21ST CENTURY CURES: INCORPORATING THE PATIENT PERSPECTIVE

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

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FRIDAY, JULY 11, 2014

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

The subcommittee met, pursuant to call, at 9:00 a.m., in room 2322, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Shimkus, Murphy, Blackburn, Gingrey, Lance, Cassidy, Guthrie, Griffith, Bilirakis, Ellmers, Upton (ex officio), Pallone, Engel, Capps, Schakowsky, Green, Barrow, Castor, Sarbanes, and Waxman (ex officio).

Also present: Representative DeGette.

Staff Present: Clay Alspach, Chief Counsel, Health; Gary Andres, Staff Director; Mike Bloomquist, General Counsel; Sean Bonyun, Communications Director; Leighton Brown, Press Assistant; Paul Edattel, Professional Staff Member, Health; Brad Grantz, Policy Coordinator, O&I; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Macey Sevcik, Press Assistant; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Jean Woodrow, Director, Information Technology; Ziky Ababiya, Minority Staff Assistant; Eric Flamm, Minority FDA Detailee; Karen Lightfoot, Minority Communications Director and Senior Policy Advisor; and Rachel Sher, Minority Senior Counsel.

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

Mr. PITTS. The subcommittee will come to order. We are going to have early votes, so we are going to have to start. We understand the minority members are on their way.

The chair will recognize himself for an opening statement. Today's hearing provides us with an opportunity to examine perhaps one of the most important aspects of the 21st Century Cures Initiative. What does medical innovation or faster cures mean for patients? Keeping our work centered on the patient and understanding the patient perspective will bring much needed focus on results for patients who may lack adequate treatment options. Remember, there are only effective treatments for 500 of the 7,000 known diseases impacting patients today.

While FDA has developed an enhanced structured approach to benefit risk assessment in regulatory decisionmaking for human drug device and biologic products, the committee recognizes the value of considering patients in decisionmaking about therapy development and access. Assessment of a drug or device's benefits and risk includes an analysis of the severity of the condition treated and the current treatment options available, and getting the patient's unique perspective should be a part of that assessment.

One of our witnesses today, Pat Furlong of the Parent Project Muscular Dystrophy, PPMD—and I must say Pat is accompanied by Mary Bono Mack, a distinguished former member of this committee. Welcome, Mary. And Pat will explain how this organization was founded to create opportunities for families waiting for therapies to stop Duchenne muscular dystrophy from claiming young lives. To quote Pat Furlong, "Patient-focused drug development acknowledges the need to gather input from patients and their caregivers to create a more complete assessment of the benefit-risk equation, encouraging predictability, and increased flexibility within the review process. The clock is ticking for patients who need and deserve access to promising therapies."

I would like to applaud her tireless work drafting guidance PPMD recently released that actually quantifies patient priorities and preferences. This guidance will serve the Duchenne community and every other patient community because it provides a path for other patient groups to follow. This was an enormous undertaking, and I am confident it will make a substantial contribution to the entire medical community.

I would like to welcome our witnesses today and look forward to learning more about the assessment of benefits and risks central to medical product development, regulations, and healthcare decisionmaking and the tradeoffs between desired benefits and tolerable risk. Thank you.

Any member on the majority side seeking recognition?

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

The Subcommittee will come to order.

The Chair will recognize himself for an opening statement.

Today's hearing provides us with an opportunity to examine perhaps one of the most important aspects of the 21st Century Cures Initiative: what does medical innovation or faster cures mean for patients. Keeping our work centered on the patient and understanding the patient perspective will bring much needed focus on results for patients who may lack adequate treatment options. Remember, there are only effective treatments for 500 of the 7,000 known diseases impacting patients today.

While FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drug, device and biologic products, the Committee recognizes the value of considering patients in decision-making about therapy development and access. Assessment of a drug or device's benefits and risks includes an analysis of the severity of the condition treated and the current treatment options available and getting the patient's unique perspective should be a part of that assessment.

One of our witnesses today, Pat Furlong of Parent Project Muscular Dystrophy—PPMD—will explain how this organization was founded to create opportunities for families waiting for therapies to stop Duchene muscular dystrophy from claiming young lives. To quote Pat Furlong, "Patient focused drug development acknowledges the need to gather input from patients and their caregivers to create a more complete assessment of the benefit-risk equation, encouraging predictability and in-

creased flexibility within the review process. The clock is ticking for patients who need and deserve access to promising therapies." I would like to applaud her tireless work drafting guidance PPMD recently released that actually quantifies patient priorities and preferences. This guidance will serve the Duchene community and every other patient community because it provides a path for other patient groups to follow. This was an enormous undertaking, and I am confident it will make a substantial contribution to the entire medical community.

I want to welcome our witnesses today and look forward to learning more about the assessment of benefits and risks central to medical product development, regulations, and healthcare decision-making, and the tradeoffs between desired benefits and tolerable risks.

Thank you, and I yield the remainder of my time to _____.

Mr. PITTS. The chair recognizes the vice chairman, Dr. Burgess for the remainder of time.

Mr. BURGESS. And thank you, Mr. Chairman.

And Dr. Woodcock, thank you for joining us again. It is always good to see you, always good to have you as a witness. You always provide valuable testimony. And our second panel representatives. I also want to acknowledge just as the chairman did, many of the patient organizations that you represent have worked well with our office and myself over the last several years.

Mr. Chairman, the laudable goals of the 21st Century Cures Initiative, and they are indeed laudable, but we got to remember, at the end of the day, it is all about patients. Doctors want to heal. We want to cure. That is why we entered the profession. No doctor ever wants to tell a patient there is nothing more we can do. The good news is that the golden age of medicine is really right around the corner. The doctors of tomorrow will have tools at their disposal unlike any before in human history. The ability of tomorrow's doctor to alleviate human suffering is going to be unparalleled and unmatched in history. Yet every day that goes by where these tools are not realized is a day that patients and their families have to struggle through the pain and suffering of their condition.

Every day counts for these Americans and for their families. For those who struggle with rare diseases, their struggle is only compounded by the lack of biomedical research. For those patients, it is difficult to see over the horizon. We have much work to do on this committee, and we have done a lot in the past. We particularly celebrate the 2-year anniversary of the Food and Drug Reauthorization Act that was just a few days ago. That was a good template. It was a good method for moving forward, and I appreciate that the Cures initiative is following that template, but there is no doubt that we can do much more.

I welcome the testimony of our witnesses, and I will yield back my time.

Mr. PITTS. The chair thanks the gentleman.

And I now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for opening statement.

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

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

This hearing is a fitting followup to Wednesday's hearing on clinical trials. After all, it is patients who live with the diseases and

conditions for which treatments are being sought, and this hearing, which is called "21st Century Cures: Incorporating the Patient Perspective," illustrates that we should take every opportunity to understand their experience.

Congress has a long history of listening to concerns of patients. That is what I did in 1983 when I wrote the Orphan Drug Act. That law came up when I heard from a constituent, Adam Seligman, who had a rare disease called Tourette's Syndrome. Adam was forced to take a drug that he could only get from Canada because, at that time, there were no effective treatments available in the United States. When his drugs were ceased at the border, his mother made a desperate call to my office begging me to do something.

I set out to figure out why there were no drugs in the U.S. for Adam's condition. We discovered that Adam was not alone. There are 134 drugs for rare diseases but only 10 had come to market solely as a result of industry. We knew we had a problem on our hands, and we set out to solve it.

The Orphan Drug Act has been a resounding success. Today, there are over 400 drugs for rare diseases, and I want to welcome the National Organization for Rare Disorders here today and look forward to their testimony.

I am telling this story about the Orphan Drug Act not only as an example of how Congress has listened to the concerns of patients and acted on them, I tell it because it is an example of appropriate use of legislation. In the case of rare diseases in the early 1980s, there was very clear evidence of a market failure in need of congressional action.

In the context of the 21st Century Cures Initiative, we need to assure that both FDA and the drug and device companies are listening to the concerns of the patients. FDA has a long history of engaging with patients, both in the context of advisory committees and in its review of drugs and devices. In the 2012 FDA Safety and Innovation Act, Congress pushed FDA to do even more to hear patients' concerns, and I look forward to hearing more from FDA today.

From what I can tell, the agency has taken that mandate seriously and is engaged extensively with the patient community. We should ask today whether FDA has adequate resources to continue to do this work.

As I mentioned on Wednesday when we had our last hearing, when it comes to legislating in complicated scientific areas, like the conduct of clinical trials, we need to proceed with great caution. For example, one issue in the area of clinical trials that is likely to come up today is how to incorporate so-called patient reported outcomes. As I understand it, this is an area that is multifaceted and scientifically complex. Congress should ensure that FDA has the flexibility and authority to make use of these outcomes but not dictate how and when that occurs.

I hope FDA will tell us about how it is applying other novel approaches to clinical trials in their regulation of drugs and devices. I would also like to know whether the agency believes it has the authorities necessary to adopt new approaches and whether other new statutory powers are necessary.

Mr. Chairman, thank you for holding this hearing. I look forward to the witnesses' testimony. I must say in advance that there is another subcommittee scheduled at the very same time as this one, so I will try to be back and forth to participate in both of them.

Thank you, and yield back my time.

Mr. PITTS. The chair thanks the gentleman.

I now recognize the chairman of the full committee, Mr. Upton, 5 minutes for opening statement.

Mr. UPTON. I yield back my time. I will just submit my statement in order to——

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

The entire purpose of our 21st Century Cures initiative is to accelerate the discovery, development, and delivery of safe and effective treatments to America's patients. We are here today to better understand how we can incorporate the most important perspective—that of patients and their families—into the conversation.

Patients should and need to play a key part of this process if we are to be successful. As one of our witnesses, Dr. Beall has noted, "Congress should work to ensure patients have a seat at the table, because no one understands a disease better than the people who suffer and fight every day."

I would like to issue a special welcome to Pat Furlong who has continued to fight after losing her two boys, Christopher and Patrick, to Duchene. We are very humbled that you are here to help with the cures initiative. I'd also like to welcome to Dr. Marshall Summer—a parent of a child with Down's Syndrome. Parents are tireless advocates of their children and we are pleased that you are here today. Thank you and all of our witnesses for being here today.

I also would like to thank Dr. Woodcock for testifying today. Unfortunately, prior obligations prevented her from coming to Wednesday's hearing so today she will provide her expertise on both modernizing clinical trials and incorporating the perspective of patients.

As I'm sure Dr. Woodcock will explain, FDA has taken steps to incorporate the perspective of patients in the drug development process. FDA's work with Parents Project Muscular Dystrophy is a good example of collaboration, and we look forward to hearing about next steps on the guidance they put together.

However, much work remains. We would like to learn how we can leverage the successful examples of agency-patient collaboration and what other steps we can take to ensure the patient's perspective on the benefit-risk framework is thoroughly considered and incorporated throughout the cycle of the drug review process.

At our first 21st Century Cures roundtable, we learned that there are treatments for only 500 of the more than 7,000 known diseases affecting our nation's patients. Our work will not be done until we can close this gap in cures. I look forward to hearing how we can incorporate the voice of patients in this process.

I yield the balance of my time to ————————————.

Mr. PITTS. The chair thanks the gentleman.

We have two panels today.

On our first panel, we have Dr. Janet Woodcock, director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Thank you for coming again today. And you will have 5 minutes to summarize your testimony. Written testimony will be placed in the record.

So, at this time, the chair recognizes Dr. Woodcock 5 minutes for opening statement.

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

Dr. WOODCOCK. Thank you. We are here to discuss how drug development better meets the needs of patients. Decades ago, healthcare was very physician-centric and actually very paternalistic. We all recognize that today. It was kind of "The doctor knows best; don't ask any questions."

Today, the model is collaboration between the patient and the healthcare team. These changes, though, have evolved slowly in our society, and the thinking and drug development has slowly changed in parallel.

The FDA Safety and Innovation Act of 2 years ago took significant steps in this direction of patient-centric development. It contained agreements under PDUFA that FDA would sponsor at least 20 patient-focused disease-focused meetings over 5 years. Eight of these meetings have been held to date, and they have been very impactful. The first one we held on chronic fatigue syndrome, we have issued a draft guidance on drug development in this area of very serious unmet medical need. Also, under PDUFA, were agreements to advance the development and use of patient-reported outcome measures. These are measures that the patient can fill out to say from their point of view how well they are feeling, how well the treatment is working, what adverse events they are experiencing.

We are having an expert meeting next week and will continue to work in collaboration consortiums to try and advance the science of patient reported outcomes. This is very important to really scientifically incorporate the patient's perspective into clinical trials.

Additionally, under FDASIA, FDA was to advance the development and use of a structured benefit risk framework in drug approval decision, and this work is under way, and it really explicitly provides for considering the burden of disease, the impact of current therapies, both for good and for ill, and the tolerance of risk from the patient's point of view, and this is an extremely important set of factors that need to go into the benefit-risk decision, but we need to do this in a scientific manner and a structured manner and we are rolling out the structured benefit risk framework.

Now, we know that for people with very serious diseases who may lack good therapy or actually lack any therapy, access to new treatments is their number one priority, and that is why expediting drug development programs in these areas is so important. If you look at the diagram that we have here that was provided, these data and the diagram were actually developed by the Pharma organization, talks about, shows the drug development process, and it is starting on the left, it shows you start with many thousands of compounds, up to 10,000 compounds at one end, the beginning, and after 9 to 13 years, you may end up with one safe and effective drug on the market.

The clinical development phase, which is the gray phase, the middle phase on this diagram, is the longest and by far the most expensive phase.

In contrast, the FDA review phase, of which much attention has been paid to, is actually the very small slice there, the white slice

toward the end of the process, right before the drug gets on the market and is typically at this time less than a year in duration.

So FDA has made strenuous efforts, really, to help reform and modernize the clinical development phase of drug development because that is the major bottleneck. Not only is it expensive and long, many products fail in this phase, and there is a tremendous opportunity cost there where other treatments could have been developed.

Now, the FDASIA included several innovations to this process and the most striking being the breakthrough therapy designation program, so if we could have the next diagram. Thank you. This was mandated by Congress and was specifically directed at that clinical development phase, so that we could help when therapies were particularly promising and were designated, we could help move them through that phase more quickly. The BT designation has been enthusiastically subscribed. We have had over 160 requests in the 2 years since the legislation was passed. We have actually—and this is the really surprising part, we have granted 52 designations. So what Dr. Burgess said about we are on the verge of a new era in therapeutics, I think, is reflected by this. We would not have seen this a decade ago, and we have approved six products: four new products and two new indications.

Now, it is too early to judge really the impact of the breakthrough designation program; is it really going to be able to speed up drug development? However, I will say the four products we approved, their clinical development time was 4.5 years, so much shorter than what I showed in the earlier diagram.

Also, in FDASIA were clarifications of the application accelerated approval, and we issued a final expedited draft guidance in May that includes, in response to stakeholders' requests, examples of rare diseases and includes more information on the use in rare disease. However, it is clear much more needs to be done to modernize the clinical trial process. That is the big bottleneck now in getting discoveries to patients. This can't be done, though, by FDA alone. We don't execute this process. All the stakeholders need to participate, and I think the series of hearings that have been held and the 21st Century Initiative can help provide the framework for significant reform in this process.

Mr. PITTS. The chair thanks the gentlelady.

[The 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 HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"21st-Century Cures: Modernizing Clinical Trials and Incorporating the Patient Perspective"

July 11, 2014

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Ranking Member Pallone, 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 modernizing clinical trials, incorporating the patient perspective, and several FDA activities intended to promote pharmaceutical innovation.

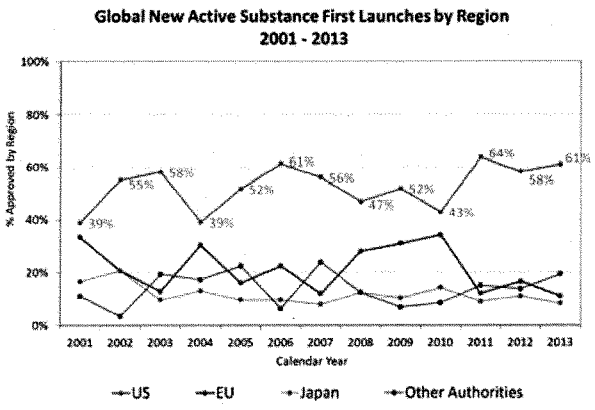
In recent years, there have been important advances to help ensure that therapies for serious conditions are approved and available to patients as soon as there are sufficient data to show that the therapies' benefits outweigh their risks. Despite this progress, there is much more work to be done. Many scientific discoveries still need to be translated into treatments for patients in need of new lifesaving therapies.

FDA is committed to doing our part to help bridge this gap. We have been actively scrutinizing, strengthening, and streamlining our regulatory processes at various steps along the path from drug discovery to drug approval, including the clinical development phase—the longest and most expensive period of drug development. As part of this effort, we have developed and successfully used a number of flexible and innovative approaches to expedite the development and review of drugs to the benefit of millions of Americans. FDA routinely works closely with drug sponsors to apply flexibility, including use of biomarkers, surrogate endpoints, non-traditional trial designs, and other available tools to expedite the development of products to treat

both common and rare diseases. Particularly for drugs intended to treat life-threatening and severely debilitating illnesses, FDA exercises the broadest flexibility in applying its statutory standards. We also have initiated and participated in many efforts to address the underlying scientific and clinical trial infrastructure challenges that affect the cost and timeliness of drug development. Some of these challenges need to be addressed by those outside of FDA; but we continue to look for ways to streamline the clinical development phase, where possible and within our purview.

Statement of the problem

FDA's approval process is now faster than anywhere else in the world (see figure below). Just last year, three-quarters of the new drugs FDA approved were approved in the United States before the European Union (EU) and Japan. Currently 90 percent of drugs that represent an advance over existing treatment are reviewed and decided on in 180 days, some in considerably fewer days.



Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2014)

Despite the growing success and speed of the approval process and revolutionary advances in genomics more than a decade ago, FDA was among the first to underscore that the science necessary to translate these discoveries into treatments—development of biomarkers, genomic data, modernized clinical trial designs, computer modeling, and advanced imaging technology—was not keeping pace. As a result, the process of drug development leading up to submission of a marketing application is often inefficient, costly, and slow.

What is needed to reduce the cost and length of drug development? Although no simple set of initiatives will quickly produce a flood of new treatments, much can be done to improve drug development, both in the short and long term. Today I want to talk about FDA's efforts to increase the speed and efficiency in several areas in the clinical trial phase of drug development. These include:

- Accepting flexible clinical development designs; such flexible programs may use surrogate endpoints, or have fewer than the two traditional randomized, controlled trials of efficacy, or have other non-traditional elements.
- Meeting frequently and working closely with industry sponsors throughout the development process to plan efficient clinical trial programs and agree on needed data, a process that has been shown to shorten drug development by up to several years.
- Helping create clinical trial networks and "master protocols," where appropriate, to greatly reduce the cost of conducting clinical trials and reduce the time needed to carry them out.
- Using surrogate endpoints, both in accelerated approvals (approvals based on an unvalidated surrogate endpoint that is reasonably likely to predict clinical benefit) and traditional approvals (i.e., approvals not requiring confirmatory evidence of efficacy post-

market). Surrogate endpoints have been the basis for 60 percent of rare-disease approvals.

- Listening carefully to patients and organizations that represent them to learn more about how they perceive benefits, risks, and unmet needs.
- When appropriate, encouraging the use of "adaptive" trial designs that allow design modifications as information about drug response accumulates, leading to more efficient studies.
- When appropriate, encouraging "enrichment" strategies to enroll patients more likely to respond to drugs under study, thereby reducing trial size and helping to direct drugs to patients who will benefit from them.
- Allowing the use of a wide range of study designs, including single-arm studies, when patient populations are extremely small, as in some orphan diseases, and the natural history of the disease is well-characterized and the drug's beneficial effects are large.
- Collaborating with scientists in industry and academia on biomarker development; and
- Identifying opportunities for streamlining regulatory processes.

I also want to point out some hurdles to efficient drug development, which require support for outside research and collaboration with other key stakeholders, including the National Institutes of Health (NIH), industry, and patient groups, to translate discoveries into treatments. These include basic research into a range of important diseases, such as Alzheimer's disease, whose causes are still poorly understood and for which drug development has proven particularly challenging.

Flexible Trial Design

People with serious or life-threatening illnesses, particularly those who lack good alternatives, have told us repeatedly that they are willing to accept greater risks in order to gain access to new approved treatments.

FDA has long taken a flexible, rather than one-size-fits-all, approach to clinical trial design, urging that trials be designed as efficiently as possible to determine whether new drugs under investigation are safe and effective for their intended use, taking into account the severity and rarity of the disease and unmet need. A new study published in the *Journal of the American Medical Association* found that more than a third of 188 novel therapeutic drugs for 208 indications (uses) between 2005 and 2012 were approved on the basis of a single pivotal clinical trial, and in many cases, trials involved relatively small groups of patients for shorter durations.[1] All of this is possible, of course, when the drugs demonstrate strong beneficial effects.

Over 60 percent of drugs for rare diseases are approved on the basis of a single pivotal study, often because the cause of the disease is well understood and the pivotal study is supported by evidence of pertinent pharmacological effects, and because the natural history of untreated disease for many orphan conditions is well-characterized. All patients in such trials are given the new treatment, and the results are compared with the well-characterized natural history.[2] Thus, for example, last year, FDA approved Imbruvica (ibrutinib), a treatment for mantle cell lymphoma, based on an "open-label, single-arm trial," which means that every patient received the treatment and the trial was unblinded; i.e., both patients and researchers knew they were receiving the orphan drug under study. The results were compared to how well the 111 participating patients had responded to previous treatment for their disease. These designs are

[1] Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012. *JAMA*, 2014; 311(4): 368-377.
[2] Sasinowski FJ. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Drug Information J. 2012; 46:238-63.

appropriate where there are objective responses (tumor shrinkage and recurrence, survival) where observational bias is limited, and where the natural history is clearly different from what treated patients experienced (tumors do not shrink spontaneously; survival is greatly increased).

In some cases, of course, small trials will not do the job. Some trials require large numbers of patients to demonstrate drug effects. This is often the case in studies of cardiovascular disease, where study endpoints, such as heart attack or stroke, while important, are not common.

