the available treatments, who might use it, how much risk would they be willing to take, okay, to control their seizures. If you move a seizure drug or a drug for heart failure or something over to obesity, you say to yourself 30 percent of all adult Americans have obesity. How much risk of uncertainty of, say, heart attacks or strokes are we willing to take in that population—all right, that's just an example—versus where you're treating epilepsy where the people are facing risks if they continue to have seizures, right. And that's the conundrum that we're in. These drugs that we would approve for obesity, millions of Americans might be exposed to them, and they need to be relatively safe, unless, again, we were able to restrict them to the very people suffering from the most severe types of obesity. But that would be unlikely given the prevalence of the condition in the United States.

In fact, we initially talked about this limited use scenario that we're talking about for antibiotics also for obesity because the benefit risk for somebody who is severely obese is different than someone with mild obesity, or somebody who is severely obese and has a lot of morbidities from it. Heart disease. They have severe arthritis, mobility problems, and so forth.

So the problem with, I think, obesity drugs is that eating is such a basic human instinct and function, any drug that's going to significantly interfere with that is going to have powerful effects and may have effects in multiple domains, and we need a lot of creativity in that area to move forward.

Mr. LANKFORD. We get into the issue of FDA making decisions for doctors and the labeling issues and the warnings and that kind of such, and I know that's a constant struggle for you because you're testing for a certain thing and you haven't tested for other things. You put that into the market and physicians may use it off label.

Dr. WOODCOCK. Uh-huh.

Mr. LANKFORD. How is that moving within FDA? And quite frankly, with your opinion, in the culture of FDA? Do you feel like you're clamping down on labeling and adding more because there's this barrier between do you restrict more or do you give more information to doctors and just overload them with information and say, read it, make the decision, because you're going to go off label anyway, or is it stronger off label, don't use it, restrict it, from FDA's perspective?

Dr. WOODCOCK. Well, generally speaking, and I think this isn't well understood, but FDA accepts the fact that off label use can be appropriate, and that's a part of the practice of medicine for most drugs, okay.

There are drugs that we have special restrictions that are called REMS, and these were put in as part of the FDAAA legislation 6 years ago, I believe, and we had them before through regulation where you'd restrict distribution of a drug, and sometimes you have to say we're only using it for this.

And a premier example is, like, the drug Accutane is for severe acne. It's a very effective drug, and severe acne can be a really bad

condition, but it was widely used for all kind of acne because it works, right. But it's a major human teratogen, and so it causes major birth defects if used in a pregnant woman. And we were getting reports every year of use in pregnant women every year, every year, even women who were started on the drug and never had a pregnancy test.

So we, you know, put gradually more and more restrictions, and now that drug is highly restricted in that you have to get pregnancy tests before or not be of childbearing potential to get Accutane if you're a woman. And we hate to do that because that really burdens the healthcare system. On the other hand, we have some of these very dire side effects that the healthcare system has not shown itself to be capable of managing without further intervention.

So you're right, we walk a narrow line there. We don't want to overly restrict, but sometimes the side effects are so dire, and it might be that the drug might not be available unless he had that restricted program in place.

Ms. SPEIER. Can we speak about pediatric cancer for a moment? Within the NIH budget less than 4 percent of the funding goes to the research around pediatric cancer, and there's a lot of off label use of drugs for pediatric cancer. So can you just give us a sense of where FDA is in terms of evaluating drugs for paeds, as they refer to them.

Dr. WOODCOCK. Well, we've had a strong pediatric program because the Best Pharmaceuticals for Children Act, BPCA, and so there has been quite a response by the pharmaceutical industry to those programs. And, you know, they get extra exclusivity if they fulfill certain requirements. We just celebrated 500 drug labels that have been updated with pediatric information.

Now, that said, though, pediatric cancer is different, and why? Because the cancer arising in a child is usually not the same as the adult condition. And these pediatric programs were set up to study conditions that occur in adults and then study them lower and lower ages and then get that information. But it stands to reason that the kind of mutation that would occur in a child, you know, when they are just born or when they're young, is different than the kind of mutations that occur over a lifetime in a cell type and cause cancer. So that progression that we see in other diseases hasn't happened as much in the pediatric diseases, and I believe the pediatric cancer community is concerned about this.

We've tried to encourage companies to study right away drugs in childhood cancers if they seem appropriate. Often you'd study a disease in adults first and then study children, but in fact, when you have a life-threatening disease like cancer it's appropriate to study the children right away also. But the question is, what is the right drug for that cancer in children?

I personally believe that the genomic revolution that we were talking about earlier where we begin to understand the sequences, the driving mutations in the cancers is really going to help us, but we also are finding some of the pediatric cancers are actually multiple diseases put together, just like an adult cancer is.

So we have a pediatric oncologist, a very senior pediatric oncologist on staff at the Center for Drugs, and we are really trying to encourage development in this area.

Mr. LANKFORD. Mr. Meehan, you had a question?

Mr. MEEHAN. Just a final question, and maybe it's not fair to even ask it, and if you don't want to respond don't. But thinking outside the box, I mean, you labor in the vineyard, and there must be times where you sit and think, you know, if we built the mousetrap a little different way, maybe we could have success. And I'm asking the question sort of guided by the fact that you're hearing some of these wealthy industrialists or others who are saying that with their life's savings now they want to be the person, for instance, that cures Alzheimer's, and they're going to put everything into this effort. And I don't know whether that is the kind of thing that we ought to be encouraging, where we say, let's just cure Alzheimer's, let's create this Center for Excellence that does it, let's keep it here in the United States so they don't send it overseas to do it, which they're referring to. Does that make sense or are we better off doing what we're doing trying to not choose winners and losers?

Dr. WOODCOCK. That's a really profound question, I think. I mean, I really can't give advice to Congress. I believe that patient advocacy groups in many diseases have made tremendous strides in advancing the treatments and cures for their diseases. So that disease focus can be very beneficial in getting treatments advanced and so forth, and they've done a great job, partly because they understand what's needed. And often what's needed is these clinical trial networks getting the outcome measures, doing the natural history, really understanding the disease very well, so when treatments come along they don't fail, you know, they can be tested rapidly and figure out how desirable they are.

Mr. MEEHAN. You have mentioned communication a number of times. Are we missing opportunities in this age of the ability of the NSA to drill down into the most intimate details anywhere? But no, we're collecting more information than we've ever done before. We've got the ability to assimilate information better than we have before, and we are creating more medical records, albeit they're still too much on paper and other kinds of things. But with this bulk of records out there, are we losing an opportunity to mine what we already know to significantly enhance or advance the ability to understand the things that we're trying to take on?

Dr. WOODCOCK. I don't know. Often the medical records, for example, aren't detailed and standardized well enough to provide these natural history outcomes that we'd really like to have. We have the Sentinel System that we've set up, which is really pretty, I think, novel and innovative. We have 120 million lives of data all behind the firewalls of the data partners, the insurance companies, or healthcare system. But we have it all standardized, we can query it, and we use that for drug safety analysis, okay. So we use that existing data. And they're starting to randomize, cluster randomize within these kind of systems and answer important questions by doing experiments out there.

I believe that telemedicine and recruiting people through social media and so forth is probably something we really should do, and

that would be a way to really reach patients who are out there and whose doctors aren't telling them or they don't know about availability of trials and so forth. I think we've just started to scratch the surface on how well that can serve us.

Mr. MEEHAN. Well, I thank you. I guess we could go on all day. But I am very, very grateful for the work that you do and for your presentations here today. Thank you.

Thank you, Mr. Chairman and Ranking Member, for holding this hearing.

Ms. SPEIER. Actually, the gentleman from Pennsylvania just triggered, and your response triggered a question for me. The ClinicalTrials.gov. At Google you can actually elevate your status, so to speak, by paying for it. And so if you were to Google cancer, you can have ClinicalTrials.gov come up first. Who would be responsible for making that decision as to whether or not that should be an expenditure we make?

Dr. WOODCOCK. That site is maintained by the National Library of Medicine, it's part of NIH.

Ms. SPEIER. Okay. So that's a question to ask them.

Let me just conclude, Mr. Chairman, by saying that I think we've got just a gold mine in you, Dr. Woodcock, and I thank you for the competency and professionalism that you've showed for so very long. And I hope that this will be a beginning of an opportunity for us to find more ways to work together, and I really think that pursuing the manufacturing of drugs here in the United States is worthy of our time and attention, and your assistance would be greatly appreciated.

Dr. WOODCOCK. Absolutely.