Adaptive Trial Designs

FDA is also actively involved in developing adaptive trial designs, including designs with Bayesian adaptations based on interim assessments of biomarkers. Using this approach we try to find ways to adapt a clinical trial to the circumstances of the specific questions being asked in a way that is as efficient as possible but still gives us confidence in the results. The goal of these designs is to reduce trial duration and trial size. Importantly, these adaptations are performed with close attention to statistical rigor.

FDA is also conducting an internal research project to evaluate the amount and type of safety data required for new indications for cancer drugs. The goal is to identify ways to reduce the burden on sponsors, when submitting supplemental applications as well as regulatory review time, while ensuring patient safety. This research will be completed in November 2014.

Clinical Trial Enrichment

You also expressed interest in new tools to lower the cost of clinical trials. FDA issued guidance in December 2012 that explained how those developing drugs can use potentially powerful

strategies to demonstrate a drug's effectiveness using clinical trial data.[3] Appropriate use of what we call clinical trial enrichment strategies could result in smaller studies, shortened drug development times, and lower development costs.

Working Closely with Drug Sponsors

As part of goals within the prescription drug user fee agreements included in the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA works closely with sponsors of new drugs to design a development and review pathway for each drug that best reflects the disease and patients it is intended to treat, the drug itself, and other treatment options. Sponsors who avail themselves of the opportunity to meet with FDA early in development have substantially reduced the time from the start of human testing—when FDA first becomes involved—until marketing approval. For the 181 new drugs approved from 2008 - 2013 (for which a clinical development time could be calculated), the sponsors of the 67 applications who met with FDA before submitting their Investigational New Drug (IND) applications had a median development time of only 6.6 years, compared to 8.0 years for applications for which such a meeting did not occur (a mean reduction of 1.4 years). The median drug development time for applications for which a meeting with FDA was held at the end of the Phase 1 (EOP1) milestone was 1.1 years shorter than for applications for which an EOP1 meeting did not take place. For orphan drugs, drug development was a median of 2.1 years shorter.

In April 2014, we approved Zykadia (ceritinib), a new drug for patients with a certain type of late stage, non-small-cell lung cancer (NSCLC). It is one of four targeted therapies for lung cancer that have been approved since 2011—therapies that are the result of a new and forward-thinking approach to understanding the disease and its causes. FDA granted breakthrough

[3] Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.

designation to this drug, streamlining the development and review process with an "all hands on deck" approach. In fact, due to the enhanced understanding of how drugs like Zykadia work (by blocking anaplastic lymphoma kinase (ALK) and inhibiting the growth of lung cancer) and the frequent interactions between FDA and the drug's sponsor, it took less than four years—versus the roughly 10 years it used to take—from the initial study of the drug to FDA approval. This approval process exemplifies the strength of the collaborative process between FDA, industry, health advocacy organizations, and other stakeholders, while ensuring that FDA maintains its independent role in ensuring safety and efficiency of the product. And it illustrates the dedication and enthusiasm of FDA reviewers who carefully, but quickly, analyzed complex study results to allow for earlier approval and patient access to this new drug.

Surrogate Endpoints

The Accelerated Approval pathway allows for the use of surrogate endpoints, reasonably likely to predict a clinical benefit to get certain drugs for serious conditions more rapidly to patients. But many observers are not aware that FDA has also commonly used well-established surrogate endpoints for traditional approvals. Indeed, for the 94 new drugs approved by FDA between 2010 and 2012, 45 percent were approved on the basis of a surrogate endpoint. Once a surrogate is well established to predict clinical benefit, it can be used in traditional approvals and accelerated approval is no longer required. This saves time and the cost of the follow-up, confirmatory, clinical trial data collection required under accelerated approval.

For example, FDA regularly relies on a surrogate endpoint for approval of new therapies for diabetes, including several major new therapies in recent years, greatly expanding the physician's armamentarium for treating this disease. All were based on a well-established

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December 2012 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf.
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laboratory test (the HbA1C test, a measurement of hemoglobin with attached sugar in the blood that reflects the extent and persistence of elevated blood sugar) as a surrogate for clinical improvement, rather than requiring the sponsor to conduct decades-long studies to demonstrate an effect on long-term health. Moreover, it is critical that these endpoints are supported by sound science. As science evolves, we may discover that some of these endpoints are not accurate predictors and such discoveries are likewise critical.

Biomarkers and Targeted Drug Development

One of the most promising areas for advances in drug development is in predicting which patient populations will best respond to a new drug therapy, thereby enabling drug development to focus on the "subpopulation" most likely to benefit. This "targeted" approach is believed to be one of the keys to lowering drug development costs and expediting approval, at least for the population for which the drug can be quickly and effectively identified as a successful therapy. For example, within the last decade, the high-quality data submitted in applications and our collective understanding of the genetic and molecular underpinnings of lung cancer have enabled us to move from classifying the disease by what can be seen under a microscope to looking at the patient's molecular profile and classifying and treating the cancer by specific subtype. Scientists can now identify "driver oncogenes," which cause a normal cell to become cancerous and promote the growth of a patient's tumor. They can develop targeted therapies aimed at shutting down these aberrant genes and pathways—an example of an approach called personalized medicine. A targeted treatment is directed to the patients who will respond, while sparing others the potential for toxicity and delay in receiving other potentially effective treatments.

In the early 1990s, only 5 percent of FDA's new drug approvals were for targeted therapies. Twenty years later, that number had risen to a quarter of new approvals, and in 2013, 45 percent

of FDA's approvals were for targeted therapies. Examples include several recently approved and important treatments for cancer, such as Mekinist, Tafinlar, Imbruvica, and Zykadia. The use of targeted therapies is expanding rapidly. Indeed, approximately 80 percent of new compounds FDA has designated as "breakthrough" therapies are targeted. Furthermore, accumulating evidence reveals that total development times for targeted therapies are up to two years less than for drugs aimed at broader treatment populations.

It is critical to understand, however, that our ability to use genomic data or to identify useful biomarkers depends on how well scientists understand the molecular and genetic causes and pathways of disease. The level of their understanding, in turn, depends on the strength of the foundational research into given diseases.

In some disease areas, we have made tremendous progress in our understanding of the causes of the disease and interventions that can treat or cure it. For example, decades of research on cancer and HIV/AIDS have given us critical insights into the pathways through which these (and related) diseases can be attacked, leading to discovery of biomarkers that predict disease progression as well as drug activity. Predicting likely progression allows selection of patients who will have many or earlier study endpoints, and thus use of fewer patients; predicting likelihood of response to treatment also allows for smaller studies and directs treatment to those who can benefit. FDA has been an active partner in developing and bringing therapies to market in these areas. This has resulted in important breakthroughs, rapid drug development, and a robust pipeline of new therapies.

However, the scientific community still lacks a complete understanding of the biology underlying disease such as Alzheimer's disease. As a result, many rational and well-intentioned

approaches to develop disease biomarkers or surrogates for clinical endpoints have encountered unanticipated obstacles. While progress has been made on developing biomarkers for disease progression, these obstacles have made the development of biomarkers to assess drug activity difficult, and the treatment options for Alzheimer's disease remain extremely limited.

Scientific understanding of diseases varies widely and is likely to remain the most important limiting factor for developing targeted therapies and personalized medicine. When we do not understand the disease pathways, biomarkers appearing to be linked to disease progression often fail because they are not, in fact, in the causal pathway for the disease. The surprising Phase III failure of torcetrapib—Pfizer's would-be blockbuster to prevent heart attacks by raising HDL (the "good" cholesterol)—illustrates the risks of relying on an unvalidated, albeit seemingly reasonable, biomarker that turns out not to predict treatment outcomes.

Master Protocols and Clinical Trial Networks

One of the most serious limiting factors in drug development is the time and expenses required to design and conduct the Phase 3 clinical trials needed to demonstrate drug safety and effectiveness. As the President's Council of Advisors on Science and Technology (PCAST) observed in their 2012 report on drug innovation:

> *Clinical trials constitute the largest single component of the R&D budget of the biopharmaceutical industry, at approximately $31.3 billion, representing nearly 40 percent of the R&D budget of major companies. Unfortunately, there is broad agreement that our current clinical trials system is inefficient. Currently, each clinical trial to test a new drug candidate is typically organized de novo, requiring substantial effort, cost, and time. . . . .Navigating all of these requirements is challenging even for large pharmaceutical companies, and can be daunting for small biotechnology firms. Even in*

the best cases, the complexities add considerable time to trials—subtracting time from a successful drug's eventual time on the market without competition.[4]

Drug development need not necessarily be done in this way. There are often much better alternatives to reinventing the wheel every time a new clinical trial begins, including, where appropriate, the development of clinical trial networks and master protocols. The recently initiated Lung Cancer Master Protocol (Lung-MAP) is an excellent example of a new, less-costly paradigm for developing drugs, one that benefits both drug companies and patients. A master protocol creates a single clinical trial infrastructure that can test many drugs at the same time. Development of such a protocol requires close coordination with CDER reviewers, scientists in academia, NIH, and possibly other organizations, and the protocols themselves typically go through a peer review process. In the case of Lung-MAP, patients are assigned to one of five different drugs being simultaneously tested, based in part on their genetic profiles and their likelihood of responding to the study drug, and additional drugs can be added, while others are dropped, over time. The goal is to increase efficiencies through the use of a common biomarker screening platform, a common algorithm for assigning patients to multiple protocols ongoing concurrently, and the potential for sharing control patients across protocols for a given biomarker profile, all of which are possible because of the infrastructure established for the master protocol. FDA is highly supportive of master protocols.

Public-Private Partnerships and Stakeholder Engagement

Just like the September 2012 "Report on Propelling Innovation in Drug Discovery, Development, and Evaluation," from PCAST, FDA believes that bridging the gap between drug discovery and development can only be achieved through creative collaborations. Public-private partnerships enable stakeholders to leverage expertise and resources for the conduct of mutually

[4] "Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation," President's Council of

beneficial research activities in the pre-competitive domain. And indeed, CDER is involved in at least 22 unique science-driven, public-private partnerships that promote development of research tools, platforms, clinical databases and predictive models to advance knowledge of disease and safety profiles of drugs. The recent approval of Zykadia, as mentioned earlier, for patients with a certain type of late-stage (metastatic) non-small-cell lung cancer, benefited from FDA's collaborative efforts with industry, health advocacy organizations, and others to identify the molecular underpinnings of cancer that would make it possible to classify and treat cancer by specific subtype.

FDA is also a partner in the Clinical Trials Transformation Initiative (CTTI)—a public-private partnership whose mission is to identify and promote practices that will increase the quality and efficiency of clinical trials. CTTI now comprises more than 60 organizations from across the clinical trial enterprise. Members include representatives of government agencies, industry representatives (pharmaceutical, biotech, device, and clinical research organizations), patient advocacy groups, professional societies, investigator groups, academic institutions, and other interested parties. CTTI is actively pursuing many new initiatives to reduce the time and cost of clinical trial programs, such as development of streamlined protocols and data collection recommendations for clinical trials of hospital-acquired bacterial pneumonia. Another example of a CTTI project with the potential to affect the clinical trial enterprise is its collaboration with FDA's Sentinel Initiative (Sentinel is FDA's active surveillance system that uses pre-existing electronic health care data from 18 data partners, capturing information on more than 150 million patient lives). A working group comprised of CTTI and Sentinel investigators is elucidating current barriers and identifying appropriate processes for the use of such electronic health care data to facilitate the conduct of clinical trials.

Advisors on Science and Technology, The White House, Washington, D.C., September, 2012, p. 20

FDA also is partnering closely with many public-private initiatives, advocacy groups, and consortia. As one example, the Agency is a member of the recently announced NIH-led Accelerating Medicines Partnership (AMP), which is attempting to identify biological targets most likely to respond to new therapies and uncover biomarkers that may help predict clinical benefit in drug development in Alzhemier's disease, among others. FDA is working closely with the NIH's National Center for Advancing Translational Sciences (NCATS) to accelerate research on rare disease through NCATS' Innovative Therapeutics for Rare and Neglected Diseases program. We are also working with the Coalition Against Major Diseases (CAMD) to identify new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer's and Parkinson's diseases. The Agency's Drug Development Tool Qualification process also provides a mechanism to evaluate and qualify novel drug development tools (biomarkers, clinical outcome assessments, animal models under the Animal Rule) for an appropriate context of use. Recently, we deemed a "fit-for-purposed" drug development tool for Alzheimer's disease that CAMD has developed. These represent just a few of our many collaborations. See more at *http://blogs.fda.gov/fdavoice/index.php/page/5/#sthash.bWxzFv0M.dpuf*.

Lastly, FDA is engaged with TransCelerate Biopharma, Inc. (TCB), a non-profit organization established to facilitate pre-competitive collaboration among biopharma companies with the goal of accelerating the development of new medicines by identifying ways to make the clinical trial process more efficient. FDA is engaged in TCB's efforts to improve the conduct and efficiency of clinical trial sponsor oversight of clinical sites, clinical site qualification, and development of a common protocol template.

Regulatory Science

The 21st century has seen rapid advances in biomedical research. New cutting-edge technologies have led to thousands of new drug candidates including: the sequencing of the human genome; combinatorial chemistry, a new method of chemical synthesis that makes it possible to prepare thousands of compounds in a single process; biosynthesis, which enables scientists to synthesize complex chemicals in living cells; and high throughput screening, which allows researchers to quickly conduct millions of genetic, chemical, or pharmacological tests. In addition, cutting-edge electronics and materials science have the power to transform medical devices, and research on nanotechnology-based materials will provide a better understanding of the safety of the use of nanomaterials in over-the-counter drugs. FDA's regulatory science research agenda is critical to help translate new technologies and basic science discoveries into safe and effective real-world diagnostics, treatments, and cures and to reduce the time, complexity, and cost of product development.

There can be no doubt that further modernizing and streamlining the science of how products are developed and evaluated is a complex challenge requiring new models and approaches that stress cross-sector and cross-disciplinary research. Advancing regulatory science has been one of FDA Commissioner Hamburg's key initiatives. New biomedical innovations may be enhanced by partnerships such as the Biomarkers Consortium, which promotes the development and qualification (or regulatory acceptance) of biomarkers (of which surrogate endpoints are a subset), using new and existing technologies.

Consideration of Additional Approval Pathways

PCAST also recommended the creation of a drug approval pathway under which sponsors could propose, early in the development process, to study a new drug for initial approval that would be

reserved for use in a specific subgroup of patients that would allow a narrower development program than required for traditional approvals. While FDA has existing authority to approve products for subpopulations, in practice, drug development protocols generally evaluate drugs in a broader population, resulting in larger, lengthier trials. PCAST notes that a more clearly defined Special Medical Use or Limited Population pathway could encourage novel development programs for limited, well-defined subpopulations and complement FDA's existing efforts to get drugs to small, in-need populations faster. Such a pathway needs to consider the implications of market entry of a product for limited use. For example, an important consideration is how to encourage appropriate prescribing with the approved limited use for a specific population. Legislation focused on a pathway for drugs for serious or life-threatening bacterial and fungal infections in patients with unmet medical need—a particular area of unmet medical need highlighted in the PCAST report—has been introduced to address this issue, and we welcome the opportunity for continued discussions with stakeholders.

Having multiple approval pathways is important because they give drug sponsors options to help get therapies to patients needing them faster. Different pathways may also prove better for different products. In June 2013, less than one year after the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA issued draft guidance to bring more clarity to the accelerated approval program and other expedited programs for drugs and biologics that target serious conditions, so as to further encourage the use of these programs, *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf*. That guidance was finalized in May 2014. Although FDA has been able to speed the availability of drugs and biologics for serious conditions that provide a meaningful therapeutic benefit to patients over existing treatments under the accelerated approval program since 1992, FDASIA clarified that authority in legislation and emphasized FDA's ability to

consider epidemiologic, pharmacologic, or other evidence developed using biomarkers or other scientific methods or tools in determining whether an endpoint can support accelerated approval.

Accelerated approval for drugs and biologics 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 or vaccine.

Further, the Agency oversees other programs that expedite the availability of new drugs for patients with serious conditions. For example, as part of FDASIA in 2012, Congress gave FDA new authority to designate drugs as breakthrough therapies. Breakthrough therapy designation is a program designed to expedite the development and review of drugs that are intended to treat a serious condition and which preliminary clinical evidence indicates may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints. The breakthrough therapy program has already been well-utilized. As of June 13, 2014, CDER has received 164 requests for breakthrough therapy designation. CDER has granted breakthrough therapy designations for 48 of those requests, denied 83 such requests, and approved six breakthrough therapy drugs. CBER has had 31 breakthrough therapy designation requests, four of which it has granted and 26 of which it has denied.

FDA Efforts on Patient Engagement

In accordance with our commitments in the Prescription Drug User Fee Act of 2012 (PDUFA V), FDA has initiated the Patient-Focused Drug Development (PFDD) program. The objective of this five-year effort is to more systematically obtain the patient's perspective on a disease and its impact on patients' daily lives, the types of treatment benefit that matter most to patients, and the adequacy of available therapies for the disease. As part of this commitment, FDA is holding

at least 20 public meetings over the course of PDUFA V; each of which will focus on a specific disease area. We have already held patient meetings on several major diseases.

After conducting a public process to nominate disease areas for Fiscal Years 2013-2015, FDA held the first PFDD meeting on April 25, 2013. This meeting focused on chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME), sometimes called CFS-ME, a debilitating disease for which there are currently no FDA-approved treatments.

Here, we heard directly from patients, patient advocates, and caretakers about the symptoms that matter most to them, the impact the disease has on patients' daily lives, and the patient experience with currently available treatments. FDA staff, including members of FDA's Division of Pulmonary, Allergy, and Rheumatology Products, listened carefully to the personal accounts of this devastating condition.

After the meeting, we released a report titled *The Voice of the Patient: Chronic Fatigue Syndrome and Myalgic Encephalomyeliti*, a detailed summary of the meeting. In this report we documented, in the patients' own words, what disease impacts and treatment approaches mattered most to them. This summary included patient testimony at the meeting, perspectives shared in 230 docket comments, as well as unique views provided those joining the meeting via webcast. Moreover, on March 11, 2014, FDA also released draft guidance (found at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM388568.pdf)* for industry entitled "*Chronic Fatigue Syndrome/Myalgic Encephalomyelitis:*

Developing Drug Products for Treatment." The purpose of the guidance is to assist sponsors in developing drug products for the treatment of CFS-ME.

The PFDD reports, such as the one developed after the CFS-ME meeting, will serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily lives. These reports will strengthen the structured framework for benefit-risk assessment in the new drug process, which FDASIA (Sec. 905) requires and which is currently in development, that will be used to help communicate patients' values to the FDA review team during product review. FDA believes that the long-term impact of the PFDD program will be a better, more informed understanding of how the entire drug development community might find ways to develop new treatments for diseases.

Soon after the CFS and ME meeting, in June 2013, we conducted similar meetings on HIV and lung cancer, and the summary reports are now available on our website. The reports for our recent meetings on narcolepsy and sickle cell disease will be posted soon. We have also held meetings on fibromyalgia, pulmonary arterial hypertension, and metabolism.

By the end of FY 2015, we plan to have conducted at least 16 PFDD meetings to hear from patients suffering from and living with a wide range of conditions. These are currently identified on our webpage:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm. For the remaining two years in PDUFA V, we will conduct another public process to identify the diseases that will be addressed during that time.

We are gratified by the enthusiastic response within the patient community to PFDD, and we look forward to continued input from these meetings—and to the long-term benefit they can offer for drug development in important therapeutic areas.

In addition to these efforts, CDER established the Professional Affairs and Stakeholder Engagement program that will serve as a focal point and enhance two-way communications and collaboration with health professional organizations and patient advocacy and consumer groups about drug products.

CONCLUSION

FDA welcomes the opportunity to constructively engage and work with Congress and stakeholders in an effort to improve review efficiency and effectiveness while maintaining the high safety and efficacy standards for which FDA approval has become the global "gold standard."

Thank you for the opportunity to testify today. I am happy to answer any questions.

Mr. PITTS. I will begin the questioning, recognize myself 5 minutes for that purpose.

Dr. Woodcock, what is FDA's plan to advance biomarkers and the use of patient reported outcomes data during the drug development process and post-market setting?

Dr. WOODCOCK. Many years ago, a decade ago, we recognized that there was no structured scientific process to provide the evidentiary basis for use of a biomarker in decisionmaking, and so doctors and biomedical researchers would float new biomarkers, but there was no rigorous process by which they could be evaluated to see if they were really useful. So we actually established a process for this. It is not really in our mission, but we established it, and it is called the Biomarker Qualification Process. And we also work with the European medicine agencies and the Japanese regulators so that this would be a worldwide activity. And consortia can come into the FDA and propose a biomarker, a new biomarker, and we give them advice on what needs to be done, and then—and also for patient-reported outcomes. And if, in fact, that evidence is developed, then we will publish a letter that is public, and so will the EMA if they accept it and so forth, and then any developer can use that biomarker or measure in a development program and will rely on it for the context of use.

We have 79 projects by different consortia in different phases of this process right now.

Mr. PITTS. Good. Describe your plans for implementation of the structured benefit-risk framework you mentioned that—transparent to the public and the sponsor so that the assessment of data from clinicals trials and other studies by FDA reviewers can be better understood and acted upon.

Dr. WOODCOCK. Yes. Well, this is an iterative process. We have had public meetings. Then we went back, and we are piloting this in the different drug review divisions and having the medical officers work through this framework that we have developed and see what the results are. Then when we have those results, we will go back through a public discussion and get input on how this can be improved, so this is not something that can happen overnight.

It is a scientific process, and actually, we feel that we don't have the tools right now. They exist out in society in science, but we haven't applied them, these rigorous analytical tools to the benefit-risk decision, and so we have had workshops on this, various scientists come in and advise us, so we will have a public process once we have gathered more experience.

Mr. PITTS. I have been hearing a lot about FDA's efforts to improve the quality of pharmaceutical manufacturing. Where do U.S. drug manufacturers currently stand when it comes to producing quality medicines? Can you tell me a little bit about your plans in this area?