Mr. LANKFORD. I'd agree with that as well. And I also want to thank you for the time to be able to spend here and the time, both in preparation of your written statements. You made a comment earlier that you don't give advice to Congress. Again, that would be one of the few Americans that doesn't do that. That's the wonderful thing about a republic, everyone can give advice to Congress.

But through this there were a lot of to-do's that come out of this. Let me give one statement just from me on it. You're doing a lot of pilots, you're doing some outside-the-box thinking of what can we do on that. We want to encourage that and to say continue to do that. The companies, we have a lot of companies that are now IPOs that are jumping in with different ideas.

Dr. WOODCOCK. Uh-huh.

Mr. LANKFORD. We want to continue to encourage the innovation that helps everyone. I'd also like to continue to encourage you, as you've already started in your office, in communicating with the advocacy groups for each of these different diseases. They want the communication with you.

Dr. WOODCOCK. Yes.

Mr. LANKFORD. As much as you can spur that and then also connect the dots between groups, for instance, what's happened, as you mentioned before, with the cystic fibrosis organization. There may be others that are interested in that that may not even know that is occurring, but if it fast tracks that and if there are ways that these different outside groups can do, they are looking for things that will help. If there are things you can clearly articulate that

would help, they would like to know that, and they need to be able to hear that from you. They are very connected to NIH in the funding. They need to be connected to you in the same way to know not only what's the research out there that's being done, once the research is done, how can we fast track solutions.

Dr. WOODCOCK. That's right.

Mr. LANKFORD. So, I would encourage that, as well as increased information to physicians on clinical trials so that for these rare diseases, especially, physicians know about the clinical trial process and can get their patients into it. Be much better than the compassionate use and other ways, and we can have the research ongoing on it.

So those are quick admonitions in that, but you need to let us know as well what we need to do statutorily, and we'll continue the conversation about the antibiotics. But if there are things that you need from us, we want to help in that.

Dr. WOODCOCK. Thank you.

Mr. LANKFORD. And we'll work in a bipartisan way to be able to get that done.

So with that, with no other questions on the dais on that, this hearing is adjourned.

[Whereupon, at 4:25 p.m., the subcommittee was adjourned.]

APPENDIX

MATERIAL SUBMITTED FOR THE HEARING RECORD

Opening Statement
Rep. Jackie Speier, Ranking Member

Subcommittee on Energy Policy, Health Care and Entitlements Hearing on "FDA Checkup: Drug Development and Manufacturing Challenges"

December 12, 2013

Mr. Chairman, Thank you for holding this important hearing.

I also want to thank the witnesses, and particularly Paul Hastings, CEO of OncoMed Pharmaceuticals for being here. OncoMed is located in my district, and is doing groundbreaking work on stem cell therapeutics that could provide important alternatives for the treatment of cancer. He brings a crucial understanding of the FDA approval process, and the successes and challenges that remain in that process.

I also want to thank Dr. Woodcock for being here, and for the great work she is doing to improve the pathway for drug approvals and manufacturing, and for working with us to understand the challenges the FDA faces to ensure that our innovative bio-technology sector remains just that—innovative, and able to efficiently move new products from early stage developments, through the clinical trial process, and to approval and full scale manufacturing. I know she expected to focus on the modernization of drug manufacturing, but I would also like to discuss some of the initiatives underway at FDA under the PDUFA (Prescription Drug User Fee Act) reauthorization and the Food and Drug Safety and Innovation Act (FDASIA)—both passed last year.

Last night I hosted a special order hour to highlight the critical work of the NIH in funding basic research and providing grants to fund early stage groundbreaking treatments. All that is for nothing if the newly discovered drugs and treatments cannot be brought efficiently and safely to market.

I am very proud that the biomedical industry really started in my district with the founding of Genentech in South San Francisco in 1976. Since that time, the biotech industry has grown dramatically in my district and across the country. Over the years its growth has also posed a challenge to the FDA, and its ability to assess and approve these new drugs and devices for both safety and efficacy. I have facilitated several meetings with the FDA and companies in

my district to discuss their concerns with the process, and how that process needed to improve. FDA listened.

In the past the FDA was criticized for being unpredictable and risk adverse, to the point of discouraging beneficial products and biomedical innovation. The industry has consistently pushed for more transparency and a predictable process, with better Agency communication. FDA listened.

While we must make sure this industry --in both development and manufacturing-- is not crippled by either government action or inaction, we must also make sure that the FDA has the resources to properly do its job.

I am very concerned that as a result of the sequester, a portion of the new fees that the industry agreed to pay under the Prescription Drug User Fee Act reauthorization in 2012 to help improve and speed the process are being withheld. This is unconscionable, and we must pass the bi-partisan Food and Drug Administration Safety Over Sequestration Act (FDA SOS) immediately.

The Agency clearly recognizes the need to modernize and improve its record, and FDA Commissioner Hamburg launched an innovation initiative soon after she took command in 2009. In 2011 the FDA cleared 35 "innovative" drugs, including advances in treating hepatitis C, lupus, pneumonia, and several different cancers and orphan diseases. According to the FDA, all but one of these drugs was approved on or before the target dates set by the statute. But others still lagged, faced delays and unexpected demands for additional clinical trials.

We must make sure that FDA does not shortchange its attention of drug applications from one therapeutic area while it concentrates on other high priority areas. Oncology, for instance, is a high priority and the Agency has used various procedures to accelerate the approval of cancer drugs. Indeed, the FDA and others have highlighted recent approvals of oncology products as evidence of its commitment to biomedical innovation. There are also other areas with serious disease burdens – obesity and diabetes are good examples – where regulatory standards remain unclear and the Agency's performance may have lagged. Disorders like Alzheimer's, Parkinson's and multiple sclerosis impose widespread suffering, but their complex biology has made them notoriously elusive targets for drug development, and the regulatory process seems to mirror this complexity.

Importantly, FDASIA (fuhdaysia) contained measures to help foster more timely patient access to new medicines; enhance FDA's regulatory science capacity; encourage future innovation and strengthen the FDA's high safety standards. FDASIA also provided FDA with a novel accelerated drug development instrument, known as the "breakthrough therapy" designation, allowing FDA to assist drug developers to hasten the development and evaluation of new drugs utilizing preliminary clinical evidence that a drug may offer a significant improvement over currently available therapies for patients with potentially fatal or life threatening diseases.

This is all good news.

Opening Statement

Congressman Matt Cartwright

Committee on Oversight and Government Reform

Subcommittee on Energy Policy, Health Care and Entitlements

***Hearing on:* "FDA Checkup: Drug Development and Manufacturing Challenges"**

December 12th, 2013

Thank you, Chairman Lankford and Ranking Member Speier.

All Americans depend on the Food and Drug Administration to ensure that drugs brought to market in the U.S. are both safe and effective. It's critical the agency develops and implements the proper safety protocols to protect public health. At the same time, the FDA must have the tools necessary to speed up the drug approval process to take advantage of advances in biotechnology and medicine. The Food and Drug Administration Safety and Innovation Act is an important step forward in improving how drugs are developed and manufactured. Congress must continue to examine how best to aid the FDA. It's also imperative that in the future Congress funds the agency at the appropriate level. We cannot, as we have in the past, let indiscriminate cuts in spending impede the important work the FDA does in preventing drug shortages and making sure that men, women, and children receive the best medicine available.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MAR 21 2014

The Honorable James Lankford
Chairman
Subcommittee on Energy Policy, Health Care and Entitlements
Committee on Oversight and Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the December 12, 2013, hearing entitled "FDA Checkup: Drug Development and Manufacturing Challenges," before the Subcommittee on Energy Policy, Health Care and Entitlements, Committee on Energy and Commerce. This letter is a response for the record to questions posed by certain Members of the Committee, which we received on January 24, 2014.

If you have further questions, please let us know.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

Enclosure

cc: The Honorable Jackie Speier
Ranking Member
Subcommittee on Energy Policy, Health Care and Entitlements

We have restated each Member's questions below in bold, followed by FDA's responses.

The Honorable James Lankford

1. **The President's Council of Advisors on Science and Technology (PCAST) issued a report on Propelling Innovation in Drug Discovery, Development, and Evaluation, which states that "Without the need for new legislation, the FDA could expand its use of Accelerated Approval to address more types of serious diseases with unmet medical need and to use intermediate clinical endpoints. The agency would also need to signal to industry that this path for approval could be used for more types of drugs, and to specify what kinds of candidates and diseases would qualify.... This will require a robust exercise of FDA's existing authorities and, possibly, additional authorities."**

    a. **Does FDA plan to expand its use of Accelerated Approval through regulatory or administrative processes? If so, what is the plan and what is the timeline for implementation?**