Dr. WOODCOCK. Well, I think the major problem here is that many of our essential drugs are not made in the United States, and they are made all around the world, and sometimes they may only come from a single source, and this is, I think, a real vulnerability to medicine. And in addition, we used to be a manufacturing powerhouse in drug manufacturing, but those jobs have moved offshore. And I think now we have an opportunity, with new modern

manufacturing methods, such as continuous manufacturing, to actually build a high-tech industry in the United States that actually will make the drugs we need here in this country. And FDA has been collaborating with this manufacturing community to help bring this about, and we are very interested in seeing this happen.

Mr. PITTS. Now, we have recently heard a lot about Lung-MAP, the Lung Cancer Master Protocol trial. There are other examples of similar innovative trial designs, like I–SPY for breast cancer. What else needs to happen before these types of trials are no longer front-page stories?

Dr. WOODCOCK. That is a good question. We also have been advocating for this for many years, and it is wonderful to see it start to become a reality. The concept, I think, in drug development needs to be turned on its head in clinical drug development, and instead of, for each investigational drug, there is a whole clinical trial program developed with different clinical trials that take a very long time, as you heard on Wednesday, to get started and so forth, that there are networks that are available that investigational drugs can be plugged into. This will provide independence of an assessment but also really decrease the time and expense of assessing whether these drugs are safe and effective.

But what needs to happen, I think, is we need to expand this to more diseases. The NIH is very interested in antimicrobials in setting up a network, and other groups are looking into this, and I think you may hear today from some patient groups say Cystic Fibrosis has really successfully set up the infrastructure to have cystic fibrosis drugs rapidly evaluated once they reach the clinic.

Mr. PITTS. The chair thanks the gentlelady.

Now recognizes the ranking member of the subcommittee, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. I am going to have to—since I just got here.

Mr. PITTS. OK. You want to yield to Green?

Mr. PALLONE. Yes.

Mr. PITTS. All right. Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman.

Dr. Woodcock, welcome back. I want to thank our chairman, ranking member, and Dr. Woodcock for testifying. In a time where revolutionary science and technological development, we have an opportunity to target specific patient populations, advance personalized medicine, and transform how we approach the prevention and treatment of disease, one of the goals I think is particularly worthy of exploration is the idea of personalized medicine, in which a patient may be able to receive more tailored drugs and treatment suited to his or her specific condition.

Our understanding of the human genome is the key to that goal. Academics and researchers tell me, another piece is the potential for researchers and developers to discuss these drug and device innovations with patients during the development phase.

Dr. Woodcock, can you give us your views on the upsides and downsides of any increasing permissibility of communication between patients and developers during the clinical trial phase of development?

Dr. WOODCOCK. It is a very interesting question. We have seen from the 1990s, where only 5 percent of drugs were targeted; in

2013, 45 percent of the drugs we approved were targeted in some way. There are barriers to locating patients and joining up patients who have specific conditions, subsets with appropriate investigational therapy, and these diseases are fragmented into smaller and smaller subsets. It is harder and harder to find these people who might be eligible for a given therapy.

The Lung-MAP trial is one way of doing that where it has multiple investigational arms in one trial, so people can come in, and they can be spread out. But there is great interest, of course, with more patient activism in using social media and other ways to actually match up the right patients with the right investigational drugs, and I think this is one of the challenges right now of the clinical trial enterprise.

Mr. GREEN. Well, increasing patient involvement in FDA's decisionmaking surrounding drugs, devices is a significant yet challenging endeavor. Can you provide your suggestions on how mechanisms need to be developed to accurately measure what meaningful outcomes for patients are, both in the clinical outcomes and the quality of life? Can we do that?

Dr. WOODCOCK. Yes. That is what I was referring to with Chairman Pitts is that there is a science of measurement, and patient-reported outcomes is one science. How do you measure how a patient feels from their point of view? And there are ways to do this, but these measurements have to be developed. We approved many drugs based on their impact on quality of life, so that is completely possible, but what needs to be done is this science needs to be developed, and we are participating in that. As I said, we have an expert meeting next week on patient-reported outcomes.

Mr. GREEN. Well, and the patient involvement process has to be data driven and improve the overall efficiency of drug development and maintain FDA standards of safety and effectiveness. How can Congress support the FDA in incorporating patient perspectives in regulatory decisionmaking in a way that helps deliver that innovative, safe, and effective medicines to the patients sooner?

Dr. WOODCOCK. Well——

Mr. GREEN. Do you need statutory authority, or do you think you already have it?

Dr. WOODCOCK. To my knowledge, we have the authority to do this, and I think you will hear from the next panel, for example, how patient groups can develop draft guidance, submit it to the FDA. They can run processes that actually incorporate all their points of view and those of the expert scientists, so more of that needs to be done, but I don't know that it needs more statutory authority.

Mr. GREEN. Can you do it within current resources, because again, you are specializing, instead of a broad brush—and I assume it costs more when you do an individual?

Dr. WOODCOCK. Yes. Well, when you have 7,000 diseases that need good treatments and most of them don't have them, it would be very difficult for FDA alone to develop the standards for patient reported outcomes in each one of those diseases, much less the clinical outcomes. So much more participation of the medical and patient community is needed in drug development, and we need to

find better ways to do that, but I am not sure that is through legislation.

Mr. GREEN. OK. And without a doubt, our greater resources, but again, our committee has worked over the years to try and provide those resources——

Dr. WOODCOCK. Yes.

Mr. GREEN [continuing]. To the FDA and look forward to working with you.

Thank you, Mr. Chairman. I yield back.

Mr. BURGESS [presiding]. The gentleman yields back.

I recognize myself for 5 minutes for the purposes of question.

Dr. Woodcock, again, good to see you, good to have you back in the committee. So you have talked about how the FDA routinely works with sponsors to apply flexibility, including the use of biomarkers, surrogate endpoints, and nontraditional trial designs, and other available tools to expedite the development of products to treat both common and rare diseases.

With respect to the common diseases, how is the FDA working with sponsors to apply these innovative development and review methods?

Dr. WOODCOCK. Well, for example, hypertension is a common disease. We approve drugs for hypertension based on a surrogate measure, blood pressure, that is very well accepted, and for a number of years ago, we looked at automated blood pressure monitoring, and we decided it was unbiased, and so we decided that you really didn't need a control group in the same way that you would for most other diseases because you have an unbiased measure, and so we issued new approaches to studying hypertensive medicines. So that is an example.

Mr. BURGESS. What could happen so that the FDA could use this more frequently?

Dr. WOODCOCK. Well, 45 percent of the drugs that we approved over the last several years used a surrogate endpoint. So we do use that when it is appropriate and it is available. For many diseases, we don't know what the right surrogate is, and that is why many of the accelerated approvals have been confined say to cancer and HIV is because the science, a great deal of science has been driven in those conditions, and we understand the biomarkers. But for other diseases, there needs to be more scientific development, and that is why we are using this, for example, biomarker qualification process to try and get more biomarkers developed that we can use, but we can't just dream them up and use them.

Mr. BURGESS. I thought that was your job. Well, let me ask you this. Are there situations where a majority of the scientific or research community believes that a certain biomarker sufficiently predicts the clinical outcome, but the FDA has yet to accept that?

Dr. WOODCOCK. There may be. I think there is a lot of controversy around use of these. You heard some of that on Wednesday. There are two sides to this. If you rely upon a surrogate, often, especially when it isn't well validated, there is more uncertainty about whether or not the drug is actually going to work or not, and so there are different points of view. And as we have all been saying, the community, the patient community really ought to have—and treating community ought to have—a lot of input into how

much uncertainty should be tolerated, given the circumstances of that disease.

So there are situations where there is disagreement amongst various parties, external and internal, about the use of a surrogate.

Mr. BURGESS. Are you able to give us any examples of that, of a surrogate that the FDA may not right now be willing to accept?

Dr. WOODCOCK. Well, for example, raising good cholesterol, all right. We had a series of trials on that. Everybody thought raising good cholesterol would be really good, and in fact, it turned out to be either neutral, or in one case, it actually increased mortality, so we no longer accept that surrogate. That is the kind of example where—and there are many others like that.

In bone density, for osteoporosis, estrogens do a very good job and they decrease fractures. Although they have other liabilities. But some other agents were tried, and actually, they increased bone density, but they also increased fractures, and so we have to be careful when we use these surrogates to make sure that we are getting the intended results, clinical results.

Mr. BURGESS. Thank you for that.

Let me ask you a question that is a follow-up from when we visited in April.

Do you have an update on the status of the FDA's guidance on biosimilars naming and when that guidance will become final?

Dr. WOODCOCK. Well, I certainly would like to get that guidance out as soon as possible. We are working diligently on that, and I don't have any further update.

Mr. BURGESS. But that was submitted as a question in April, and we are awaiting an answer.

Now, also, along with that, I asked if anyone in the administration, outside of the FDA, had provided the agency with suggestions or recommendations with respect to this guidance.

Can you, if the answer to that is yes, can you provide us with the name or names of those individuals?

Dr. WOODCOCK. We would have to get back to you on that.

Mr. BURGESS. And again, we anxiously await your answer.

My time is expired.

I will recognize the gentleman from New Jersey, the ranking member, 5 minutes for questions.

Mr. PALLONE. Thank you.

Mr. Chairman, you asked a lot of my questions, so I am going to have to move on to other things.

But Dr. Woodcock, we heard a lot at Wednesday's hearing about the accelerated approval program at FDA, and as you know, the program allows for earlier approval of drugs that treat serious conditions and fill an unmet medical need, and the drugs are approved on the basis of surrogate endpoints which we also learned about on Wednesday, and of course, a critical requirement of the system is that companies conduct studies to confirm the clinical benefits suggested by the surrogate endpoint, and these studies are called phase 4 confirmatory trials. So a critical part—I want to ask about the phase 4 trials. What challenges has FDA faced with respect to phase 4 trials? Do sponsors complete in a timely manner?

Dr. WOODCOCK. Well, it is sometimes difficult to complete these trials, and the reason is that if you had a serious and life-threat-

ening disease and we approved a treatment for it, you probably would be somewhat reluctant to enter a trial where you had a maybe 50 percent chance of not getting the treatment. So what we often do is ask that trials be conducted in a different stage of disease or something where it actually hasn't been studied yet, so then we can get the results since that might take time.

So I think in the early years of the program, we didn't track this as well as we should, and we did have a lot of trouble getting these trials completed. But in the current era, we are on top of this, and generally speaking, the sponsors are diligent in trying to get them completed, generally, but they have difficulty sometimes enrolling patients in these trials.

Mr. PALLONE. Another important component of the program is that when the surrogate endpoints do not ultimately show the anticipated clinical benefit, FDA could be faced with needing to remove the indication or take the drug off the market, and I imagine that is also no easy task.

Can you describe what is involved with removing the indication or taking a drug off the market and what challenges does the FDA face there?

Dr. WOODCOCK. Yes. Generally, if the confirmatory trial failed to show benefit, the first thing we ask is the sponsor to voluntarily withdraw the drug or the indication from the market. It is only if the sponsor does not agree to do that, then we go into a long administrative process, which includes hearings and formal findings and so forth, and this can take a long time if the sponsor can test our finding that the drug isn't effective.

Mr. PALLONE. Now, just a couple of years ago, we included some provisions to improve upon the accelerated approval program, and the FDA Safety Innovation Act of 2012. For example, the law made it clear that FDA could rely upon evidence developed using biomarkers or other scientific methods or tools when assessing surrogate endpoints. Can you describe what impact those legislative changes had on the program, and are there any other changes that you feel are necessary to allow you to make full use of the most recent scientific developments with respect to surrogate endpoints?

Dr. WOODCOCK. I think the legislation was very helpful. We have taken it quite seriously. We have issued guidance, final guidance on expedited programs, and probably the biggest change that the legislation brought about was its focus on intermediate clinical end points, and we had to have quite an internal discussion about what that means, and I think you will see us approving more products under accelerated approval based on these intermediate clinical endpoints.

Mr. PALLONE. All right. Well, thanks.

Again, it is clear to me that this is an extremely complicated area and one that is not necessarily conducive to further legislation, but I wanted to ask last about the master protocol.

At the hearing on Wednesday, some panelists described some of the inefficiencies that exist in the way that clinical trials are currently conducted, and one of the suggestions for addressing those inefficiencies is to create a master protocol. So I just wanted to ask, first, can you tell us more about this, what is a master protocol? How would it help to improve the way we conduct clinical trials?

Has FDA been involved in the development of a master protocol, and are there particular diseases that the master protocol is more appropriate for than others, and if so, which ones, and are there other areas where it might be expanded?

Dr. WOODCOCK. Well, master protocol is one version of using clinical trial networks or standing clinical trials to evaluate investigational therapies where the drug development program isn't just for one therapy. It is for any therapy for that disease. So master protocol, though, has to be somewhat disease specific. You can't just have a general overall master protocol, right. It has to be focused on one disease.

For example, the Lung-MAP trial is on squamous cell cancer of the lung that is advanced but five different agents right now are being studied all at once within that protocol, and that is a huge efficiency. But there are other versions of standing trials or trial networks that also could be used in other diseases. And as I said, the Cystic Fibrosis Foundation has a kind of network of clinical excellence where they actually sequenced the genome of all their patients, and so they are ready when a targeted therapy comes along. They are ready. They can put those patients into the protocol, and that tremendously improves the efficiency.

So it is a long conversation that probably can't be had in 5 minutes, but I have long advanced this concept and tried to push this concept because the current clinical trial paradigm is not sustainable.

Mr. PALLONE. All right. Thank you very much.

Thank you.

Mr. BURGESS. The gentleman's time is expired.

The chair recognizes the gentleman from Pennsylvania, Dr. Murphy, 5 minutes for questions, please.

Mr. MURPHY. Thank you.

And good morning, Doctor. It is always good to have you here.

Let me start out by asking about it is important for the medications and research to advance those but also for those that are already approved, and so let me ask you, we had passed the PDUFA laws a while ago, certainly that was supposed to help us get more generic drugs in the queue, but what has happened is we got 1.5 billion authorized over 5 years, what has happened is approval times have gone up, and there are fewer approvals, even though the law was supposed to reduce all those.

Can you give me some indication of what is going on and what FDA is going to do about that?

Dr. WOODCOCK. Certainly. We are well aware of these issues. In June, we received 625, I believe, generic drug applications, so the rate of submission is well above what was projected in the negotiations that we held.

However, on October 1, the deadlines kick in for timelines for review of generic drugs, and we are fully prepared to meet those timelines as well as deal with this large backlog of pending.

We had to hire a large number of people and totally revise our processes, reorganize the generic drug review offices and conduct many other changes, and that is what we have done over the past 2 years in preparation for the deadlines coming into effect on October 1.

Mr. MURPHY. Thank you. Another question here about some labeling issues. The abbreviated new drug application that would allow generic manufacturers—this is a proposal for FDA to change a label without FDA's prior approval but then come back later on, and the FDA itself has recognized, and say, quote, "consistent labeling will assure physicians help professionals and consumers that a generic drug is as safe and effective as its brand name counterpart," unquote. But there is a concern out there that allowing these changes take place and then go backfill them later on can cause a lot of confusion in studies that have asked pharmacists and physicians this, so I am wondering where this issue stands in clarifying this.

Dr. WOODCOCK. Well, we have received comments on the proposed rule. It was a proposed rule, and we received many comments. We are analyzing the comments, and subsequent to that, we will have to go forward with a rulemaking process.

The proposed rule contemplated that we would actually have less disparities of labels in the marketplace on this because of this proposal because we would put up a Web site, and we would also require conformance of labels, which we cannot carry through right now, given the current systems.

Mr. MURPHY. A lot of us back in January asked to meet with Commissioner Hamburg and others about this, and I am not sure those things have taken place yet, so I hope this gets expedited and that these issues are addressed because I think it still leads to some confusion. So I am not clear yet in understanding even why this proposed rule was set up there to allow individuals to change the label and then come back later and ask permission.

Dr. WOODCOCK. Well, currently, generic labels do not always match the innovator and they do not change their label in a timely manner, and so there will be labels out there for quite a bit of time, even with serious safety issues like new box warnings that don't conform to the innovator label, so we are trying to address this situation. And also, as generics are now 85 percent of all drugs dispensed to consumers—that they should have the opportunity, since their drugs are the ones that people are being exposed to, to submit their findings of adverse events and suggest label changes, proposed label changes and actually execute them.

Mr. MURPHY. Well, I just hope that you will meet with the committee staff members and the companies to help clarify this because it still is not clear to me why this would be allowed, and I think it would end up confusing.

I want to bring up one last thing just while you are here. I had sent a letter a few weeks ago to Dr. Hamburg. I am sure you didn't see this, but one of the things that is out there, too, is complications that are oftentimes reported in the media about caffeine, whether it is—and sometimes toxic levels people take.

Dr. WOODCOCK. Yes.

Mr. MURPHY. Through over-the-counter things, pure caffeine or some of these supplements out there for athletes, et cetera, and yet it is also in everything from chocolate to coffee and other things we promote all the time, so I am hoping, at some point, FDA can also give some recommendations in terms of individual levels per drink,

per dose, per day, per male, female, the genders, for weight, age, whatever that is.

Dr. WOODCOCK. Yes.

Mr. MURPHY. Because it is still pretty confusing, whatever those products are that they can be beneficial, but I hope you will expedite that.

Dr. WOODCOCK. Thank you.

Mr. MURPHY. Thank you.

I yield back.

Mr. BURGESS. The gentleman's time is expired.

The chair recognizes the gentlelady from California, Mrs. Capps for 5 minutes for questions, please.

Mrs. CAPPS. Thank you for holding this hearing, to our chairman and ranking member.

Thank you, Dr. Woodcock, for your testimony.

This is an issue very dear to me, and as you know, I am incredibly concerned about our Nation's history of excluding minority groups, especially women, from all levels of medical research, from the lab rats to the most advanced clinical trials. And reports have shown that even when these groups are included in trials, there are often too few participants in the groups to analyze the effects on them or the analyses are simply not run or reported.

I am sure you are familiar with the case of Ambien, commonly prescribed medication that recently had its label changed because it metabolizes differently in women than men, meaning that women had been receiving an inappropriately high does of this drug for over 20 years.

In addition, in spring, a report entitled "Sex-Specific Medical Research Why Women's Health Can't Wait" was released, which provides evidence for the further inclusion of sex and gender in scientific research. And the FDA's own August 2013 report, which was initiated by the inclusion of My Heart for Women Act in the FDASIA legislation, showed that there is still much work to be done to make sure that women are fully represented in clinical trials and that the safety and effectiveness of the information is readily available.

I know the FDA is continuing to work on an action plan to address these disparities, so Dr. Woodcock, can you give us an update on where the agency is on this?

Dr. WOODCOCK. Certainly. I would expect that that would be released, we would be timely in its release. I believe there was a statutory deadline or not, or there is some expectation, so we are working diligently on the action plan, yes.

But I will say for drug development, which is what I am discussing here, that we did a study, for example, the class of 2010, the product that we approved, we found that about 45 percent of the participants were male, all right.

And we found that almost all the submissions included the required gender analysis, which has been required for drugs for 20 years, because I oversaw that when I first joined the Center for Drugs in 1994. So it is by regulation, so we do have these, but I think the transparency of the information is the problem, and we are working on that, and I really am committed to making that in-

formation more transparent so people understand what we know and what we don't know.

Mrs. CAPPS. I think you put your finger on something, and I want to highlight a bipartisan letter I led, signed by the women of the House of Representatives, urging this agency to include clear and actionable strategies. And I think what you said about transparency and the reporting in the action plan is a way to address this issue once and for all.

At Wednesday's hearing this week, I also asked the panel about the tools FDA is developing that could supplement our knowledge base, especially in the light of less robust clinical trial designs. The FDA Sentinel system, which I understand is making progress, if slowly, to conduct post-market passage surveillance of drugs and devices, could help spot issues like adverse drug interactions more quickly. I believe the Sentinel program holds great promise, and that is why I worked to get the Sentinel Assurance for Effective Devices Act included in FDASIA to continue progress on the program and ensure the design for both drugs and devices. Could you update us on the development of the Sentinel program, please, and what other resources or authorities do you need to get the system up and running to protect consumers more effectively and expeditiously.

Dr. WOODCOCK. Well, I think use of electronic health data, which is rapidly becoming available, and the electronic health records and so forth, has tremendous promise for actually finding out what happens in the real world for medical products, both that are approved recently and those that have been on the market a long time, and that is what the Sentinel system is intended to do.

We have run a mini-Sentinel network for 5 years, and that was between drugs and biologics. We paid for that out of our money that we have, and we are recompeting that to put up the Sentinel system, so that contract proposal is out on the street, and we hope to establish the real Sentinel system, which will be a large-scale system for surveillance.

Now, as far as medical devices, we require a unique identifier or some kind of identifier in the medical record electronically so that we are able to capture that because the Sentinel system uses those electronic records to get the information, and I will repeat for everyone that it does not take any personnel information and move it to some central database. It strictly runs those analyses within the healthcare system and then the results only are combined.

So that has tremendous promise. We feel very good about that. We actually are piloting running active surveillance on there, so when we approve a drug and we have a question about it, we can watch over time and see what actually happens. And as more and more people get on electronic health records, we can really have more insight in what is happening.

So that is where we are with that, and it is resource limited. I have to pull resources from other activities to fund that, but I believe very strongly that this is the future.

Mrs. CAPPS. Thank you. I appreciate that.

Mr. PITTS [presiding]. The chair thanks the gentlelady.

Now recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you.

Dr. Woodcock, thank you for appearing. It is always good to see you.

I understand that a number of the challenges that have led to the duration and cost of conducting clinical trials in the U.S. to increase essentially are outside of FDA's purview. That being said, clinical trials are conducted to generate evidence used in the application for FDA approval, so my first question, how early do you typically communicate with these pharmaceutical companies, to discuss their trial design before the investigational new drug application is submitted?

Dr. WOODCOCK. Well, we have agreements under PDUFA, that prescription drug user fee program, and for novel products or novel indications, say they are testing a disease that really doesn't have any treatment, companies can come in and have a pre-IND meeting. That meeting is before they start their clinical trials, their first in human studies, and we talk about that development program so they can start thinking about how that is going to be done.

We do have information, it is preliminary, but looking at our information, it seems that companies that have more interactions with the FDA are able to get their products through more quickly, through the entire clinical trial process than companies that haven't had interaction with the FDA during the development process. But there are formal meetings that are held at different times under the user fee program, and those minutes are tracked, and we track the meetings and so forth, so there is quite a process for interaction during drug development.