FDA is committed to employing a flexible approach, with respect to products to treat serious conditions in patients with unmet medical needs. As described in the draft guidance for industry, Expedited Programs for Serious Conditions—Drugs and Biologics, issued in June of 2013, the Agency has various programs, including Accelerated Approval, intended to ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks. The Agency believes that this draft guidance, and the final version anticipated this year, will facilitate broader use of the accelerated approval program in appropriate therapeutic areas.

    b. **Does FDA need any additional legislative authority to expand the use of Accelerated Approval as suggested by PCAST?**

The accelerated approval provisions included in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), amending section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), provide that FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

The provisions of FDASIA facilitate broader use of accelerated approval to expedite patients' access to important treatments for serious conditions. The new provisions provide additional flexibility concerning the implications of available therapy on eligibility for accelerated approval. They also provide clarification concerning the use of clinical endpoints (intermediate clinical endpoints) as a basis for accelerated approval. In addition, the new provisions make clear that FDA has the authority to consider pharmacologic or other evidence developed using biomarkers or other scientific methods or tools, in conjunction with other data, in determining whether an endpoint is reasonably likely to predict clinical benefit. By indicating that FDA should take into account ". . . the severity, rarity, or prevalence of the condition . . ." in considering whether to grant accelerated approval, FDASIA reinforces the Agency's long-standing commitment to regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options.

The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers and human immunodeficiency virus (HIV) disease where an effect on tumor growth or viral load can be assessed rapidly, but demonstrating an effect on survival or morbidity generally requires lengthy and sometimes large trials because of the duration of the typical disease course.

FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and study planning and conduct of confirmatory trials.

2. How does FDA plan to address the wide deviation in review times between therapeutic drug areas?

FDA's Center for Drug Evaluation and Research (CDER) developed a standardized review model that applies to the review of all new drug applications (NDAs) and biologics license applications (BLAs). The model is called "21st Century Review" and has been applied to all applications across all review divisions starting in FY2009 for original BLAs and new molecular entity (NME) NDAs, with final integration of all application types, beginning in FY2012. CDER staff have received extensive training on this new review model, which was designed to ensure consistent application of best practices across all review divisions. Implementation of the new review model has been very successful and served to lay the groundwork for implementation of the "Program" for review of NME NDAs and new BLAs, which is a new performance goal under PDUFA V.

While CDER's Office of Hematology and Oncology Products (OHOP) has established a commendable track record in expediting the review of promising new drugs for patients with cancer, the same principles and best practices utilized in OHOP are also applied in other divisions and offices to expedite the review and

approval of promising new drugs that treat serious and life-threatening diseases and meet an unmet medical need. For example, a new drug that treats the underlying cause of cystic fibrosis in some patients with that rare genetic disease was approved in January 2012 by the Division of Pulmonary, Allergy, and Rheumatology Products several months ahead of the PDUFA goal date.

Under the new Breakthrough Therapy (BT) program that was part of FDASIA, FDA has made an institutional commitment to work closely with sponsors to expedite the development and approval of new drugs for serious and life-threatening diseases that provide a substantial improvement over currently available therapies. This commitment includes involvement of senior FDA leadership in individual programs. While almost half of the BT designations granted by FDA to date have been for drugs intended to treat hematologic and oncologic diseases, many other CDER review divisions have also granted BT designations and are committed to supporting the goals of the program, including utilizing all the available tools to expedite development and approval of these promising new drugs.

3. **PDUFA financial reports lack detail of various categories of spending, specifically, the direct costs of reviewing new human drug applications (i.e., New Drug Applications (NDAs), Biologics License Applications (BLAs) and supplements) and headcount allocation summaries for user-fee-funded activities.**

    a. **Does FDA plan to provide more detailed information on prescription drug user fee collections, allocation, obligations of PDUFA user fee revenues by different categories of expenditures (e.g., contract services), and carryover balance to identify efficiencies in a resource constraint environment?**

FDA has historically provided detailed information on various activities related to the PDUFA program in the annual financial report including:

- Breakdown of fees collected by type: application, product, and establishment
- Breakdown of obligations by type: Personnel Compensation and Benefits, Travel and Transportation. Rent, Communications, Contract Services, Equipment and Supplies and Other.
- Carryover balances since 1993
- Summary of cash collections received, ceilings and offsets since 1998
- Breakdown of claims on carryover and resulting available carryover
- Breakdown of total process costs broken out by FDA component (CDER, CBER, ORA and HQ)
- Breakdown of total process costs broken out by obligations from appropriations and obligations from user fees
- Waiver and exemption data for last five years of program
- Breakdown of costs associated with ORA

Beginning with the FY 2013 PDUFA Financial Report, FDA will provide additional information including:

- Breakdown of total spending by FDA component since 2004
- Breakdown of total full-time equivalents (FTEs) by FDA component since 2004
- Breakdown of total spending, broken out by obligations from appropriations and obligations from user fees since 2004
- Waiver and exemption data for last 10 years of program
- Dollar value of exemption and waiver categories for last 10 years of program

FDA is committed to financial transparency in, and the efficient operation of, the PDUFA program. The Agency will continue to evaluate opportunities for enhancing both transparency in future financial reporting and the cost-effective management of the PDUFA program.

4. **Does FDA plan to work with the National Institutes of Health to update clinicaltrials.gov to make it more accessible to both patients and doctors?**

The National Institutes of Health (NIH) is responsible for the operation of the *ClinicalTrials.gov* database and implementation of the elements related to the database. FDA has worked with NIH on various aspects of the implementation of *ClinicalTrials.gov* and will continue to do so in the future.

5. **Does FDA plan to update or reorganize FDA's website page that explains the process of expanded use, so that patients and doctors can better understand the program?**

We are assuming that "expanded use" is referring to "expanded access," and our response is based on that assumption.

In 2013, CDER updated its website to include educational/training materials intended for individual investigators and for doctors seeking access to investigational drugs outside of a clinical trial for their patients (i.e., "expanded access" (EA), sometimes referred to as "compassionate use") (see *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm.*). These materials were developed as part of a two-year collaboration between CDER and the NIH Clinical Center, which requested such training in order to help their investigators in submitting IND applications and EA requests, as well as assist individual investigators outside of NIH who are part of NIH's research collaboratives. (Some of NIH's collaboratives include the Clinical and Translation Science Awards (CTSA) program, which is a large network of academic research institutions, as well as web-based training programs that can be accessed throughout the United States and other countries throughout the world.

One of the website updates includes training materials for "IND Applications for Clinical Treatment: Treatment of a Single Patient in Emergency Setting," also known as emergency

INDs, which are a type of expanded access IND, available at *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343022.htm*.

The emergency IND materials were tested and piloted at the NIH Clinical Center to assess their utility for investigators and were also reviewed extensively by CDER's Office of New Drugs. The emergency IND webpage includes:

1) Physician checklist for an IND application for emergency treatment, which is a 2-page form that provides the requesting physician with a description of the criteria for an emergency IND, *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/UCM343041.pdf*. This form may be completed electronically or printed out and completed by hand, and may be e-mailed or faxed directly to the review division, in order to begin the emergency IND request process.

2) Emergency IND application timeline, which describes the steps involved in submitting an emergency IND application, with additional links within the document to required forms or guidance documents: *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/UCM343024.pdf*.

3) Emergency IND eligibility tool graphic to help investigators assess in what circumstances an emergency IND may be available: *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/UCM343034.pdf*.

The second FDA website update included a comprehensive training materials "tool kit" for investigator-initiated IND applications, available at *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm*.

This tool kit contains descriptions, links to required forms, guidances, and a broad range of other information intended to provide information regarding regulatory processes and procedures in four categories:

1) IND applications for clinical investigations, including overview, contents and format, regulatory and administrative components, non-clinical components, and clinical components;
2) IND application reporting, including overview, protocol amendments, information amendments, safety reports, and annual reports;

3) IND application procedures, including overview, exemptions from IND requirements, interactions with FDA, clinical hold, and investigator's responsibilities; and
4) IND applications for clinical treatment (expanded access), including overview, contents and format, treatment of a single patient in emergency setting, treatment of a single patient in non-emergency setting, and treatment of a group of patients.

We have been communicating with stakeholders regarding the availability of these materials at public meetings and educational conferences, at a recent NIH IND regulatory training conference held at NIH (materials are due to be posted on NIH's website in the near future) via NIH Clinical Center's research networks, and through interactions with individual research investigators.

The feedback on the training materials that we have received thus far has been overwhelmingly positive. A tremendous amount of thought, work, and consultation with the target audience for the materials went into the development of these tools with the intent of facilitating the IND application process.

6. The PCAST report cited inefficiency in clinical trials as an obstacle to drug innovation. What steps is FDA taking to make trials less costly and more efficient?