Mr. GINGREY. So you, as a manager, would be, maybe at that particular time, you make sure that your reviewers are not requesting overly burdensome data that really is not necessary so that the process can be speeded up?

Dr. WOODCOCK. Well, there is always a push and pull. Scientists of all stripes always want more data, and that is scientists in the companies and scientists in the FDA, and so we have to walk that path between getting more data and actually the cost that is generated. And we have made a number of efforts under the CITI collaboration that we do with Duke University and many, many, many other partners to try and figure out how to streamline clinical trials as far as data collection, for example. But it is difficult.

We have 1,600 meetings a year under the PDUFA, and when we meet with companies, the supervisors are there, the senior medical officials are also at these meetings.

Mr. GINGREY. Well, that is the whole purpose of 21st Century Cures, of course, and as we get to the second panel and we hear about the associations and from the families, I am sure they are going to talk about how we can speed this process up.

The last question. At our first 21st Century Cures hearing, we heard that only 19 drugs, outside of cancer and HIV space, have been approved by the accelerated approval pathway since 1992, and I understand that you wrote a blog post after that hearing about how a number of drugs that were being considered under accelerated approval ultimately received traditional approval, so these statistics, according to your blog, were somewhat misleading.

Can you provide some examples of when that occurred as well as the process involved?

Dr. WOODCOCK. Certainly. Well, for certain rare diseases, we may decide, for example, that the surrogate is fine, OK, and it correlates with clinical benefit. Then the term "accelerated approval" is a little misleading. It sounds like it is faster than regular approval, but actually, if we give regular approval on a surrogate, it is just as fast as accelerated approval, but you don't have to do confirmatory studies afterward because we already believe the surrogate.

So, for a lot of, say, rare deficiency diseases where there is something missing, you may be able to show that you actually, when you replace that protein in the body, you give the activity back to the person, right, and so you may not have to show clinical outcomes. It is still a surrogate, but we feel it is good enough because we understand the problem that something is missing, and you deliver an active drug to the site of action of where the problem is, and that would be enough.

So, in many cases, we are able to do traditional approval with the surrogate; that means that the patients and the sponsor don't have to go through all these confirmatory trials. I described the difficulties of that when you have a serious disease; you have approved a drug; and then you ask people to be randomized after approval.

Mr. GINGREY. Dr. Woodcock, thank you.

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

Mr. PITTS. The chair thanks the gentleman.

I recognize the gentlelady from Florida, Ms. Castor, 5 minutes for questions.

Ms. CASTOR. Well, thank you very much.

Thank you, Dr. Woodcock, for everything you are doing to ensure safe and effective drugs are available for the American public and those with health challenges.

This is a hearing about the patient involvement in FDA drug approvals, and I think we can agree, they deserve a seat at the table when companies are developing drugs and medical devices within the clinical trial process. I have long been a supporter of the Department of Defense's Congressionally Directed Medical Research Programs known as the CDMRP. CDMRP funds peer-reviewed research into breast cancer, autism, ovarian cancer, prostate cancer, and other diseases. And since 1993, the patients have been involved and have been a part of CDMRP, and they have a consumer reviewer as part of a peer-review panel to represent the stakeholder community, and it has been very successful in combining patient perspectives and needs with scientific research and bringing those perspectives together.

Has FDA, as you begin to consider improving patient involvement, have you looked at CDMRP to see if there is anything you can borrow from that in the drug approval process?

Dr. WOODCOCK. We have not, and that is a good suggestion, so we would be happy to do that.

Ms. CASTOR. OK. You mentioned previously that the Patient-Focused Drug Development Initiative that was included in PDUFA

was designed to allow FDA to hear from patients on how a disease impacts their life, and I understand you are scheduled to hold 20 public hearings. Share with us who FDA has met with so far. Have you started those hearings? If so, what have you learned already?

Dr. WOODCOCK. Well, we have learned the devastating impact, I think, of the diseases, of these different diseases on people's lives it just incredible. We had one on chronic fatigue syndrome—that was our first one—HIV, lung cancer, narcolepsy, sickle-cell disease, fibromyalgia, pulmonary arterial hypertension, and inborn errors of metabolism, and we plan to have 16 of these meetings completed by the end of 2015, but we recognize this is just a drop in the bucket of what people suffer from.

So what we are trying to do is really model how people can do this, and hopefully, it could be done more—not put on by the FDA but by the patient groups themselves in the medical community that serves them so that they can assemble more of this information and kind of multiply the effect of this, and we are already seeing some of that. NORD, for example, has offered to help with rare diseases, for example, to have more input that way because our resources are limited. We are not going to be able to cover all the different diseases.

Ms. CASTOR. Good. So I expect we will hear from the patient organizations later today and their view on how they can be helpful and we can be effective.

I think the wave of the future really is the information we will be able to gather through the electronic health record, so it is interesting to hear what you have done already with the Sentinel initiative. I heard from research institutes back home that are doing so much in genomics and personalized medicine that they think these larger networks are the wave of the future. You say you don't need additional legislation to continue, but you are having to borrow resources from this and that.

Dr. WOODCOCK. Yes.

Ms. CASTOR. So is your advice to the committee that we need to do more in technology when it comes to improving timelines on clinical trials by focusing on these networks and the electronic health record?

Dr. WOODCOCK. The electronic networks have much promise in doing clinical trials.

If we could move clinical trials more out into the community and have people out in the community, like most cancer patients in the U.S. who have diseases that are untreatable don't get into trials because they are being treated at places that aren't running trials. So we need to move this out into the community, make those folks eligible.

And I am on the Steering Committee of the Lung-MAP trial, and I really urged that we make sure that we are out there in the community so that anyone who has lung cancer has an opportunity to participate in this research and perhaps have a more effective therapy.

So I think the electronic health records, that is a huge different area that we are working on in how to do clinical trials utilizing that infrastructure that is emerging.

Ms. CASTOR. Great. Thank you very much.

Mr. PITTS. The chair thanks the gentlelady.

I now recognize the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

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

A portion of your testimony has focused on the FDA's efforts on patient engagement. It is my understanding that ClinicalTrials.gov was intended to be a resource that provides clinical study information for patients, for healthcare providers, and for researchers. But it seems to me that the site lacks considerable information and has proven to be difficult to navigate.

Dr. Woodcock, would you please comment on the current utility of the ClinicalTrials.gov.

Dr. WOODCOCK. Well, I think that it has provided, along with the requirement of the medical editors of the journals that things be registered before they are going to be published—provided tremendously more transparency into what clinical trials are ongoing in the United States.

And that has been a big achievement. All right? So we know, the issue of publication bias and everything is minimized because we know what trials have been done.

However, I agree that, certainly for patients, I think that initiation of trials and understanding where there might be a trial that might be ongoing that might be available to them has also been effective, although, as you said, there are technological issues that remain. So it has made tremendous progress in transparency.

Mr. LANCE. Is there a way that you and we can work together to improve it? And I am not suggesting that you are in any way responsible for the challenges that remain. But moving forward for the better health of the American people, how together can we improve it?

Dr. WOODCOCK. Well, the FDA Amendment Act required that regulations be issued around the results——

Mr. LANCE. Yes.

Dr. WOODCOCK [continuing]. Section of this and that they consider whether to require the submission of clinical trial results for unapproved products, because much of the lag in getting results in there is that the products still are not on the market.

So NIH is the lead for this rulemaking and I think they would be in the best position, and, also, they operate the infrastructure for this database.

Mr. LANCE. Thank you.

In another area, in the past several hearings, we have discussed the difficulty of various institutions communicating one with another and a lack of coordination often leads to inefficiencies.

What methods are currently in place to reduce redundancies in clinical trials? And what steps can we take together to ensure that we are not doubling up on research or making the same mistakes over and over?

Dr. WOODCOCK. Hopefully, most things would eventually come out and be published. But certainly in the drug development area, there is interest in more sharing of earlier data and sharing of failures.

But this has proven to be very a intractable area——

Mr. LANCE. Yes.

Dr. WOODCOCK [continuing]. For transparency. All right?

Mr. LANCE. Yes.

Dr. WOODCOCK. But we have continued to work on that.

Mr. LANCE. Yes.

Dr. WOODCOCK. As far as some of the things that were referred to in the prior hearing, which I was able to listen to some of, they were talking about some of the inefficiencies, say, of IRBs, where you might have to have 100 IRBs that looked at——

Mr. LANCE. Yes.

Dr. WOODCOCK. And I believe that there are efforts to try and address this. It is not an FDA issue. But, really, we came out a number of years ago in saying that central IRBs would really be preferable in these large multi-center trials.

And then the contractual agreements that take so long to set up with each specific site is something that has been taken on. They have tried to develop model agreements and so forth.

But that is something that the standing trial addresses because you sign this contractual agreement once and then you can do multiple investigational agents.

Mr. LANCE. Are we moving in the direction of central IRBs, in your judgment?

Dr. WOODCOCK. Yes. There is certainly a consensus, I think, in the clinical trial investigator community that that is desirable, but various universities, naturally, are legally concerned about their own——

Mr. LANCE. Of course.

Dr. WOODCOCK [continuing]. Liabilities and so forth. And so there is a push and pull about that.

Mr. LANCE. I think this is an area that we should engage in further investigation to make sure that we move forward in a manner that does not result in redundancies.

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

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentlelady from Illinois, Ms. Schakowsky, for 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock. I think you are really an excellent witness. I appreciate your answers.

Dr. WOODCOCK. Thank you.

Ms. SCHAKOWSKY. I wanted to go a little bit further on the problem that Congresswoman Capps raised about the underrepresentation of women.

I know you said that you found that, actually, women were overrepresented, but recently the Congressional Caucus for Women's Issues sponsored a meeting with leading women heart experts—both clinical and research experts, physicians.

Those experts raised concerns that the lack of representation from women in clinical trials is limiting our ability to effectively treat women with heart disease. They were focusing in on heart disease.

And according to those experts, for the last 50 years, women's heart treatment has largely been based on medical research about men.

And even today, despite that fact, what they said is that women make up more than 50 percent of the U.S. population, that women comprise only 24 percent of participants in all heart-related studies.

And, additionally, scientists from the Women's Health Research Institute at Northwestern—that is in my district—have raised concerns about the disproportionate number of adverse drug effects that occur in women due to the lack of sex-based clinical research.

And, as you know, the biological, physiological, hormonal differences in males and females impact the rate of drug absorption, distribution, metabolism, elimination and, ultimately, affect the drug's effectiveness.

According to those experts, the lack of requirement for drug manufacturers to take this into account and document any sex variability early in the drug development pipeline before a drug has been released places consumers, especially female patients, at an increased risk of adverse drug effects.

So I want you to respond to that.

Dr. WOODCOCK. Certainly.

Ms. SCHAKOWSKY. Many of us were really left with a very disturbing feeling because heart disease is the major killer of women right now.

Dr. WOODCOCK. Right. Well, I think we have to—what are the facts on the ground. All right? One of the reasons for the disparities that they are mentioning is actually the fact that men suffer heart disease earlier in life than women.

Ms. SCHAKOWSKY. Although, let me just point out, they also said that the growing number, even though it is lower——

Dr. WOODCOCK. Yes.

Ms. SCHAKOWSKY [continuing]. Is younger women getting heart attacks and heart diseases.

Dr. WOODCOCK. Yes. Yes. So that the reason for maybe maldistribution in the trials is because there is an age cutoff, and there always has been.

In our survey, we found that there were—19 percent of the people in the trial in these 147 studies we looked at were over 65, which is more than in the general population, obviously, but of sick people, that is still low representation, right—to save people with heart disease.

Generally speaking, there is often a cutoff—age 75—and we are trying to eliminate those cutoffs for age and concomitant conditions so that the population will be more representative.

But to your original point, we have always required male and female animals in the toxicology studies. All right? We require what we call population pharmacokinetics, PK/PD, early in drug development.

And our clinical pharmacologists look at blood levels and exposure in men and women and we understand that, usually, and that is modern drug development.

So there are multiple trials that are done that look at exposures, in other words, achieve blood level by gender and other factors, liver failure, kidney failure and so forth.

And we can look at the phase 3 trials to see if they are—there has been a requirement in the regulations since, I think, 1994 that sponsors submit a gender analysis with their application.

Ms. SCHAKOWSKY. Is this incorrect, then? It says women comprise only 24 percent of participants in all heart-related studies.

Dr. WOODCOCK. Well, that may be true. And that may also include medical devices. It also may have to do with this age disparity when onset of disease.

Ms. SCHAKOWSKY. I really hope that you will look at that because it is a great concern. It is a growing problem for women.

And let me just give you an example of what—she said women, because we have different symptoms of heart disease—she said, if you have some of these symptoms of nausea, dizziness, go to the emergency room, but say, "I am having chest pains" because, without that, you may not get an electrocardiogram and you may be misdiagnosed. We need to help women.

Thank you. I yield back.

Mr. PITTS. Chair thanks the gentlelady.

Now recognize the gentleman from Louisiana, Dr. Cassidy, 5 minutes for questions.

Mr. CASSIDY. Hello, Dr. Woodcock. I always enjoy your testimony.

Dr. WOODCOCK. Thank you.

Mr. CASSIDY. I mean that as a big compliment.

So, next, real quickly—because I want to talk about something else—but does FDA—you mentioned that some institutions may be nervous about their liability if they refer their IRB activity to a centralized IRB.

Dr. WOODCOCK. Correct.

Mr. CASSIDY. Except so many do, we know that is a false argument.

Is there any way FDA can reassure those institutions? Because the gentleman from Mayo suggested it is a cultural issue. He didn't mention anything about legal. Thoughts?

Dr. WOODCOCK. Right. Yes. I heard his testimony.

In my experience, that there are legal—there are concerns of the—counsel of the various——

Mr. CASSIDY. Attorneys are always nervous. Right? I mean, they don't make money if they are not nervous. I hate to be cynical, but——

Dr. WOODCOCK. Yes.

Mr. CASSIDY. Is there any way FDA can send reassurances regarding that?

Dr. WOODCOCK. Well, we have tried. In guidance and so forth, we have encouraged this. And in the city initiative, we had a whole discussion and dissemination of information about central IRBs. But possibly there is more that we can do to encourage this.

Mr. CASSIDY. OK. Let me then bring on—you mentioned something intriguing earlier, that there may be some at high risk for disease; so, therefore they will be more risk-tolerant.

Dr. WOODCOCK. Yes.

Mr. CASSIDY. Now, I have a family member, a nephew, with Down syndrome. And I am looking on the alzheimers.org Web site, and they mention how virtually 100 percent of adults with Down

syndrome by age 40 will have evidence of the tangles associated with Alzheimer's.

Dr. WOODCOCK. Yes.

Mr. CASSIDY. Now, what are the issues regarding—wow. This is a group of adults who are 100 percent at risk for a terrible condition.

Dr. WOODCOCK. Right.

Mr. CASSIDY. But there are other issues involved as well.

What are your thoughts about this? How do we make stuff available for folks incredibly at risk for such a terrible disease?

Dr. WOODCOCK. Yes. Well, with Alzheimer's, there are a number of problems. The basic problem is we still don't understand the disease well enough and the interventions that have been tried, which have been in late-stage disease when people are already demented, have failed to work.

Mr. CASSIDY. Now, as I gather, though, the problem is predicting at an earlier stage those at risk. Correct?

Dr. WOODCOCK. That is correct. If you want to intervene early. We recently issued a draft guidance saying that, OK, if you want to intervene earlier, we would accept an end point that is subtle cognitive testing.

Mr. CASSIDY. I accept that.

But how do you decide which population is at such high risk? Because, if you have a control group—you follow what I am saying—only 10 percent are really going to be at risk.

Dr. WOODCOCK. Right.

Mr. CASSIDY. You with me? This is a really expensive study.

Dr. WOODCOCK. That is right. And so we advocate techniques called enrichment, which you try to use biomarkers or other tests to figure out. There are genetic conditions that increase your risk for Alzheimer's disease.

Mr. CASSIDY. So speaking of Down syndrome as one example?

Dr. WOODCOCK. That would be one example. Yes. There are others.

Mr. CASSIDY. And can you give us the progress of that. So if you accept these, are people now using these?

Dr. WOODCOCK. Well, we need agents to use them in. So that is part——

Mr. CASSIDY. And I am sorry. "Agents," you mean as in——

Dr. WOODCOCK. I am sorry. Investigational interventions that we can test in the people.

And that is part of the problem. The science of understanding what causes Alzheimer's and what you can intervene in that would actually delay or prevent the disease is not mature enough.

And we have approved a couple imaging agents for Alzheimer's, but they aren't 100 percent. And you would maybe be kind of advanced——

Mr. CASSIDY. But, for example, I know hyperinsulinemia is thought to be a potential risk factor.

Dr. WOODCOCK. Yes. I know that.

Mr. CASSIDY. And I think there are some studies suggesting that Actos might give some benefit.

Dr. WOODCOCK. Yes.

Mr. CASSIDY. Presumably, it would be at an earlier stage, not a later stage, would be a non-metabolic syndrome indication for the use of Actos. Fair statement?

Dr. WOODCOCK. Yes.

Mr. CASSIDY. So there is at least some of that. I guess I pose that to ask the degree to which that has been, again, the current state. I will go back to what is the current state of using that sort of thing?

Dr. WOODCOCK. Right. So the current state, if someone decided to do a trial—and I believe there have been some intervention trials, not of Actos, but an earlier intervention at high-risk—in higher-risk people—they might identify people they felt were high risk for one reason or another, randomize them to this intervention or not, and then we would allow use of neurocognitive testing even before they had symptoms, if they had subtle changes, and if the treatment group did better than the placebo group, we could give accelerated approval.

Mr. CASSIDY. So I guess you have got the framework. It is just a question of someone coming forward to take advantage of it.

But how long would such a study, do you imagine, take to complete its course? Twenty years?

Dr. WOODCOCK. No. No. But we need to have better measurements that stick to these biomarkers and other measurements, like of subtle cognitive function, where we—the NIH and us and others are working on this.

Because the earlier you can intervene—if you have a very targeted test that can identify people early, they don't have any symptoms, but you can tell their brain isn't working as well as it should, and then it will decrease over time. So that is kind of the rate-limiting step.

But I agree. Prevention is very difficult because there you want to intervene on people who are well and treat them for a long time and expose them to something with the hope that, at the end of the day, they are not going to get whatever bad outcome.

Mr. CASSIDY. We are out of time. Thank you very much.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentleman from Virginia, Mr. Griffith, 5 minutes for questioning.

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

Dr. Woodcock, as others have said today and, also, what I have heard in some of our informal conversations is that you not only do a good job as a witness, but that you are doing a good job overall.

Dr. WOODCOCK. Thank you.

Mr. GRIFFITH. And so I appreciate that, and thank you so much for being here today.

You and Dr. Cassidy had a little conversation about lawyers. Some lawyers are always nervous. Other lawyers are always looking for a way to solve the problem.

And so maybe we need to get some of those lawyers on your team and some of the corporate teams to solve the problem, figure out how we can make these things work, because I do think it is important.

As you probably know, I am one of those who advocates that we try to move a little quicker in those areas where we have problems that we don't have solutions for currently and, also, favor what is known in some State laws as right to try when you have a situation where doctors have tried everything and folks are given a diagnosis they have got months to live or their condition is going to be fatal.

I am one of those people who believes that we ought to let them go ahead and try whatever it is they are willing to pay to do because the FDA can't protect you if you are going to die from something that might kill you.

Dr. WOODCOCK. Right.

Mr. GRIFFITH. I mean, it is going to happen one way or the other. You might as well have the right to try something.

That being said, I know there are a lot of issues surrounding that. I am not sure we have time for for that discussion today.

And I know that there is another panel, and I want to hear from the patients as well because they are involved in this process.

So respecting you greatly, I yield back my time.

Mr. PITTS. Chair thanks the gentleman.

Now recognizes gentlelady from North Carolina, Mrs. Ellmers, 5 minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman.

And thank you, Dr. Woodcock, for being with us again today.

This is such an important issue. As you know, we had our panel on Wednesday. And it seemed to me that it was a general consensus that everyone is looking for ways to expedite this and to make it more efficient and get those drugs to market sooner so that we can be taking care of our patients more effectively.

In your testimony and in the discussions that we have had today, you have touched on the biomarkers and targeted drug development to benefit disease populations, obviously.

As all of our representatives here, we all have constituents with rare diseases, heart-breaking. Especially right now in my community, I have a very good friend with ALS. And as I am learning more and realizing, we have had a number of members of our community diagnosed with ALS. So this is something that is very important to me right now.

And I am just looking at the idea—as far as the target approval process being appropriated and applied through the FDA, it seems to be that we are looking at cancer and HIV. Where do some of those rare diseases fall within that?

And you had mentioned and there was discussion about the master protocol and that seems to be applied more to cancer or HIV. Where can some of the rare diseases fall in there? And what can we do to help make that happen?

Dr. WOODCOCK. Well, any rare disease would be a great candidate for a standing network, a network of experts—and I think you may hear more about this from the next panel—where they are ready to evaluate any therapy that advances through the early, the nonhuman, stages.

So they could pick that up right away and test it quickly. In the meantime, until that happens, they can get what we call natural history, which I know sounds very wonky.

But people are asking—just now Mr. Cassidy—like how long does Alzheimer's progress from presymptomatic to symptomatic. Well, we need to know that so that we can design the trial correctly.

In rare diseases, even more difficult because nobody knows. And, usually, they get experts together and say, "Well, in my opinion, it takes this long." Right? And they are usually wrong because they have only seen a few people.

So we are encouraging these natural history studies, these networks. First, they look at the people and they can look at the biomarkers, too.

So what changes in ALS? What can we measure? Could we measure something that gives us indication that treatment might be working? Right?

And then, as soon as a therapy becomes available, then you can rapidly get people into a trial and there would be no delays because there is no delaying an ALS.

Mrs. ELLMERS. Right. Exactly.

And that is obviously part of the concern. And certainly I agree with my colleague in talking about right to try. This would be a perfect example of decisions that families and patients can make.

I do want to talk about—you had also mentioned listening carefully to patients and families.

Dr. WOODCOCK. Yes.