FDA recognizes that greater efficiencies in conducting clinical trials will help promote the development of new products and therapies benefitting the public health. FDA is taking various steps, including developing policies and soliciting stakeholder feedback, to help sponsors improve the efficiency of clinical trials they conduct. For example, in 2013, FDA issued guidance for industry entitled "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring." This guidance document describes strategies for monitoring activities that reflect a modern, risk-based approach. Further, the guidance document encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight, in part, by taking advantage of the innovations in modern clinical trials (e.g., increasing use of electronic systems and records). As an example of soliciting stakeholder feedback, FDA held a public hearing in 2012 to obtain input from interested persons on FDA's scope and direction in modernizing the regulations, policies, and practices that apply to the conduct of clinical trials of FDA-regulated products. FDA sought feedback on specific good clinical practice regulations, policies, and practices that may need clarification or revision to facilitate advances in the ways that clinical trials are conducted, remove impediments to the use of innovative approaches, or otherwise improve the conduct of clinical trials. FDA has previously provided, and will continue to provide, a forum for FDA and stakeholders to discuss scientific issues and proposed solutions to inefficiencies within clinical trials.

The Honorable Patrick McHenry

1. **To date, the FDA has held two public hearings, issued four general draft guidances, and conducted approximately 50 formal meetings with prospective sponsors of biosimilars on the Biosimilars Price Competition and Innovation Act (BPCIA). Along the way, you and others at FDA have said that you intend to provide the public and stakeholders with more detailed guidance and other policies that flesh out key BPCIA implementation issues. After more than three years we still do not have much insight into how the FDA is going to interpret it. Please tell us what we can expect to see from the FDA in terms of BPCIA implementation policy in 2014 and beyond and please be specific.**

To date, FDA published the following four draft guidance documents to assist those sponsors interested in developing biosimilar products:

1. Guidance for Industry on Biosimilars: Q&As Regarding Implementation of the BPCI Act of 2009 available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf*
2. Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf*
3. Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf*
4. Draft Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf

FDA is carefully reviewing and considering the comments submitted to the docket for the Agency's draft biosimilar guidance documents and the November 2010 and May 2012 public hearing dockets. We will take into consideration all received comments as we move forward in finalizing these guidance documents. We intend to develop additional guidance documents regarding biosimilar products and interchangeable products, including the following:

1. Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009
2. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
3. Considerations in Demonstrating Interchangeability to a Reference Product
4. Labeling for Biosimilar Biological Products
5. Reference Product Exclusivity for Biological Products Filed under 351(a), PHS Act.

The Honorable Scott DesJarlais

1. **There is great concern regarding the growing threat of antibiotic resistance in our hospitals and communities, and the need for new antibiotics to tackle this threat. What strategies is FDA putting in place to ensure that new antibiotic approvals address the evolving nature of bacterial infections?**

FDA is working on a number of different activities to facilitate the development of antibacterial drugs so that health care providers have new antibacterial drug therapies to treat their patients.

FDA, as well as the European Medicine Agency (EMA), NIH, and the Centers for Disease Control and Prevention (CDC) have participated in a number of meetings held by public-private partnerships to address a number of important topics to facilitate the development of new antibacterial drugs. Meeting hosts include the Brookings Institution: Engelberg Center for Health Care Reform, the Foundations for the National Institutes of Health Biomarkers Consortium, and the Clinical Trials Transformation Initiative.

Along with CDC and NIH, FDA co-chairs the Inter-Agency Task Force on Antimicrobial Resistance. We also participate in the Transatlantic Task Force on Antimicrobial Resistance (TATFAR).

FDA continues to meet with drug companies that are developing antibacterial drugs to provide recommendations/advice on antibacterial drug development pathways. FDA staff has been working with drug companies to update susceptibility test interpretive criteria ("breakpoints") in the labeling for their products. To date 126 of 207 product labels for reference-listed systemic antibacterial drugs for human use have been updated.