Mrs. ELLMERS. And do you consider and give more weight—that is one of our questions, is how much weight are you giving to the patients and families? And there again, from our perspective in Congress, what can we do?

You know, as we have heard everyone agreeing that we need to make a difference here and we can move things forward, how open is the FDA to this possibility? And what can we do right now to make this happen?

Dr. WOODCOCK. Well, as I said in my testimony in the beginning, medical culture has changed over the years. It used to be very doctor-centric and now it is patient-centric. And the FDA culture and drugs is a medical culture. And so that has changed at the same time, but slowly.

So we have been working, though, very diligently with patient groups and so forth to try to get the patient point of view more central to the evaluation of benefit and risk and what it means to the person who actually has the disease, is going to take the drug.

To answer your question what can be done, I think a lot of this needs to be done out in the community. The patient groups need to get organized and develop these. Some of them are working with PCORI and trying to use that mechanism to get more information available and so forth.

We have gotten draft guidances from different groups, including Muscular Dystrophy, that really are a statement of, "This is what we care about. This is what we value. This is what we want you to look at." And we will pay extremely close attention to those, and those are extremely valuable.

Mrs. ELLMERS. Thank you, Dr. Woodcock.

And I yield back the remainder of my time.

Mr. PITTS. The chair thanks the gentlelady.

We are voting on the floor. We have 10 minutes left in the vote. We have three more questioners.

Mr. Guthrie recognized for 5 minutes for questioning.

Mr. GUTHRIE. Thank you, Mr. Chairman. I will try to be brief.

I will echo what the others said about your testimony. Appreciate it.

But since we started this 21st Century Cures and—everybody's excited. Both sides are trying to see how we can do this better.

And I have heard from a lot of groups and I have heard several times that the oncology division seems to be one people really like to work with and it works well. Some of the other divisions in expedition is not as well to work with.

And I have always believed—Jack Kemp used to say, "Don't study failures and point out the problems. Let's look at successes and see how it can be replicated."

So within your own agency, you are having wonderfully successful programs, at least according to the feedback I have gotten, and some not as fun as the ability to work with.

So I guess my question is: Is there any impediment to saying, "Hey, this"—the oncology is what we hear about more, not that the others aren't, but we hear more—is there any impediment to taking what is happening there and transferring to other agencies? Is there something Congress can do to make it easier or is it just learning and moving forward?

Dr. WOODCOCK. Let me tell you that 10 years ago, I heard a lot of negative comments about our oncology group. All right? And now we have therapies that are so effective. They are really on fire.

They see that, for their patients they took care of—they are all oncologists, hem onc doctors—that these new treatments would really have made a difference for those people. And so they are doing everything they can to get those treatments out.

And I think what we need, we need the same kind of inspiring therapies in these other areas. And I do think the doctors—they are doctors. They are physicians. They care about patients in their disease area.

And this breakthrough—I don't know whether you can see it here, but you see that other disease areas are coming up and we are designating—in neurology and anti-infectives and psychiatry, we are designating potential breakthroughs. And so this type of thing will really help.

But, also, of course, we try to have a management structure, multiple mechanisms whereby we have consistency and uniformity of our approach and our procedures, and I think we do quite well in our procedures.

But I think the attitude may have something to do with the underlying science. We had a war on cancer. It is starting to pay off. And we need to really expedite that.

Mr. GUTHRIE. Well, thanks.

And I have a bill particularly to put the same professional budget judgment status for Alzheimer's, which we are going to spend in 2050 $1 trillion. This is not loss of income, loss of productivity.

Dr. WOODCOCK. Right.

Mr. GUTHRIE. That is $1 trillion spent on that disease.

That is when I am 86. So that is when my children and our grandchildren will be taking care of us. So, hopefully, we can have the same inspiration and do that, particularly in Alzheimer's.

Dr. WOODCOCK. I can assure you that, if they were promising treatments for Alzheimer's, we would jump right on them.

Mr. GUTHRIE. Appreciate that. Thank you very much.

And I will yield back.

Mr. PITTS. Chair thanks the gentleman.

Recognizes the gentlelady from Tennessee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you so much, Dr. Woodcock. I have basically one question that I do want to get to.

Looking at the QIDP and the moving forward of that, it can give up to 5 years of additional data exclusivity. Bipartisan effort. We were all for it.

What I want to know from you is: How many QIDPs has the FDA designated to date? How many products have actually been approved to date? And do you believe that the QIDP is an important designation?

Dr. WOODCOCK. It is absolutely important.

Mrs. BLACKBURN. OK.

Dr. WOODCOCK. We have granted 50 designations for 34 unique molecules. And in the last several weeks, we have approved the first two medications that are designated, the first two antimicrobials.

Mrs. BLACKBURN. Excellent.

Dr. WOODCOCK. So that is making a difference. We do feel, though, that probably more needs to be done.

Mrs. BLACKBURN. And in that "more needs to be done," give me a couple of examples of what you think the next step should be. I would be interested in that.

Dr. WOODCOCK. Well, we are very interested in the pathway that people call limited population antibacterial drugs or other streamlined pathways for development that would be matched with some sort of symbol or logo that would enable doctors and other prescribers to recognize that it was from a limited program. We think that would also allow us to streamline the development program.

Mrs. BLACKBURN. Excellent.

And for the second panel, I want to welcome a fellow Tennesseean, Dr. Marshall Summar, who is going to be speaking on behalf of the National Organization of Rare Diseases.

So welcome. We are delighted you are here.

And I would yield back.

Mr. PITTS. Chair thanks the gentlelady.

Now recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it.

And thank you for your testimony, Dr. Woodcock.

I asked these questions a few months ago and I didn't get a response. So I am going to see if I can get a response this time. Appreciate it if you can answer.

Can you tell me how many treatments were approved with novel biomarkers used for the first time?

Dr. WOODCOCK. No. I don't have that in the——

Mr. BILIRAKIS. Can you get that information to me as soon as possible?

Dr. WOODCOCK. I would be happy to. It is a very interesting question. Yes.

Mr. BILIRAKIS. And then next question: Have any accelerated approval occurred within novel biomarker in never-before-treated disease?

Dr. WOODCOCK. Oh, yes. All the time. And I can get that for you. I don't have it, again.

Mr. BILIRAKIS. Please.

How many new biomarkers did the FDA accept for a first-time use in the last 5 years?

Dr. WOODCOCK. Certainly.

Mr. BILIRAKIS. Can you get that for me?

Dr. WOODCOCK. Absolutely.

Mr. BILIRAKIS. OK. Very good. Thank you very much.

I know we don't have a lot of time; so, I will yield back. Thank you, Mr. Chairman.

Mr. PITTS. Thank you.

There is 2 minutes left in the vote on the floor; so, we are going to recess. There are two votes. As soon as we have the second vote, we will come back and reconvene with our second panel.

Again, Dr. Woodcock, thank you for coming. You have been a terrific witness.

Dr. WOODCOCK. Thank you.

Mr. PITTS. Members will have follow-up questions. We will send them to you. We would ask that you please respond.

Thank you. And thank you for your patience.

The subcommittee stands in recess.

[Recess.]

Mr. PITTS. Time of recess having expired, we will reconvene the subcommittee on Health and introduce our second panel.

In our second panel, we have five witnesses. I will introduce them in order of their presentation. First, Ms. Pat Furlong, Founding President and CEO of the Parent Project Muscular Dystrophy; second one, Mr. Robert Beall, President and CEO of Cystic Fibrosis Foundation; third, Mr. Richard Pops, Chairman and CEO of Alkermes; fourthly, Dr. Leonard Lichtenfeld, Deputy Chief Medical Officer of American Cancer Society; finally, Dr. Marshall Summar, Director of Scientific Advisory Committee, National Organization for Rare Disorders.

Thank you all for coming. You will each be given 5 minutes to summarize your testimony. Your written testimony will be placed in the record.

Ms. Furlong, we will start with you. You are recognized for 5 minutes for your opening statement.

STATEMENTS OF PAT FURLONG, FOUNDING PRESIDENT AND CEO, PARENT PROJECT MUSCULAR DYSTROPHY; RICHARD F. POPS, CHAIRMAN AND CEO, ALKERMES; MARSHALL SUMMAR, M.D., DIRECTOR, SCIENTIFIC ADVISORY COMMITTEE, NATIONAL ORGANIZATION FOR RARE DISORDERS; ROBERT J. BEALL, PH.D., PRESIDENT AND CEO, CYSTIC FIBROSIS FOUNDATION; AND J. LEONARD LICHTENFELD, M.D., DEPUTY CHIEF MEDICAL OFFICER, AMERICAN CANCER SOCIETY

STATEMENT OF PAT FURLONG

Ms. FURLONG. Thank you.

Good morning, Chairman Pitts and members of the committee.

My name is Pat Furlong. Twenty years ago I joined other parents to form Parent Project Muscular Dystrophy to end Duchenne, one of the many forms of muscular dystrophy and the most common lethal genetic disorder diagnosed in childhood.

In 1984, I received the horrific diagnosis on my two sons, Christopher and Patrick, and both of my sons are gone now. I wage this crusade in their honor.

Much has happened over the past 15 years to transform the Duchenne clinical and research landscapes, and much of this is a direct result of the actions by Congress and this committee, notably the enactment of the Childs' Health Act in 2000, and the Muscular Dystrophy CARE Act 1 year later. Since the MD CARE Act was enacted, we have seen about 10 years added to the lifespan of patients with Duchenne.

There has been an improvement in quality of life driven largely by the development and dissemination of care standards so that all patients can be diagnosed accurately and as early as possible and provided with the highest quality of care.

The MD CARE Act also transformed the Duchenne research landscape. What was just 12 years ago a near-barren field has evolved into a robust area of research where multiple potential therapies are in clinical testing and several others are in early stages of development.

Despite these advancements, Duchenne remains a fatal disease without any FDA-approved therapies. Most boys end up in wheelchairs by their mid-teens, and only a few live beyond their late 20s.

Our community needs therapies and we need them fast to. To achieve this goal, PPMD has led groundbreaking efforts over the past year to address two major impediments in our request to end Duchenne.

One is a lack of regulatory understanding of patient and parent perspectives on benefit-risk; and, two, a lack of clear guidance or direction to the biopharmaceutical companies designing these clinical trials.

PPMD partnered with Johns Hopkins University to conduct the first-ever scientific survey on benefit-risk perspectives. The survey involved 120 parents of Duchenne children. It validated what we have known anecdotally for years.

Because Duchenne is 100 percent fatal at a young age, many patients and families are willing to accept higher levels of risk in return for the prospect of potential benefit.

The data has been shared with the FDA and was recently published in an academic journal. Now the FDA must ensure its reviewers apply this evidence to their decisionmaking process.

Another impediment to drug development, particularly in rare diseases, is the absence of a clear guidance from FDA when it comes to designing clinical trials. Small patient populations, limited knowledge about the condition and a lack of accepted or validated biomarkers are some of these challenges.

At the invitation of the FDA, PPMD led a comprehensive 6-month effort to convene key stakeholders—patients, parents, clinicians, researchers and industry—to write a draft guidance document that would address trial design and many other issues. This was submitted to the FDA last month, marking the first time a patient group has led the development of such a product.

Now the FDA must step up promptly to review the draft, gather stakeholder input and issue a guidance document under the Agency's name.

While each of these projects is focused on Duchenne, each also offers a template or a model that could be applied to other diseases or other conditions, particularly rare diseases, and I hope other organizations will take on similar programs.

So what can Congress and Federal agencies do moving ahead? First, you can make sure that the patient perspective on benefit-risk and other issues is considered by reviewers of the FDA.

One way to do so could be by establishing a nonburdensome step where reviewers would disclose how they did or did not take such information into account making their decisions on a drug application. This would shed light on for what many considered a mysterious process and could be done in a very simple manner.

Second, I suggest an even greater focus on regulatory science so the FDA keeps pace with the breakneck speed of innovation. Specifically, NIH could bolster support for regulatory science research and infuse that into clinical and translational awards. Incorporating a regulatory perspective earlier in the pipeline can maximize the likelihood that candidate therapies will be ready for the rigor of the FDA.

Finally, I would encourage greater flexibility in clinical trials, particularly rare fatal conditions like Duchenne that have small populations. Business-as-usual trial designs simply do not hit the mark when working with these populations.

The Duchenne community has traveled a great distance over the past 15 years, thanks in significant part to the leadership of this very committee, leadership that will continue on Monday with action by the full committee on the MD CARE Act amendments.

For far too many families, my own included, this journey has not been fast enough. We stand ready to work with your committee to make sure the 21st Century Cures Initiative ends Duchenne and so many other rare diseases.

Thank you.

Mr. PITTS. Chair thanks the gentlelady.

[The statement of Ms. Furlong follows:]

Testimony of Pat Furlong
Founding President & CEO
Parent Project Muscular Dystrophy

Committee on Energy & Commerce
Subcommittee on Health
July 11, 2014

Good morning Chairman Pitts, Chairman Upton, Ranking Member Pallone, Ranking Member Waxman and Members of the Committee.

My name is Pat Furlong. Twenty years ago, I joined other parents to form Parent Project Muscular Dystrophy to end Duchenne, one of nine forms of muscular dystrophy and the most common, lethal genetic disorder diagnosed in childhood. Ten years earlier, in 1984, I received the horrific diagnosis that my two sons, Christopher and Patrick, had this disease. Though both my sons are gone, I wage this fight in their honor.

Today I am going to briefly describe a journey spanning two decades that shows what is possible when all sectors – public and private – come together to pursue breakthroughs in research and to advance into innovative treatments.

Before I begin, I want to commend Chairman Upton, Congresswoman DeGette, and the Committee for undertaking the 21st Century Cures Initiative. This committee has a long history of leadership on research, drug development and public health issues, and the Cures Initiative is much-needed.

Nearly 15 years ago, this Committee shepherded through Congress the Children's Health Act, which created or strengthened multiple programs focused on childhood disease and disability. This law contained a small but important provision that directed the National Institutes of Health to expand research into all forms of muscular dystrophy, including Duchenne. At the time of this enactment, the NIH commitment to muscular dystrophy overall was less than $10 million annually, and Duchenne research was almost non-existent.

The following year, recognizing that an even more comprehensive effort was needed, Congress enacted the Muscular Dystrophy Community Assistance, Research and Education or MD CARE Act, a law that also was marked up by this committee.

The MD CARE Act and its 2008 amendments have transformed research and clinical care for Duchenne and the many other forms of muscular dystrophy. And today, a modest, but essential, update to this law is now moving through Congress. I thank the members of the Health Subcommittee for marking up this legislation late last month, and we look forward to forthcoming action by the full committee.

Focused on all forms of muscular dystrophy, the MD CARE Act was in my view the single biggest advancement for the Duchenne community since Lou Kunkel and his team identified the gene that causes Duchenne back in 1986.

To give you a sense as to how far we have come since the law's enactment in 2001, consider that, at that time, most boys lived only into their late teens. Today, the average life span for some young men – while still far too short – is about 10 years longer.

Also, in 2001, the Duchenne therapeutic pipeline was barren with very few academic researchers and no industry players – big or small – involved in the field. Today, we have about a dozen Duchenne therapies in clinical testing, and many more candidates in earlier stages of development.

Despite the many scientific breakthroughs driven by the MD CARE Act, Duchenne remains a fatal disease without any disease-modifying therapies or approved treatments. Most boys end up in wheelchairs by their mid-teens and face a steady decline of muscle function as they age.

Our community needs therapies, and we need them fast.

To accelerate the development and delivery of effective therapies to patients, PPMD has led two projects over the past year to address major gaps in the process:

- The first-ever scientific survey of our community on benefit and risk preferences; and
- The first-ever, patient-initiated drafting of a guidance document for industry sponsors for consideration by FDA as a formal adopted process.

Because Duchenne is 100 percent fatal at a young age, many patients and families have long said they would be willing to accept higher levels of potential risk in return for the prospect of certain benefits. Last year, PPMD partnered with Johns Hopkins University to conduct the first-ever scientific survey of about 120 parents of children with Duchenne.

This survey validated our community's higher risk threshold, even when balanced against a non-curative treatment, such as prolonging the ability to walk, and absent an increase in lifespan. This data was shared with the FDA and was recently published in an academic journal. Now, FDA must ensure its reviewers apply this perspective to their decision-making process.

Another significant impediment to drug development, particularly for those working in rare disease, is the absence of clear guidance from FDA when it comes to designing clinical trials. Small patient populations, limited knowledge about the conditions and a lack of accepted or validated biomarkers that indicate a potential treatment is working are some of these challenges.

At the recommendation of the FDA, PPMD led a comprehensive, six-month effort to convene key stakeholders – patients, parents, clinicians, researchers and industry – to develop a draft guidance document that would address trial design and other issues. This document was submitted to FDA last month, marking the first time a patient group has led the development of such a product.

Now, FDA must step up to promptly review the draft, gather stakeholder input and issue a guidance document under the agency's name. A docket has been opened, a good first step, but we must see more activity this summer and fall.

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So what can Congress and FDA do moving ahead?

Beyond holding a stakeholder meeting and issuing a draft guidance document, FDA must make sure its reviewers recognize the benefit/risk perspectives of our community. The message from the survey is quite clear – given the alternative of death at a young age, our community is willing to accept a higher degree of risk.

One way to ensure that the patient perspective impacts the review process would be to establish a non-burdensome step wherein reviewers disclose how they did – or did not – take such information into account in making their decisions on a candidate therapy. This would shed light on what is for many a black-box process and could be done in a non-burdensome manner.

Beyond such transparency, I would urge an even greater focus on regulatory science so that the FDA keeps pace with the breakneck pace of industry drug development. In addition to bolstering support for regulatory science research, NIH must infuse a regulatory science component into all translational awards. By incorporating regulatory science considerations earlier in the pipeline, we can maximize the likelihood that candidate therapies will be ready for the rigor of the FDA process.

Finally, I would encourage greater flexibility in clinical trials, particularly for fatal rare diseases like Duchenne that have smaller populations. Business-as-usual trial design simply will not hit the mark when working with such populations. Specifically, we should be open to post-hoc or post-trial analysis to continue gathering important information on benefits and risks without making for unnecessarily lengthy and burdensome trials.

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The Duchenne community has traveled a great distance over the past 15 years, thanks in significant part to the leadership of this Committee. But for too many families, my own included, this journey has not been fast enough, and we think every day about those whom we have lost.

We need treatments and therapies, right now, so we can end Duchenne and address the thousands of other rare diseases in need of treatments and cures.

I applaud the Committee for focusing on this important issue, and look forward to contributing to this work going forward.

Mr. PITTS. Mr. Beall, you are recognized for 5 minutes for your opening statement.

STATEMENT OF ROBERT J. BEALL, PH.D.

Mr. BEALL. Thank you very much for this invitation to present this testimony.

The story of cystic fibrosis is clearly a story of determination of hope and optimism. The progress that we have documented in our submission really shows what is possible when a system works well, when patients, when stakeholders and the regulatory agencies collaborate to develop life-changing treatments.

Cystic fibrosis is clearly a life-threatening genetic disease that affects about 30,000 individuals in the United States. There has been tremendous progress in life expectancy over the decades.

In the 1950s, people with cystic fibrosis barely lived to elementary school. But there are people that are living today with cystic fibrosis in their 30s and 40s, and some are even going beyond.

But we still lose too many patients at very young ages. The increase in life expectancy is due in large part to groundbreaking advancements and treatments made possible because of the Cystic Fibrosis Foundation, our patient community and our industry collaborators.

Two years ago the FDA approved Kalydeco, the first drug to treat the underlying causes of cystic fibrosis in a small subset of people with the disease. Hailed as a game-changer, it has transformed the lives of those taking this drug.

It is a perfect example of personalized medicine. I might mention that the FDA approved this drug in near record time, 3 months before the prescribed PDUFA date and months before the EMEA.

Just 2 weeks ago we saw another breakthrough in cystic fibrosis. It happened when—the positive data from a phase 3 clinical trial for a new therapy that is targeted at 40 percent of the CF population.

This data was released by Vertex Pharmaceuticals Company. These products would not have been possible without the breakthroughs that have taken place in basic research, in all the efforts that our foundation has made over the years.

The CF community was thrilled to learn that the trial participants showed a significant improvement in lung function, weight gain, and 30 to 40 percent reduction in exacerbations. That is the time that they would have to go to the hospitals or have IV infections.

So this is clearly a game-changer for these patients. Obviously, Vertex plans to submit the new drug application to the FDA by the end of the year for this treatment.

What is exciting about this progress is that these drugs would not have been possible were it not for the Foundation and our patient community. Our commitment to scientific discovery and drug development is at the root of our success, but it hasn't been easy and it hasn't occurred overnight.

In 1965, we created the first patient registry in the United States, now a model for chronic disease. Because of this registry, we have a documented natural history of cystic fibrosis.

We have the mutation analysis on most of these patients, as Dr. Woodcock referred to this morning, and we have the ability to have post-marketing phase 4 follow-up on these new drugs as they are introduced to the community.

The same year, 1965, we created a care center network. 90 percent of all patients seen in the United States are seen at these CFF-accredited and funded care centers.

In 1989, through our support, the CF gene was discovered, 12 years before the human genome was completed.

In 1998, we established a Clinical Trials Network, the first Clinical Trials Network founded solely by a nonprofit organization like the Foundation. It is a critical component of our ability to conduct CF clinical trials efficiently and effectively.

In 1999, the CF Foundation pioneered a successful venture philanthropy model to derisk companies from investing in CF research drug development.

It was our initial investment of $42 million in a small biotech company in San Diego that ultimately led to Kalydeco. Vertex would not have had Kalydeco and the other drugs announced last week were it not for the Cystic Fibrosis Foundation.

The CF Foundation spearheads collaboration across all sectors, and this same collaborative spirit extends to the Foundation's strong partnership with the Food and Drug Administration.

With the FDA, we are committed to collaboration and bringing strong data to the table. As often has been stated, the CF Foundation comes with data, not demands.

Just last week we met with FDA officials to discuss strategies for clinical research design that may not occur until 5 years from now.

However, curing a disease is never easy, and even more risky is the approval of drugs without sufficient data to assure efficacy and safety.

If this happens, you place patients immediately at risk and you risk losing the opportunity to test drugs that could have a real impact and beneficial effect.

So, in closing, what can Congress do for us? Congress should make sure that patients have a seat at the table, as was just referred to.

Congress must provide the necessary resources so that the FDA can attract the best and the brightest. And Congress must provide the NIH and FDA sufficient resources for regulatory sciences, as also mentioned.

But, finally, Congress may also encourage that they look at the CTSA program, a network of care centers that are funded by the NIH, and see how they might use these to be able to facilitate Clinical Trial Network and the development of patient registries in other rare diseases.

So, once again, thank you for this opportunity to add the CF community's perspective to this important discussion.

Mr. PITTS. Chair thanks the gentleman.

[The statement of Mr. Beall follows:]

July 11, 2014

Robert J. Beall, Ph.D.
President and CEO
Cystic Fibrosis Foundation
6931 Arlington Road
Bethesda, MD 20814

Written Testimony for Hearing: "21st Century Cures: Incorporating the Patient Perspective"
Committee on Energy and Commerce, Subcommittee on Health

Summary and Recommendations

This testimony will outline exciting advancements in the development of new cystic fibrosis treatments, the challenges and risks inherent in developing treatments for this rare disease, the need for a balance between accelerating treatments and ensuring they are safe and effective, and what Congress can do to help move treatments more efficiently to patients.

The Foundation's policy recommendations include:

- Ensure that patients have a voice in drug development, review and approval,
- Support the creation of mechanisms to accurately measure what meaningful outcomes are for patients,
- Support the creation of mechanisms to generate comprehensive, quality data to help make the analysis of risks versus benefits less burdensome for patients,
- Ensure a well-resourced FDA, and
- Monitor implementation of the Food and Drug Administration Safety and Innovation Act (FDASIA)

Written Statement

On behalf of the Cystic Fibrosis Foundation and all of those in the cystic fibrosis (CF) community, we greatly appreciate this opportunity to provide testimony for "21st Century Cures: Incorporating the Patient Perspective," a hearing in the Energy and Commerce Committee's Health Subcommittee. We commend the Committee for initiating this dialogue and for promoting a climate that supports the advancement of biomedical innovation.

The story of cystic fibrosis is one of hope and optimism, a remarkable example of what is possible when patients, industry and other stakeholders collaborate to develop treatments that are changing the lives of those with the disease. This testimony will outline exciting advancements in the development of new cystic fibrosis treatments, the challenges and risks inherent in developing treatments for this rare disease, the need for a balance between accelerating treatments and ensuring they are safe and effective, and what Congress can do to help move treatments more efficiently to patients.

The Foundation's policy recommendations include:

- Ensure that patients have a voice in drug development, review and approval,
- Supporting the creation of mechanisms to accurately measure what meaningful outcomes are for patients,
- Supporting the creation of mechanisms to generate comprehensive, quality data to help make the analysis of risks versus benefits less burdensome for patients,
- Ensure a well-resourced FDA, and
- Monitor implementation of the Food and Drug Administration Safety and Innovation Act (FDASIA)

Cystic Fibrosis and New Genetically-Targeted Treatments

Cystic fibrosis is a life-threatening genetic disease that affects 30,000 children and adults in the United States. It is primarily a lung disease caused by a defective gene that makes the body produce mucus that clogs the lungs and leads to serious infections.

Life expectancy for those with CF has risen remarkably during the past six decades. In the 1950s, those with CF didn't live to go to elementary school – now people with cystic fibrosis are living into their 30s, 40s and beyond.

This is due in part to groundbreaking advancements in treatments that target the disease from every angle. As genetically-targeted treatments move through the CF drug pipeline and on to patients, this disease is at the forefront of a new era in personalized medicine and is a model for what can be achieved when stakeholders collaborate on the development of treatments for a rare disease.

January marked the two year anniversary of FDA approval of Kalydeco™, the first treatment to target the root genetic cause of CF in a subset of people with the disease. In the two years since its approval, many of the nearly 2,000 patients worldwide who take the treatment are breathing easier, gaining weight, and even being removed from lung transplant lists. FDA approved this drug in near record time, almost two months ahead of the drug's review date.

In another major advancement, positive data for phase 3 clinical trials for a new targeted therapy were recently released by Vertex Pharmaceuticals, evaluating the effect of a combination treatment of Kalydeco and lumacaftor (VX-809), which could treat nearly 50% of the total CF population.

The CF community was thrilled when the clinical trial data showed that people ages 12 and older with two copies of the F508del mutation who received the treatment had significant improvements in lung function and other key measures of the disease. Those receiving the combination, in addition to experiencing improved lung function, also had improved weight gain and significant reductions in the rate of pulmonary exacerbations and associated hospitalizations and IV antibiotic use. Vertex

Pharmaceuticals plans to submit a New Drug Application to the FDA for this treatment by the end of the year.

These successes, in rapid succession, represent a real turning point in the lives of those diagnosed with CF and are opening doors that could lead to a cure for CF in our lifetime.

The Cystic Fibrosis Foundation Drug Development Model and the Challenges Ahead

Getting to where we are today was a long and complex process, resulting from the Cystic Fibrosis Foundation's strategic and coordinated approach to curing the disease. The main focus of the CF model is collaboration across sectors, as the Foundation, academia, industry, government, patients and the medical community work together to develop treatments. Included in this is the CF Foundation's work to invest in basic and translational research, support the development of a clinical trials network dedicated to CF therapeutic development, initiate and enhance a patient registry including rich data about the treatment of CF patients, and advance a "venture philanthropy" model for therapeutic development.

With the success of Kalydeco and promising potential disease modifying treatments, many complicated therapy development challenges lie ahead. Although the combination therapy described above could benefit a large portion of the CF population, there are many children, teens, and adults with no therapy available to address the underlying cause of the disease. The Foundation and its partners are committed to a development program that will bring the promise of these drugs to the entire CF community.

The development program necessary to achieve this goal will be complex. We will increasingly be targeting very small segments of the orphan CF population, and conducting trials in such small populations is difficult. Trial design, trial participant accrual, and data analysis are all difficult in these trials. The CF Foundation will be bringing multiple drug developers together for various combination

trials, a complex undertaking. In addition, we believe that there will be additional "generations" of CF disease-modulating drugs, and achieving prompt accrual to these trials will pose significant challenges.

Ensuring the Balance between Speed & Safety and Efficacy

CF patients and their families have shown their commitment to the CF Foundation's therapy development program by their generosity. They contribute generously to the Foundation through financial contributions, through volunteer action, and as participants in clinical trials.

We owe it to those patients to develop the strongest possible new therapies and to ensure that the drugs we develop are safe and effective. For CF patients living with a chronic disease, the adverse effects of any drug must be weighed carefully against the therapeutic benefit.

As policy options are considered, it is important to find a balance between accelerating drug discovery and innovation, while also ensuring that patients have safe, effective treatments. Although patients are willing to take a certain amount of risk when it comes to treatment, approving therapies based on data collected early in clinical research, prior to more rigorous study, could pose a health risk for patients. We must keep in mind that positive data based on what works in the lab, or even in phase 2 clinical trials, may not translate to tangible benefits for patients.

Furthermore, it could endanger progress towards the development of other treatments. Those who receive a drug for which there are limited data may not be willing to participate in further clinical trials for other drugs to treat their illness, or be open to trying other treatments backed by better quality data.

When finding the balance between accelerating drug discovery and innovation and ensuring safety and efficacy, there must be clear communication about the benefits of current therapies so that patients can make informed decisions about clinical trial participation of new therapies and about changes in their treatment as new therapies are developed. Patients are the ones assuming this risk, and

they need to know and help define which treatments will have a meaningful impact on their quality of life.

The decisions that must be made by the FDA and patients are difficult and complex, and drug developers, physicians, researchers, patient organization and other key actors need to be forthright in communicating concrete data so they can make the most informed decisions. In this era of personalized medicine, decisions are only going to become more complicated in the years ahead.

A good example of a tool for providing patients useful data that is used by the CF Foundation is the publishing and dissemination of CF patient registry data on quality of care at accredited CF care centers. This allows patients to have comprehensive information with which to make decisions about how best to choose care providers.

What Can Congress Do?

First, Congress should work to ensure patients have a seat at the table, because no one understands a disease better than the people who suffer and fight every day.

In particular, it is important to support the development of mechanisms to accurately measure what meaningful outcomes are for patients, both in terms of clinical outcomes and their quality of life. Developing these mechanisms is challenging, but it is critically important. Providing greater resources for regulatory science at the NIH, FDA, and other federal agencies is a key component to making this goal a reality.

Congress should also create mechanisms to generate comprehensive, quality data that will make the analysis of risks versus benefits easier for patients. It is important to think creatively throughout the development cycle, especially for those drugs approved rapidly and those that are being used long-term by patients.

For example, supporting continued study after a drug is marketed to patients generates data that are vital to monitoring the long-term impact of a treatment. Right now, the CF Foundation is funding the GOAL study, enrolling patients to carefully monitor the effects of Kalydeco on an ongoing basis, and this provides invaluable insight into the long-term impact of this relatively new drug.

Finally, as the Committee develops policies to advance and accelerate treatments to patients, a crucial component is ensuring a well-resourced FDA. While funding levels are set by the Appropriations Committee, as an authorizing Committee, Energy and Commerce is a key voice in setting funding priorities for Congress.

Sufficient funding permits the FDA to be a party to early discussions about clinical trial design, allowing enough staff time for this interaction and supporting training for personnel to develop the expertise needed to effectively and efficiently review complex treatments. Adequate resources also allow the FDA to move aggressively and rapidly when the data support a new drug's approval, providing enough staff with the sophistication needed to permit rapid review.

The Food and Drug Administration Safety and Innovation Act (FDASIA) included many provisions to encourage a patient-focused drug development and review model, but not all provisions are being implemented and others are being implemented by the agency in the narrowest way. Congress can continue to monitor the implementation of FDASIA provisions at the same time it assesses the adequacy of FDA resources for targeted medicine review.

Adequate resources also allow enough time to interact with and accept advice from external experts. The CF Foundation championed the inclusion of a provision to foster FDA staff consultation with outside experts in FDASIA. We advocated this provision of the law based on our belief that FDA review staff members were unlikely to be trained in or have a strong understanding of every rare disease and complex clinical trial design issue, and that reviewers could learn much about rare diseases and rare disease therapies by consultation with experts in the field. The expert consultation provision of FDASIA

set standards to foster such collaboration and consultation. We hope that the Committee will ensure implementation of this provision of FDASIA and that the agency will embrace the spirit of the law even as it honors the letter of the law.

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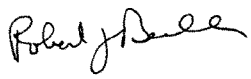
Once again, we greatly appreciate the opportunity to share our experiences and recommendations and stand ready to work with you on the challenges ahead. Thank you for your consideration.

Sincerely,



Robert J. Beall, Ph.D.
President and Chief Executive Officer

Mr. PITTS. Mr. Pops is recognized 5 minutes for an opening statement.

STATEMENT OF RICHARD F. POPS

Mr. POPS. Thank you very much.

I would like to thank you, Mr. Chairman, Ranking Member Pallone and all the members of the committee for inviting me to testify.

I just want to thank Chairman Upton and Congressman DeGette for spearheading the 21st Century Cures Initiative.

I would also like to express my respect for and appreciation for the folks on this panel and for Dr. Woodcock. We are all partners in this together, and it is an credibly important mission.

The simple and powerful concept of incorporating insights from patients is centrally important to the future of the Nation's healthcare system. And it is also one of the great opportunities for us all to have a transformative impact.

I have served as the CEO of Alkermes for over 20 years. Our company develops medicines for people living with chronic debilitating diseases, such as opioid addiction, schizophrenia, and depression. Our approach is entirely dependent upon considering the patient perspective early and consistently throughout the drug development process.

I also serve on the Boards of both BIO and PhRMA and was deeply involved in the PDUFA V negotiations, as well as the preparations ongoing for PDUFA VI, where elevating the patient voice has already emerged as a key theme for that initiative.

Today I would like to propose a new framework for patient involvement in developing new medicines, which requires engagement from all three of the major parties involved, innovative biopharmaceutical companies like ours, FDA, and the patients who stand to benefit from these medicines.

And the framework is based on three core principles.

First is that interactions must be data-driven, based on science and separate from powerful and passionate advocacy messages that patient groups otherwise deliver.

Second, the engagement framework should be actionable, not theoretical. It should improve the overall efficiency of the process rather than adding new steps in a process that is already incredibly complicated. This is particularly important for young biotechnology companies who are developing their first drugs on limited resources.

Third, the approach should preserve and enhance FDA's gold standard of safety and efficacy, which is really one of our great national treasures. I believe deeply, personally, that increased patient input can coexist with efficiency and the highest level of scientific rigor.

So from industry's perspective, there is clearly no consistent way to incorporate patient-generated input. This input would have a really meaningful impact on a range of critical decisions we and our researchers make specific to particular product candidates and certainly to the way we design clinical trials and implement them around the world. This is an important missing link.

As Dr. Woodcock mentioned and the FDA, patient engagement is not a new concept. Several provisions included in PDUFA as well as FDASIA have resulted in meaningful new expansions in patient engagement.

FDA has also been open to and has taken initial steps to include patient input into their reviews, and we can build on this. The proposed framework I am considering would build on all of these things.

The historical paradigm of drug regulation as a bilateral process between FDA and the industry is outdated. Science and society have continued to advance. Patients are organizing in new ways, and their critical role in driving innovation is becoming more the rule than the exception. We have 20th-century regulatory framework for 21st-century drug development.

To tackle these increasingly complex scientific and regulatory issues as we look to treat and cure complex diseases, all three parties can work together to develop improvements to their existing regulatory framework.

These would include new clinical trial designs, more efficient clinical trial enrollment methods, advancing FDA's evaluation of risk and benefit, and more sophisticated post-market data collection. These are incredibly exciting areas for future consideration.

We would need to evolve the way we work together, all the different parties, recognizing our shared responsibility to improve the efficiency of the development process and our accountability to assure the medicines are safe and efficacious for patients.

There will be a number of challenges to this as we move in, and these could include establishing a common threshold for data and scientific rigor that is shared by patient industry groups and FDA, modifying existing regulations to accommodate this new framework, protecting intellectual property and data, which is essential to enabling innovation and maintaining this gold standard of safety and efficacy.

As next steps, I propose that Congress, industry, FDA and patient groups come together to develop and implement this new framework, building on existing patient-focused provisions of PDUFA and FDASIA. We should also analyze existing statues and regulations to identify impediments and opportunities.

In conclusion, the concept of a new and comprehensive patient-inclusive framework is both ambitious and, at the same time, it is quite modest.

It is ambitious as it could result in a dramatic change in the way we discover and develop medicines. It is modest because it is not a new regulatory pathway or authority, but it builds on an existing foundation.

And we at Alkermes and all of our colleagues in the biopharmaceutical industry are standing by to help you in that effort. We really thank you very much for your leadership.

Mr. PITTS. Chair thanks the gentleman.

[The statement of Mr. Pops follows:]

Energy and Commerce Committee
Subcommittee on Health
"21st Century Cures: Incorporating the Patient Perspective"
9:00 am, July 11, 2014
Testimony from
Richard F. Pops
Chief Executive Officer, Alkermes, Inc.

I would like to thank Chairman Pitts, Ranking Member Pallone and all of the members of this Committee for holding this hearing today, and for inviting me to testify. I also want to thank Chairman Upton and Congresswoman DeGette for spearheading the 21st Century Cures Initiative.

The simple and powerful concept of incorporating insights of patients, individually and collectively, throughout the continuum that begins with the discovery of new drugs and extends all the way to ensuring patients have access to them – is centrally important to the future of the life sciences industry – and one of the great opportunities for us to have a transformative impact on our nation's healthcare system. I appreciate the chance to be with you this morning, and look forward to working together to develop meaningful policy proposals to bring safe and effective new medicines to patients. This is an exciting time in both science and public policy, as the future holds the promise of dramatic advancement to improve the lives of patients and the potential to reduce the overall cost of care. This is due, in large part, to the Committee's efforts in starting the conversation and we must make the most of this opportunity.

I have served as the CEO of Alkermes for more than two decades. In that time, I have been able to participate in the emergence of the biotechnology industry – a dynamic, science and patient focused industry that has transformed the lives of millions. Our company develops innovative new medicines that address the unmet needs and challenges of people living with debilitating chronic diseases such as opioid addiction, schizophrenia and depression. Our growth has been achieved by staying true to our core mission of directing our world class scientific resources to patient-inspired treatment solutions with

practical, real-world benefits. This approach is entirely dependent on considering the patient perspective early and throughout our drug development process. I also serve on the boards of other biotechnology companies and as well as that of both BIO and PhRMA. This has afforded me the opportunity to be deeply engaged in the PDUFA V negotiations as well as the preparations ongoing for PDUFA VI, where consideration of elevating the patient voice has already emerged as a key theme.

Today, I would like to propose a new framework for patient involvement in developing new medicines. In order for this framework to be successful, it will require consistent and meaningful engagement between the *three* major parties involved: innovative biopharmaceutical companies, the Food and Drug Administration (FDA) and the patients who stand to benefit. It is based on three core principles:

i. These interactions, including outcomes and decisions resulting from greater patient inclusion, must be data-driven, based on sound science, separate from other powerful and passionate advocacy messages that patient groups deliver to policy-makers.

ii. The engagement framework, for seeking and incorporating patient input, must be actionable. It must improve the overall efficiency of drug discovery, development, and regulation, rather than adding new steps in, a process that is already highly complex. This is particularly important for the young biotech companies developing their first drugs on limited resources.

iii. This new approach must preserve and enhance FDA's gold standard of safety and efficacy. I believe deeply that increased patient input can co-exist with efficiency and the highest level of scientific rigor in the drug development process.

To date, patient input to industry has been somewhat limited, often simply in response to specific information requests. To my knowledge, there is no comprehensive, transparent and consistent process for integrating patient input broadly into industry decision-making. Many companies recognize the value of the patient perspective. In fact, they are restructuring to enhance their ability to effectively seek and

integrate input from patients and patient organizations. However, from a general industry perspective, there is no standardized way to solicit, receive, or respond to patient-generated input. Information gained through this type of exchange could have a meaningful impact on a range of critical decisions we make, including the selection of specific product candidates and the design of clinical trials. This is an important missing link that can have a profound impact on scientific opportunities.

At the FDA, patient engagement is not a new concept. Historically, the FDA has frequently focused on discrete regulatory questions and decisions, such as participating in an Advisory Committee meeting for a specific product application. However, several provisions included in the PDUFA V Goals Letter and FDASIA, such as a structured benefit-risk framework, patient-focused drug development, and the policies derived from the ExPERT Act, have resulted in meaningful new expansions of patient engagement. FDA has also been open to, and has taken initial steps to include, patient input into their reviews, which now must be translated into actionable, data-driven advice and guidance. These first steps are important, but they are just that – first steps. The proposed framework would build on the momentum from these policies and programs that currently exist.

As I mentioned previously, I believe the future of drug development will require consistent collaboration between the *three* parties: innovator companies, FDA, and the patients who are affected by diseases. The historical paradigm of drug regulation as a bi-lateral process between the FDA and industry has essentially become outdated. Science and society have continued to advance, and the relationship between the biopharmaceutical industry, FDA, and patients has evolved, while the existing regulatory framework lags behind. Patients are organizing in new ways and their critical role in driving innovation is becoming more the rule than the exception. We have a 20th century framework for 21st century drug development.

To tackle the increasingly complicated scientific and regulatory questions that lie ahead (in areas such as genetic disorders, cancer, chronic diseases, and rare disorders), all three parties must be engaged and working together throughout the drug development continuum. Moving forward, this data-driven, collaborative process in industry decision-making will be able to better explore ways to accelerate new drugs to market, by proposing meaningful improvements to the existing regulatory framework. These would include, but are not limited to:

i. Clinical trial design (including issues such as patient-reported outcome measures, biomarker validation, adaptive design, and endpoint selection);

ii. Clinical trial enrollment (including outreach efforts to identify patients and provide opportunities for them to enroll in clinical trials);

iii. FDA's methodology for benefit-risk assessment for new drug applications and disease indications; and

iv. Post-market data collection (including both safety and adverse events data, and identification of promising opportunities for study of new disease indications for approved products and next-generation product development).

These are incredibly exciting areas for consideration.

Successfully improving and integrating data-driven patient participation will require all parties – industry, regulators, and patients alike – to be equally committed to evolving the way we work together and enhancing our respective engagement capacities. This will allow us to collaborate consistently, transparently, and in an appropriately action-oriented way. We must all have skin in the game – responsibility to improve the efficiency of drug development to bring new products to patients sooner; and accountability to ensure products are safe and efficacious.

As we proceed, it is important to acknowledge there will be a number of challenges that will need to be addressed in order for this effort to succeed. While not an exhaustive list, these issues would include:

i. Data and Scientific Rigor – Interactions between FDA, industry, and patient groups must be grounded in a common standard for data and scientific rigor oriented toward informing specific process improvements. To do this, patient groups, industry, and the FDA must enhance our respective levels of sophistication and receptivity to meaningfully interact in a way that embraces scientific data. Likewise, data quality standards, best practices, and other operational guidelines will need to be developed to govern enhanced collaboration.

ii. Clinical Trial Regulations – Current rules can limit our ability to solicit and incorporate patient feedback and will need to be reevaluated to accommodate the new framework.

iii. Intellectual Property/Data Protection – Any approach to more extensive collaboration among industry, FDA, and patient groups must include a thoughtful approach to enhancing data-sharing, which is essential to enabling innovation, while providing adequate measures to protect and ensure the responsible use of proprietary data and intellectual property.

iv. Safety and Efficacy – We must constantly remind ourselves, and assure patients and payers, that nothing envisioned in this framework in any way undermines the existing FDA gold standard for safety and efficacy.

There is much to be done, and I cannot claim to have all the solutions. In fact, I believe the answers will be identified only through a collaborative, interactive process involving all parties. However, I am convinced we can accomplish something profoundly important by working together, through initiatives like the 21st Century Cures process, to develop a framework for enhanced patient participation in industry decision-making, based on sound scientific data and focused on actionable process improvements.