We held numerous Advisory Committee discussions on clinical trial design in the context of specific antibacterial drug products that informed the development of recommendations on clinical trial designs. These efforts to date have resulted in the publication of updated guidance documents in the area of antibacterial drug development or non-inferiority clinical trial designs. To facilitate development of antibacterial drugs on recommended clinical trial designs, we are continuing to publish and update our draft and final guidance documents. One such guidance is a draft guidance document on developing *Antibacterial Therapies for Patients with Unmet Medical Needs for the Treatment of Serious Bacterial Diseases*. This guidance describes streamlined approaches to developing antibacterial drugs for patients with few or limited treatment options (e.g., because of resistance to existing therapies). These approaches are consistent with thinking in the context of other programs intended to expedite the availability of new therapies to address unmet medical need and articulated in FDA's regulations at 21 CFR part 312, subpart E:

...These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated...

2. Dr. Woodcock, in your opinion, what are the challenges associated with trials structured for a pathogen-based approval, where multiple sites are evaluated according to a single pathogen?

While the term pathogen-focused has been used to refer to a variety of different approaches to drug development, we note that your question focuses on a development program that would enroll patients with infections at multiple body sites caused by either a single bacterial species or a limited number of bacterial species within a single clinical trial. This approach presents scientific, practical (given the nature of acute bacterial infections), and logistical challenges for clinical trials, as well as the economic realities of the antibacterial drug therapeutic area. The following factors described below are inter-related.

Often the frequency with which a particular bacterial species causes infections is low (e.g., a particular bacterial species that causes pneumonia and/or intra-abdominal infections in only 5-10 percent of patients). Given the low frequency of a particular bacterial species causing an infection, enrolling patients in a clinical trial designed to study patients with an infection caused by an infrequently occurring bacterial species will be difficult.

The time that it takes to identify a bacterial cause of a patient's infection also makes it difficult to enroll patients with infections caused by a particular bacterial species into a clinical trial. Current diagnostic techniques to identify the bacteria causing an infection may require a day or two to do so. For serious acute bacterial infections, antibacterial drug therapy needs to be initiated urgently (e.g., within the hour or a few hours) and hence, the bacterial etiology often is not known at the time that antibacterial drug therapy is initiated. For this reason, one is typically faced with the need to enroll many, many patients in a clinical trial in order to accrue a sufficient number who have an infection caused by a particular low-frequency bacteria. Another approach would be to only enroll patients once the bacterial cause for the patient's infection has been identified; using such an approach raises the issue that the antibacterial drug therapy that was urgently initiated and given for a day or two prior to enrollment in the clinical trial may play a very important role in treating the patient's infection and would obscure the assessment of the effect of the investigational drug that is started after more than a day of prior non-study antibacterial drug treatment.

For many infections, empiric therapy or diagnostic uncertainty may lead to the use of concomitant antibacterial drug therapy consistent with the standard of care for medical practice that may have an antibacterial spectrum of activity that overlaps with the activity of the investigational drug; this overlap in spectrum of activity may obscure the assessment of the effects of the investigational drug.

A streamlined clinical trial that enrolls patients with infections at different sites in the body may have reduced capacity to detect relative deficits in performance of an antibacterial drug. There have been several instances where unexpected results from clinical trials

revealed deficits in the performance of an antibacterial drug.[1] A streamlined clinical trial that enrolls patients with infections at different body sites in a single clinical trial may have reduced capacity to detect such deficits; hence, leading to greater risks and/or uncertainty regarding the drug's true efficacy and safety profile.

Rapid diagnostic tests to determine the bacterial etiology within an hour or less are not generally available. If rapid diagnostic tests become available that could rapidly identify a bacterial etiology or significantly increase the likelihood that a particular bacterial species is the cause of a patient's infection, these rapid diagnostics could facilitate the enrollment of patients with infections caused by the bacterial species of interest in a clinical trial. To facilitate the appropriate use of an antibacterial drug with a very narrow spectrum of activity in clinical practice (e.g., an antibacterial drug that is indicated for use against a single species of bacteria), rapid diagnostic tests would likely need to be available to health care providers so that they can make informed clinical decisions regarding the use of such narrow spectrum antibacterial drug.

[1] See FDA Statement on recently terminated clinical trial with Doribax (doripenem): Safety Announcement: [01-05-2012]. Available at *http://www.fda.gov/Drugs/DrugSafety/ucm285883.htm*. FDA Drug Safety Communication. FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning: Safety Announcement: [9-27-2013]. Available at *http://www.fda.gov/drugs/drugsafety/ucm369580.htm*. Pertel PE, Bernardo P, Fogarty C, Matthews P, et. al., Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia. *Clin Infect Dis*. 2008 Apr 15;46(8):1142-51. doi: 10.1086/533441.