To that end, what might be the most appropriate next steps? First, starting immediately and moving forward, Congress, industry, FDA and patient groups should work together to develop and implement this new framework for thoughtful, data-driven interaction throughout the biopharmaceutical discovery, development, and delivery processes. As I mentioned earlier, we are not starting from scratch. This framework should build on existing patient-focused provisions of PDUFA V/FDASIA.

We should also undertake a thorough analysis of existing statutes and regulations to identify appropriate updates to encourage the kind of interaction and collaboration the framework is intended to facilitate. It is important to note, I do not think these changes to law and regulations would necessitate the creation of new programs or significant expansions of existing authority. Rather, I expect we would identify and address instances where existing requirements simply did not envision the possibility of the broad interaction we advocate today.

At its core, this proposal calls for collaboration to better access and apply the unique data and perspectives of the patient community to industry and regulatory decision-making, thereby enhancing our ability to deliver innovative new medicines to patients sooner. The concept of a new and comprehensive patient-inclusive framework is both ambitious and, at the same time, modest. Ambitious as it could result in a dramatic change to the way we discover and develop innovative medicines. Modest as it is not a new regulatory pathway or authority, but rather builds on a foundation already in place.

I stand ready, along with my team at Alkermes and colleagues in the biopharmaceutical industry, to work with you on this important effort. Once again, thank you for the opportunity to appear before you today. I would be happy to take questions from the members of the Committee.

Energy and Commerce Committee Subcommittee on Health
"21st Century Cures: Incorporating the Patient Perspective"
9:00 am July 11, 2014
Summary of Testimony from
Richard F. Pops
Chief Executive Officer, Alkermes, Inc.

We propose a new framework for patient involvement in developing medicines. In order for this framework to be successful, it will require consistent and meaningful engagement between the three major parties involved in the development of new medicines: innovative biopharmaceutical companies, the Food and Drug Administration (FDA) and the patients who will benefit from new therapeutic options. The new approach we envision is based on three core principles:

i. These interactions, including outcomes and decisions resulting from greater patient inclusion, must be data-driven, based on sound science, separate from other powerful and passionate advocacy messages that patient groups deliver to policy-makers.

ii. The engagement framework, for seeking and incorporating patient input, must be actionable. It must improve the overall efficiency of drug discovery, development, and regulation, rather than adding new steps in a process that is already highly complex. This is particularly important for the young biotech companies developing their first drugs on limited resources.

iii. This new approach must preserve and enhance FDA's gold standard of safety and efficacy. I believe deeply that increased patient input can co-exist with efficiency and the highest level of scientific rigor in the drug development process.

This framework is not without challenges. These include, but are not limited to:

i. An emphasis on data and scientific rigor,

ii. Further flexibility in clinical trial regulation,

iii. Assurances for intellectual property and data protection with any enhanced data-sharing, and;

iv. Evolving the regulatory framework for further collaboration while maintaining the existing safety and efficacy of FDA approvals.

Moving forward, Congress, industry, FDA and patient groups should work together to develop and implement this new framework for thoughtful, data-driven interaction throughout the biopharmaceutical discovery, development, and delivery processes. This framework should build on existing patient-focused provisions of PDUFA V/FDASIA.

We should also undertake a thorough analysis of existing statutes and regulations to identify appropriate updates to encourage the kind of interaction and collaboration the framework is intended to facilitate. These changes to law and regulations would not inevitably necessitate the creation of new programs or significant expansions of existing authority. Instead we would identify and address instances where existing requirements simply did not envision the possibility of the broad interaction we advocate today.

At its core, the proposal is that we work together to better access and apply the unique data, experiences, and perspectives among the patient community in industry and regulatory decision-making, in order to enhance our ability to deliver innovative new medicines to patients sooner.

Mr. PITTS. Dr. Lichtenfeld, you are recognized for 5 minutes for your opening statement.

STATEMENT OF J. LEONARD LICHTENFELD, M.D.

Dr, LICHTENFELD. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the subcommittee.

I am Dr. Len Lichtenfeld, and I am Deputy Chief Medical Officer for the American Cancer Society and truly appreciate the opportunity to be with you today to testify. The American Cancer Society is pleased to contribute to the dialogue around the committee's 21st Century Cures Initiative.

Today I would like to focus on three critical areas for the committee's consideration. One is the need for greater investment in research; secondly, expedited approval processes that continue to ensure safety and efficacy of approved drugs; and, third, making patients active partners in all aspects of research development and regulation of new therapies.

We are fortunate and blessed that today we have 14 million cancer survivors in the United States. It is a remarkable number, and it is due to more effective treatments and improved screening tools that have been made possible through research.

We must continue and expand our steadfast commitment to research, and we must continue to support researchers working on finding the next generation of cures.

Just as important, we must ensure that expedited approval processes for drugs and devices are appropriately safe, effective and accessible to patients. The goal of the 21st Century Cures Initiative is to accelerate the development and approval of new medical treatments.

There are a few other areas that can match the research and development activity in the field of cancer. It is, in fact, and has been a model of innovation.

The FDA's Office of Hematology Oncology Products has aggressively used the tools provided by Congress to speed new drugs to patients and has encouraged drug companies to be innovative in clinical trials.

In the past 8 months, three cancer drugs have been approved using the accelerated pathway. One approval was based on a trial of 111 patients, an example of research approvals happening faster and with smaller clinical trials as has been the case in the past.

Small-sized trials and accelerated approval do have drawbacks. They may not include a diverse population, which may yield an incomplete picture of how a drug might work in a broader population. Small trials and accelerated approvals also tend to be seen in deadlier cancers where there are no other good therapeutic options.

And I want to stress that the risk-benefit tolerance of a cancer patient facing a poor prognosis may be much different than for those with other available treatment options.

And, therefore, the same acceptance of reduced data on which to base FDA approval may not be appropriate in other fields or for other diseases.

Finally, I want to stress the importance of researchers, pharmaceutical companies and the FDA in engaging widely and meaningfully with patients.

The Food and Drug Administration Safety and Innovation Act requires greater patient involvement throughout the drug and device approval process. ACS CAN championed provisions to expand the FDA's patient representative program to maximize patient input during the drug development process.

We need to continue to build on that progress. Patients can provide important perspectives at various stages of medical product development and regulation.

They know more than anyone what is most important to patients, to themselves: Symptom reduction, risk tolerance and design elements that might affect trial recruitment or retention.

This kind of patient involvement should be reinforced and supported and, to this end, the FDASIA provisions requiring FDA to address challenges that have hindered patient involvement must be fully implemented.

We urge the committee to consider examining opportunities for providing greater funding to support the FDA patient representative program as well as broader continued engagement with the patient community.

Another important way patients' perspectives can inform development of therapies is through the design and use of patient-reported outcomes.

Measures of cancer therapy effectiveness sometimes include functional status, pain or quality-of-life measures, but these may be reported by the physician rather than by the patient.

Quality-of-life measures like pain or nausea should come from patients themselves, and patients should help prioritize the importance of these side effects in the overall response to a disease and the associated treatments.

When quality-of-life outcomes are vigorously measured and supported by the FDA, they should be included in a drug's labeling and they should be considered for a drug's approval.

The FDA should also be encouraged to work with industry and researchers to incorporate self-reported symptom measurements as a regular part of clinical trials.

In closing, we appreciate the opportunity to contribute to the dialogue around the committee's 21st Century Cures Initiative and look forward to working with the subcommittee and its staff. I am happy to take any questions.

Thank you very much for this opportunity.

Mr. PITTS. Chair thanks the gentleman.

[The statement of Dr. Lichtenfeld follows:]

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Statement of Leonard Lichtenfeld, M.D.
Deputy Chief Medical Officer
American Cancer Society

"21st Century Cures: Incorporating the Patient Perspective"

United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

July 11, 2014

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Chairman Pitts, Ranking Member Pallone and Members of the Subcommittee:

I am Dr. Leonard Lichtenfeld, Deputy Chief Medical Officer for the American Cancer Society. On behalf of the Society, thank you for the opportunity to testify today. The Society is a nationwide, community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing the disease, saving lives, and diminishing suffering through research, education, advocacy, and service. The Society, operating through its national office and 12 geographic divisions throughout the United States, is the largest voluntary health organization in the United States.

We are pleased to have the opportunity to contribute to the Committee's 21st Century Cures initiative – in particular to illustrate the importance of increasing and promoting the participation of patients in drug and device research and approval. No one knows better what is at stake in the quest for new and better treatments for cancer than cancer patients.

Patients must be the focus of innovation – and they must also be active partners in all aspects of research, development and regulation of new therapies.

Today, there are nearly 14 million cancer survivors in the United States thanks to more effective treatments and improved screening tools made possible through research. This research is funded every year by institutions like the National Institutes of Health (NIH) and the National Cancer Institute (NCI); by not-for-profit organizations like the American Cancer Society, other foundations, and universities; and privately by pharmaceutical companies. All of this research opens the door, and provides a pathway to patients, for new FDA-approved medications, therapies and devices that greatly impact patient quality of life. We must continue and expand our steadfast commitment to research – and we must continue to support researchers who are working on

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finding the next generation of cures. Just as importantly we must renew our commitment to making sure that the investments in research that translate into drugs and devices that are expedited through the approval process are appropriately *safe*, *effective*, and *accessible* to patients.

The Food and Drug Administration Safety and Innovation Act (FDASIA) that was signed into law in 2012 addressed the need to include patients to a greater extent throughout the FDA drug and device approval process. ACS CAN championed the inclusion of Sections 1137 and 1142 in FDASIA to expand the FDA's Patient Representative Program and its mission to maximize patient input during the drug development process. In addition, FDASIA also required FDA to hold a series of patient-focused drug development meetings on various diseases.

FDA has included patient participants in important advisory committee meetings since the early 1990s. But the FDASIA provisions codified the requirement for patients to be involved in the process of drug development and review, and we must continue to build on this progress. Patient representatives routinely serve on public FDA advisory committees that review products and therapies for the diagnosis and treatment of serious diseases such as cancer, and also serve as consultants to the FDA review division, participating in FDA/sponsor meetings where they may contribute to clinical trial design discussions, and labeling negotiations. When patients participate in these important meetings they can provide FDA and industry with important patient perspectives at various stages of medical product development and regulation, including pre-clinical, clinical trial design, and endpoints. They can share what is most important to patients – such as symptom reduction, risk tolerance, and design elements that might affect trial recruitment or retention.

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All patients, and specifically cancer patients, can provide a unique perspective on the benefits and risks of particular therapies being considered for FDA approval. This kind of patient involvement should be reinforced and supported. Provisions included in FDASIA requiring offices inside FDA to collaborate and address challenges that have historically hindered patients from participating in these important discussions must be fully implemented.

The Committee should also consider examining opportunities for providing greater funding to support the FDA Patient Representative Program, as well as broader continued engagement with the patient community. The series of patient-focused drug development meetings required in FDASIA that have been held to date have yielded successful conversations between FDA and patient groups. However, there is a need for continued communication and planned actions in the disease areas FDA identified.

One of the important ways that patients' perspectives can inform the development of therapies is through the design and the use of patient-reported outcomes (PROs) in research. While it may seem intuitive that the patient's outcome with a new treatment is the most important outcome, the current research and drug approval process focuses heavily on biologic or physician-reported outcomes. Common measures of the effectiveness of cancer therapies include overall survival, progression-free survival, time to progression, or tumor shrinkage. Sometimes functional status, pain or quality of life measures are included, but they may be reported by the physician rather than by the patient. Research has shown that when comparing a physician's measure of a patient's pain with the patient's own perception, the two measures can differ significantly. Many of the quality of life measures like pain, nausea, fatigue, depression or ability to carry out normal daily activities should come from patients themselves. Not only can patients provide important feedback

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on these symptoms, but they can also help prioritize the importance of these side effects in the overall response to a disease and the associated treatments. When these quality of life outcomes are rigorously measured and supported by the FDA, they can and should be included in a drug's labeling, and can, by themselves, be a basis for a drug's approval. The FDA should be encouraged to work with industry and researchers to incorporate self-reported symptom measurements as a regular part of clinical trials, including, for example, new technologies for monitoring patient's experiences with new treatments.

The goal of the 21st Century Cures Initiative is to accelerate the development and approval of new medical treatments. There are few other areas that can match the research and development activity seen in the field of cancer, and while there remains an incredible amount of progress to be made before we have safe and effective treatments for the hundreds of diseases we call cancer, cancer drug development has served in many ways as a model of innovation. In past years Congress has provided FDA with a number of tools to accelerate and simplify the approval process for drugs. FDA's Office of Hematology and Oncology Products (OHOP) has been aggressive about using the full complement of these tools to speed new drugs to patients and has encouraged drug companies to be innovative in their clinical trials. In the past eight months, three cancer drugs have been approved using the accelerated pathway. One approval was based on a trial of only 111 patients, another with only 163 patients and one with 129 patients. These are examples of the types of research and approvals that are happening faster, and with smaller clinical trials than in the past. Small-sized trials and accelerated approval, however, have drawbacks. They may not be able to include a diverse population in terms of race, age, sex and comorbidities, which may provide an incomplete picture of how a drug might work in a broader application, and later data may change

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our understanding of the risk-benefit ratio. These small trials and accelerated approvals also tend to be seen in cancers that are deadly and have no other good therapeutic options. I want to stress that the risk-benefit tolerance of a cancer patient facing a poor prognosis may be very different than the risk tolerance of a patient with a less deadly or more chronic disease with other available treatment options. Even within the field of oncology, it is important to note that the long-term effects of some treatments have different implications for children with cancer as opposed to older adults. Research and drug approval in the field of oncology might be seen as leading other fields, and FDA's flexibility should be continued, but the same acceptance of reduced data on which to base FDA approval on might not be appropriate in other fields or for other diseases.

In closing, I would like to reiterate the vital role of patients in the research, development, and drug approval process. Cancer patients have the most at stake in the quest to find new treatments and have important insight to offer. Every disease is unique in terms of the unmet need for therapies and the risks that patients are willing to accept in the quest for new treatments. If researchers, pharmaceutical companies and the FDA engage widely and meaningfully with patients, the result will be better treatments delivered to patients faster.

Thank you again for the opportunity to share our views.

Mr. PITTS. Dr. Summar, you are recognized for 5 minutes for your opening statement.

STATEMENT OF MARSHALL SUMMAR, M.D.

Dr. SUMMAR. Thank you, sir.

Good morning, Chairman Pitts, Ranking Member Pallone and members of the subcommittee. And thank you for inviting me today.

My name is Marshall Summar. I have the good fortune to be the Chief of Genetics and Metabolism at Children's National Medical Center here in Washington, D.C.

I have been working in the field of rare diseases for the last 29 years, and I am here today in my capacity as a member of the Board of Directors of the National Organization of Rare Disease and Chair of the Scientific Advisory Committee of NORD.

On behalf of the estimated 30 million individuals with rare diseases, NORD thanks you in the Energy and Commerce Committee for your continued strong support of the rare disease community. You have made a huge difference for us.

NORD's a unique federation of over 200 patient advocacy groups, clinicians, researchers, dedicated to helping people with rare diseases.

NORD provides resources, research advocacy, education, community and infrastructure support to the rare-disease community that small individual organizations cannot. It is the nature of rare diseases. They are small.

NORD was founded in 1983 and played an active role in the passage of the Orphan Drug Act, which is a successful model of how to incentivize the development of treatment that saves lives.

Data show that years of life lost to rare diseases declined at an annual rate of 3.3 percent after the Orphan Drug Act due to the development of new treatments.

Without these new drugs, if you take them out of the equation, the number of years of lives lost should have increased at about a 1 percent rate per year. So it has made a real impact on our patients.

Speaking personally, without these treatments, many of my patients would not be here. I thank you for what you have already done.

These efforts represent a good beginning, but there is much more we can do to improve the lives of our patients, and NORD views the 21st Century Cures Initiative as a great way to do this.

NORD's long advocated increased involvement of patients in the drug development process. We appreciate the commitment by many at the FDA to increase patient involvement, but believe much more needs to be done to make patients feel they are partners in the process. NORD will continue to work with the FDA to advance the patient role in the development and approval process.

We have developed a series of recommendations that we believe will advance not only the development of new orphan drugs and devices, but non-orphan ones as well. We look forward to discussing these ideas with the committee as the 21st Century Cures Initiative continues.

Permit me to focus on two of our recommendations.

First, we support the establishment of a commission and national plan to determine priorities, methods, resource needs and a consistent agenda on rare-disease registries and natural history studies.

They have got a lot of variation. They tend to be all over the map. To assess the drug's efficacy, we need the information on the existence, frequency, and severity of clinical findings. This information is needed before a clinical trial can begin.

We encourage the creation and maintenance of programs to create, curate, and standardize registries and national history studies which can generate this needed data.

This could be one of the most important accelerators of the treatment development and monitoring process. These registries can also be used in the post-approval process as well.

This is an area where patients can have a major and cost-saving impact on the process. Patient-entered data has been shown to be accurate and useful when collected properly.

Creative hybrids using physician-, patient- and other health professional-collected data can greatly speed the understanding, discovery, approval and monitoring process.

In collaboration with the NIH and FDA, NORD has built and is in the process of testing a rare-disease patient-driven registry national history program. The NIH's Rare Disease Clinical Research Network has already demonstrated the benefits of this approach.

In a registry I have been involved with, we have had approval of three drugs over a 10-year period with only 700 patients. So it definitely has accelerated the approval process for us.

The Patient Centered Outcomes Research Institute is developing these statistical methods and models to use data from rare-disease patient studies that will further refine this process.

They are also involved in patient-driven registries through PCORnet and will begin working with NORD on our rare disease-focused registry program. So we should have good input from multiple agencies.

All of these efforts will help our patients, but a national plan and standards would help prevent duplicated effort and resources. This is what we truly need.

The other thing we advocate is significant reform to the Institutional Review Board system. I have been working with this system for the last 30 years; so, I am pretty familiar with all of its manifestations.

Currently, all clinical trials for new treatments, whether a drug, biologic or medical device, must receive approval from an IRB.

Each institution and study site typically requires approval and protocol adjustment by its own IRB. With a large number of sites needed for rare-disease study, this is one of the greatest impediments and cost to clinical trials.

NORD recommends that Congress develop legislation that would de-risk the process and foster the creation of an IRB system that is portable across institutions.

The de-risking of the IRB process and the encouragement requirement of reliance agreements between institutions receiving Federal funding would save cost and time while accelerating the clinical trials and clinical research process greatly. This will signifi-

cantly increase the pool of study sites and allow greater patient participation.

These are just two of our recommendations. My written testimony includes the rest.

And I on behalf of NORD, I thank the committee for allowing us to testify today.

Mr. PITTS. Chair thanks the gentleman.

[The statement of Dr. Summar follows:]

21st Century Cures: Incorporating the Patient Perspective
U.S. House of Representative
Energy and Commerce Committee
Subcommittee on Health
July 11, 2014

Good morning, Mr. Chairman and Members of the Committee. I am Dr. Marshall Summar. I have the good fortune to be the Chief of Genetics and Metabolism and a Professor of Pediatrics at Children's National Medical Center here in Washington, D.C. I have spent the last 29 years working in the field of rare diseases as a physician and researcher. I am the parent of a child with Down Syndrome. I am here today in my capacity as a member of the Board of Directors and Chair of the Scientific Advisory Committee of the National Organization for Rare Disorders, or NORD.

On behalf of the estimated 30 million men, women, and children affected by one of more than 7,000 known rare diseases, NORD thanks you and the Energy & Commerce Committee for your continuing strong support of the rare disease community. We view the 21st Century Cures Initiative as a great opportunity to move the process of therapeutic development and approval forward. This is particularly important for Rare Diseases where need is often acute and classic approval models can delay life-saving treatment.

NORD is a unique federation of over 200 patient advocacy groups and voluntary health organizations dedicated to helping all people with rare diseases. NORD provides resources, research, advocacy, education, community, and infrastructure support to the rare disease community that small individual organizations cannot. NORD's support allows its member groups to focus on their primary mission, progress towards understanding, treating and curing their diseases.

NORD was founded in 1983. NORD's founders played an active role in the creation of the Orphan Drugs Act, which is a successful model of how to incentivize the development of treatments and is saving lives. Analysis of data in the United States shows that years of life lost to rare diseases declined at an annual rate of 3.3% after the Orphan Drug Act due to the development and deployment of new treatments. Without these new drug approvals, years of life lost would have increased at a rate of about one percent [ref 1]. The annual growth rate of the orphan drug market between 2001 and 2010 was 25.8 percent, compared to only 20.1 percent for non-orphan drugs [ref 2]. Since 1983 more than 450 drugs have been approved by the Food and Drug Administration (FDA) for rare diseases.

Speaking personally, without the treatments resulting from Congress and NORD's efforts many of my patients would not have survived, and I thank you for what has already been done. These efforts represent a good beginning but there is much more we can do to improve the lives of our patients and NORD views the 21st Century Cures Initiatives as a great way to do it.

Using our experience as patients, physicians, researchers and families working with rare diseases and the development of new treatments, we have developed a series of recommendations that we believe will advance not only the development of new orphan drugs and devices but non-orphan ones as well. We have provided the Committee with our recommendations and today I would like to emphasize a few of them, and to place them in the record of this important hearing. These proposals are intended to accelerate the pace of medical innovation, and improve the lives of our patients and families.. We look forward to discussing these ideas with the Energy & Commerce Committee as the 21st Century Cures Initiative continues.

Our recommendations are as follows:

1. Establish a Commission and National Plan to Determine Priorities, Methods, Resource Needs and a Consistent Agenda on Rare Disease Registries and Natural History Studies

Natural history studies and registries play a critical role in the drug discovery and development process. Without the information on the existence, frequency and severity of clinical findings, the efficacy of any treatment cannot be assessed. Without determining effective markers and surrogates of outcome, the potential for long term benefits of a treatment cannot be determined. Before a clinical trial can begin this information must be obtained but it significantly slows the development and approval process and dis-incentivizes work in the field.

We propose the creation of programs to create, curate, and standardize registries and natural history studies which can pre-populate this needed data. Not only will needed data be available for therapeutic development and approval, but previously unidentified treatment targets would become known. This effort could be one of the most important accelerators of the treatment development and monitoring process.

Patient registries represent one of the best resources to collect prevalence, demographic, natural history, and comparative effectiveness data on rare diseases. This is an area where patients can have a major and cost-saving impact on the process. Patient entered data has been clearly shown to be accurate and useful when collected properly. This data can be collected for less cost than more traditional researcher centric models. Creative hybrids using physician, patient, and other health professional collected data can greatly speed the understanding, discover, approval, and monitoring process. Standardized natural history registries, tied to tissue banking, facilitate the generation of research leads, and accelerate studies.

In collaboration with the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), NORD has built and is in the process of testing a rare disease patient driven registry/natural history program. This program will ensure that rare disease patients have adequate natural history information in order to spur drug discovery and development and shorten the process. The NIH's Rare Disease Clinical Research Network has already demonstrated the benefits of this approach with three new drug approvals for one disease in a 10-year span with a group of only 700 patients. The Patient Centered Outcomes Research Institute is developing new statistical methods and models to use data from rare disease patient studies.

All of these efforts will help our patients but a national plan and standards would help prevent wasted effort and resources. An added benefit of these efforts will be a better and more accurate understanding of the incidence and impact of these diseases on the American population.

2. Significantly Reform the Institutional Review Board (IRB) System for Assessing New Therapies

All clinical trials for new treatments -- whether a drug, biologic, or medical device -- must receive approval from an IRB. Each institution typically requires approval and protocol adjustment to its own IRB. Any changes to the study design must go through the IRBs.

This process is one of the greatest impediments and costs to rare disease clinical trials or indeed any clinical trials. One recent study required approval by more than 30 IRBs taking almost two years. The cost of our current system in hours, lost-productivity, delays, and frustration literally cannot be calculated. Surveys show that a majority of young investigators view the IRB process as a significant barrier and reason not to do research or pursue it as a career. The documents have evolved into a risk defense system with consent forms for simple studies often exceeding 20 pages.

NORD recommends that Congress develop legislation that would de-risk the process and foster the creation of an IRB system that is portable across institutions. The de-risking of the IRB process and the encouragement/requirement of reliance agreements between institutions receiving federal funding would accelerate the clinical trials and clinical research process greatly.

A system in which studies approved by the IRB at any institution that meets appropriate standards, can be performed at any other interested institution without modification will significantly increase the pool of study sites, speed the process, and allow greater patient participation. Simplifying the process to focus on information for the patient rather than risk mitigation will shorten the process and better serve the participant in research.

3. Ensure All Current Laws that Increase the Patient's Involvement are Implemented Fully

NORD believes that the patient's voice must be strengthened in the drug development and approval process. We first need to assure that current laws addressing patient involvement are being implemented fully. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 made groundbreaking strides in encouraging that patients play a greater role during the drug approval process. The FDA has implemented many of these changes admirably but there are various other measures contained within FDASIA that are not being implemented to the fullest extent, or not at all.

The FDA must include a patient or patient representative on the drug review committee as mandated by section 903 of FDASIA. While the FDA has increased patient involvement in other aspects of the drug approval process, such as in advisory committee meetings, the FDA has yet to include patients on a review panel. The FDA should be required to fulfill this mandate. Rare diseases are an excellent place to start.

While the FDA has conducted several patient-focused drug development meetings, it has yet to demonstrate how it intends to use the information to inform the drug review process. While NORD appreciates the FDA's efforts in implementing the patient-focused drug development initiative, we are particularly eager for the findings from these meetings to be incorporated within the drug review process.

NORD requests that the FDA develop a guidance advising patient organizations on how they can administer their own patient-focused drug development meetings and provide data that will be useful to the drug approval process. Under current law, the FDA is holding 20 patient-focused drug development meetings. The information derived from these meetings can be broadened substantially if FDA provides guidance on how patient organizations can independently conduct their own patient-focused drug development meetings in a manner that would enable the FDA to use the findings of these meetings to enhance the drug review process.

We advocate that patients be regarded and treated as partners with the FDA in the drug review process. At present, despite progress, patients are regarded as outside participants who are asked to occasionally consult on drug efficacy and effectiveness, usually under the auspices of the drug companies.

We urge FDA to standardize patient input within the drug review process. Currently, the level of patient involvement varies among review divisions. Patient contribution at regular and predictable times must be built into the process.

Rare disease patients, their families, and their caregivers can be most useful for the FDA when assessing the benefit-risk of a therapy. In its "Patients" white paper, the 21st Century Cures Initiative asks, "How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?"

It is NORD's opinion that patients can make significant contributions in helping to evaluate the benefit-risk of a drug. Patients must be partners with the FDA and companies in making this assessment.

4. Ensure Sufficient and Consistent Resources, Direction and Funding for the Food and Drug Administration and National Institutes of Health.

The FDA is underfunded, given the wide array of regulatory responsibilities it maintains. The FDA is continually charged by Congress with additional regulatory and oversight responsibilities, not to mention the expansion of existing responsibilities due to globalization and increasingly diverse scientific innovations. As part of the acceleration process and the changing landscape of the drug approval and monitoring landscape, the FDA will have new responsibilities. Providing the appropriate resources to these tasks is a key element to their success.

Congress must recognize the importance of the FDA and significantly increase its annual appropriation. The 21st Century Cures Initiative can accelerate the pace at which treatments reach the patient by helping FDA make the expedited review pathway the default for all treatments that qualify. These new pathways not only will accelerate the process but also will change the risk profile of the drug approval process. This is highly important to the rare disease community where the often drastic clinical picture significantly changes the risk/benefit ratio for our families in considering new treatments. FDA needs the ability to expand not only its own expertise but the available pool of experts needed in the approval process to evaluate new products and provide knowledgeable research advice.

With regard to NIH, for the U.S. to maintain its position as the world leader in biomedical research, we need to assure that the basic, translational and clinical research system remains strong. The extramural and intramural programs at NIH have created a community of biomedical scientists and knowledge that we must have to develop new treatments and understand the diseases we can't treat yet. The bulk of human biomedical research in the U.S. is funded through the NIH and the success of the peer-review process and collaborative work this has fostered is evident in the improvement in the human condition we have seen.

To maintain this system requires consistent and sometimes increased levels of funding. Downward or sporadic fluctuations result in the loss of researchers, knowledge and infrastructure that is either irreplaceable or engenders a much greater cost to replace. To incentivize the best and brightest to devote their lives to biomedical research requires consistency and predictability.

The NIH operates several programs and initiatives that are critical to rare disease research. The National Center for Advancing Translational Sciences (NCATS) conducts various initiatives that advance innovation in rare disease research. NCATS collaborates with industry partners and academia to find new therapeutic uses for existing molecules, many of which may be effective in treating rare diseases.

NCATS operates the Clinical and Translational Science Awards (CTSA) program which funds and coordinates clinical and translational research in more than sixty research institutions across the Unites States. NCATS also operates the Therapeutics for Rare and Neglected Diseases (TRND) program which collaborates with academic researchers, patient organizations, and industry to speed the development of therapies for rare diseases. Finally, the Office of Rare Diseases Research (ORDR) within NCATS supports the Rare Diseases Clinical Research Network (RDCRN) and operates a rare disease database with nearly 7,000 diseases included.

If the 21st Century Cures Initiative is to succeed in strengthening the medical research framework of this country, it must strengthen NIH funding and then remove the unpredictability of funding levels each year.

5. Commission a "National Plan for Rare Diseases"

The U.S. needs a consensus document that sets for a National Plan for Rare Diseases. We advocate that Congress commission a comprehensive agenda that evaluates the entire rare disease healthcare ecosystem, and makes recommendations on how to improve the discovery, development, and delivery of treatments to rare disease patients. Congress can follow the precedent of other National Plans it has commissioned, such as the National Plan to Address Alzheimer's.

This plan must be comprehensive and cover the entire spectrum of the rare disease landscape. It should address the duties of each public agency involved in rare disease treatment discovery, development, and delivery. This plan must also address how these public agencies can collaborate with private entities to improve the rare disease ecosystem.

Congress can strengthen the basic and translational rare disease research ecosystem by requesting the Orphan Products Board, which we believe should be reinvigorated, to publish a yearly agenda with recommendations for rare disease research and products development. A reinvigorated Orphan Products Board would be beneficial for the entire rare disease community. It would facilitate greater communication and collaboration between the FDA and the NIH, and with the Federal agencies that are instrumental in the delivery of orphan products, such as the Centers for Medicare and Medicaid Services (CMS) and the Department of Defense (DOD). These collaborations will assist in ensuring that critical orphan therapies will actually reach the rare disease patients who need them.

The Orphan Products Board should work, in consultation with the NIH and FDA, to recommend advances in innovative clinical trial designs for orphan therapies. The Orphan Products Board should also work with the Centers for Disease Control and Prevention (CDC) on epidemiological techniques and advances.

As part of the National Plan, Congress should commission a study on how better funding and coordination of rare disease research will benefit the economy and the healthcare system, as well as lower the Federal government's healthcare expenditures. Greater coordination of research will foster a more efficient use of public and private resources.

6. Enhance the Focus on Clinical Trial Design and Endpoint Development within the NIH Division of Clinical Innovation within the National Center for Advancing Translational Sciences (NCATS)

NORD also advocates enhanced focus on rare disease clinical trial design and clinical endpoints within the NIH Division of Clinical Innovation. Clinical trial design is of a paramount importance when developing any therapy, but is especially important for orphan therapies, where innovative trial designs are often needed to accommodate the small disease population. Many companies that are developing orphan therapies are small, inexperienced companies that have little practice in designing clinical trials in general, let alone trials for diseases that require an innovative trial design because of factors such as small or geographically dispersed patient populations.

We would encourage enhanced focus within the Division of Clinical Innovation on providing leadership and expertise in clinical trial design as well as consultation with sponsors on clinical trial design. In the field of rare diseases, the cost and failure rate of clinical trials could be substantially reduced by making expertise, advice and guidance readily available to those developing new therapies. The barriers for interaction need to be lowered for the NIH, FDA, PCORI and other relevant agencies.

In addition, all clinical trials must have agreed-upon endpoints. The role of the NIH Division of Clinical Innovation should include enhanced emphasis on helping develop appropriate endpoints for studies. The Patient Centered Outcomes Research Institute can help develop the tools and should be encouraged to interact closely with the Division of Clinical Innovation. This leadership early in the research process would be helpful in preventing companies and/or patient organizations from spending years and millions of dollars on biomarker research only to receive a rejection from the FDA. It would be especially beneficial to the rare disease patient population, as clinical endpoints and biomarkers are particularly difficult to establish within rare, genetic diseases.

7. Create an "Orphan Protected Class" within the Medicare Part D Program

Recently, CMS proposed the removal of three protected classes from the Medicare Part D drug coverage system. After a unified outcry from the patient community, CMS withdrew the proposal.

NORD acknowledges the need for reform within the Medicare Part D Protected Class system, and would welcome a discussion with CMS. NORD also proposes that CMS add a Protected Class for orphan therapies. There are rarely alternatives to orphan therapies that patients with rare diseases rely on, yet these drugs are no more protected than any other drug within the Medicare Part D program.

By ensuring coverage of orphan therapies within the Medicare Part D Program, Congress will assure rare disease patients that they will receive the live-saving coverage they need under the Medicare program.

8. Establish Clearer Federal Policies with Regard to Off-label use of Drugs

Many rare disease patients use drugs outside of FDA-approved uses, based on the judgment of their physicians that the drugs will benefit them and will not be harmful. Recently, reimbursement for off-label uses has been denied. Congress needs to address this issue aggressively, as many drugs will never be tested for the rare disease patient and, without reimbursement for appropriate off-label use as determined by the physician, these patients will be denied access to approved therapies that may change or save their lives.

At the same time, the government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources. The Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action.

9. Ensure Reimbursement for Medical Foods

In NORD's comments on the 21st Century Cures Initiative white paper titled, "A Call to Action", we highlight the issue of high cost-sharing within drug formularies for specialty drugs, many of which treat rare diseases. We also discuss off-label reimbursement issues, and the importance of off-label use of therapies for rare disease patients.

These are several of many reimbursement issues facing patients with rare diseases, including lack of coverage of orphan therapies under the Medicare and state Medicaid programs.

While reimbursement problems exist for all orphan therapies, we are particularly concerned about issues surrounding medical food treatments, especially the lack of reimbursement for such products.

Each year, approximately 2,550 children in our country are diagnosed with inborn errors of metabolism, requiring them to access life-saving treatments such as medical foods, foods to be modified as low protein, supplements and amino acids. These costly medically necessary foods and supplements are often not covered by insurance or public assistance, causing irreparable mental and physical damage. Families continue to struggle with the tremendous financial burden associated with these medically necessary foods.

Insurance coverage of medical foods is vital to children and adults in order to access medically necessary foods and supplements; however, there is tremendous inequity in coverage amongst the states. Although there are currently 35 states that have legislation in this regard, the legislation is subject to interpretation and more often than not, families have to pay out-of-pocket to ensure their child's well-being and survival. As there is no current cure for these inborn errors of metabolism, these treatments are necessary during the entire lifespan of the individual.

As Congress addresses the discovery, development, and delivery of treatments for rare disease patients, NORD requests that Congress stay particularly mindful of diseases that require medical foods.

Mr. Chairman and Members of the Committee, thank you for considering these and other proposals from NORD. The continued leadership of this Subcommittee on Health is critical to the rare disease community. We welcome continued collaboration.

References:

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Mr. PITTS. Thanks to all the witnesses for your opening statements. And we will now begin questioning.

I will recognize myself 5 minutes for that purpose.

Ms. Furlong, we will start with you.

Do you believe your guidance collaboration with industry is a scaleable model that can be used in other conditions, specifically, where there are unique factors that make Duchenne muscular dystrophy guidance a special case in the multi-stakeholder effort that you led with encouragement from the FDA?

Ms. FURLONG. Thank you, Chairman Pitts, for the question.

I certainly think that this methodology and process is exportable to other rare conditions. How we started the guidance or initiated the guidance was to develop a steering committee that was representative of the stakeholders, which included patients, academia, as well as industry.

From there, the steering committee identified several areas, seven working groups, actually, of things that they felt were relevant, to include diagnosis, biomarkers, clinical trial design, natural history, and benefit-risk.

And then we further developed a CAB, which is the Community Advisory Board, so that would be—incorporate the entire patient voice and any individual or patient group that wanted to contribute to the development of the guidance.

The standardization for the guidance was that it would be a reference document and that it would include documented evidence that was published or accepted for publication by the end of July.

So we felt—and we are writing up the methodology—that this methodology is exportable. It was certainly an investigation and a thorough, thoughtful, reasoned look at the community and the nuances of Duchenne.

But I believe that most rare diseases could do the same. Their issues may be slightly different and their progress to date might be slightly different, but it is certainly exportable.

Mr. PITTS. Thank you.

Dr. Beall, communication with patients to make sure they can make informed decisions about clinical trial participation is critical.

How does the cystic fibrosis community communicate with patients about the various options? And how do you think we can best translate your good practices into the Cures Initiative?

Mr. BEALL. Thank you very much.

First of all, because 90 percent of all of our CF patients are seen in a network of care centers and that we also have a Clinical Trials Network, there is a very close relationship between our physicians and the patients that are involved.

And that is critical for the recruitment of patients in the clinical trials. It is critically important for showing them the value and the risk of participating in clinical trials.

And it is that close association between the physician and the patient and the recruitment process in a very closed network that is critical. That is why I think Clinical Trials Networks are critically important.

So we also have established within our Clinical Trials Network a data safety monitoring board independent of the Cystic Fibrosis Foundation, but it is made up of experts.

And that provides a degree of assurance to every single patient that there is somebody looking out for their continuing interest and for any risk that may be inherent in any single trial.

So I think all of these things, plus we have worked very hard to try to create a culture of participation and a responsibility that each patient, when you have a small patient population, needs to participate in the process. So I think it is that reassurance that is so important.

Mr. PITTS. Thank you.

Mr. Pops, what stage of drug development could most use the assistance of patient insight about benefit expectations and risk tolerance?

Mr. POPS. Thank you for the question.

It is actually the most exciting part of the whole opportunity, that it is every stage, actually from identification of new drug candidates, all the way through to determination of the value of the medicine after the completion of the pivotal clinical trials.

And I think that is the whole idea of this framework, is creating a structure where we can get that input on a continuous basis, and I think it could fundamentally transform the way we approach these development programs.

Mr. PITTS. Thank you.

Dr. Lichtenfeld, you have discussed examples of cancer drugs that have recently been successfully approved by FDA through an accelerated approval process.

Are there best practices that we can learn from cancer and how FDA is expediting the approval process for particular drugs?

Dr. LICHTENFELD. Thank you, Mr. Chairman.

When we talk about best practices, I think the question really came up with Dr. Woodcock earlier today: What is the oncology community doing that is different than other communities?

Let's understand it is a complex process in the sense that we have research that has been building literally for decades that has produced very exciting results that is actionable and companies are standing up to create drugs for the targets that we are finding for the new immunotherapies for genetic disease, what have you, genetic markers. So we are, in a sense, at an interesting and turning-point kind of place.

But important, relevant to your question, the Office of Hematology Oncology Products has also stepped up to the plate. And as was mentioned earlier, the oncology community appreciates the efforts of the FDA staff to reach out to the patient community, to reach out to the pharmaceutical community, to reach out to those who do clinical trials, to be active participants, to be at the table.

Lung-MAP was cited several times. The American Cancer Society was grateful to be able to have contributed to that effort, among many other organizations.

But the FDA has become an active partner with the process. And so I don't know if that is a best practice or a best example. But it is that source of communication.

But let's not forget it is also the opportunity because we are now in a place that we only dreamed of just a short while ago.

Mr. PITTS. The chair thanks the gentleman.

My time has expired.

The chair recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

My questions are of Mr. Beall.

The Cystic Fibrosis Foundation has done some great collaborative work that has resulted not only in successful marketing of Kalydeco, but also the recent positive test results of a complementary drug that may extend treatment to nearly half of all patients with CF. And, of course, I commend you for your efforts.

But I wanted to ask you about a couple of points in your testimony. In your remarks, you spoke about the CF Foundation's strong relationship with the FDA and the importance of bringing good data to the table when consulting with the FDA, which I know is true. And I would like to hear more about that relationship.

Obviously, we are hearing a lot today about the need for FDA to do more to seek and incorporate patient input into its review process.

So the basic question, Mr. Beall, is: Can you tell us more about the CF Foundation's interaction with the FDA? And are there any lessons that can be learned by other disease groups?

Mr. BEALL. Well, I can give you a perfect example because, on Wednesday of this week, we had three officials, including Dr. Robert Temple, who is in the drug division at our offices, talking about the development of clinical trial protocols of drugs that might not enter into clinical trials until 3 to 5 years from now.

So that is a perfect example of this open discussion. Because we have a natural history of the disease. We know that the drugs that we have tested are treating the basic defect. We know the mechanism of action. We have a safety profile.

And now we can start to talk about the future. And I think it is that kind of example. And that goes back many, many years.

Soon after we discovered the CF gene, we talked about gene therapy and we had extensive dialogues with the FDA, not only with manufacturers, but with the FDA and the Foundation.

So I could just say that we have always had a wonderful collaboration. We have data. We have natural history of the disease because of the patient registry.

And, again, we come with data and we come with experience and we come with the networks that can make these things happen.

So I just gave you an example. That was the example.

Mr. PALLONE. No. That is fine.

We are hearing a lot about the various expedited drug review processes at FDA, and it is clearly a push by many to get the Agency to use these pathways more frequently and in more disease areas. And I share the goal of speeding the therapies to patient at the earliest possible time.

But I think we need to be cognizant of the risks that could accompany that speed, and we especially need to be concerned about such risks if we are ultimately thinking about somehow requiring more frequent use of these expedited pathways through legislation. And I know you share that concern.

Your testimony mentions the health risk that could result from approving therapies based on early data that needs more vigorous

study, but you also describe the possibility that these kinds of approvals could endanger progress toward the development of other treatments.

Can you just elaborate on both of those concerns, if you would.

Mr. BEALL. Well, certainly, one of the things when you are dealing with a small population—and now we are talking about personalized medicine where you may only have 25 patients with a certain genotype that may be approachable or therapeutic opportunities for that particular drug—if those patients were introduced to a drug that was less than effective, what happens when the next drug that could be effective—how do you do the clinical trial?

So I think that is really very critical because we want to make sure that our first introduction is drugs that are efficacious, and then we move forward to the next level. Because then you really are depriving, if you don't have safe drugs, of developing good drugs and effective drugs that could move us above the therapeutic options that we have.

So I think that that is the critical thing that we always face. There is always the risk. But now we are dealing with small populations, personalized medicine. Maybe there is only going to be 6, 10, 1,000 patients.

So I think you have to be particularly critical on that issue with rare diseases.

Mr. PALLONE. OK. Yes. I just wanted to echo another point you made in your testimony about the importance of resources.

And I couldn't agree more, that, as you say, FDA needs resources to ensure that they can rely on the best regulatory science available and they need adequate resources to enable them basically to meaningfully engage with the patient community.

And we have this 21st Century Cures Initiative, which is progressing now. We have had some sort of larger meetings and now some hearings. And my colleagues always ask what can Congress do.

And I think that the most effective thing we can do is provide adequate resources to make sure that FDA, as well as NIH, have the resources to fulfill the expectations we have for both agencies.

And I hear not only from the agencies, but, also, from my constituents, that they don't have enough resources. So I just wanted to echo again what you said.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

I now recognize the vice chairman of the subcommittee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Just before my time starts to run, could I make a unanimous consent request?

Mr. PITTS. You may proceed.

Mr. BURGESS. I would like to move that the committee make people aware that, if someone wishes to contact or communicate with the Cures Initiative, it is cures@mail.house.gov.

I know there are many people watching who think, "I would like to interact with the committee staff." So that is the way to do it.

Mr. PITTS. Thank you.

Without objection, so ordered.

Mr. BURGESS. Very well. I knew they wouldn't deny me.

Let me ask Ms. Furlong. You were kind enough to mention the work on the MD CARE Act, and thank you for that. As you know, we will likely be marking that up next week. So that is a big milestone.

Can you talk about how the MD CARE Act needs updating and the type of updating that this committee has pursued?

Ms. FURLONG. Certainly. And thank you for the question, Dr. Burgess.

The MD CARE Act was the solid foundation that set Duchenne and the muscular dystrophies—really galvanized their progress.

So the MD CARE Act was enacted in 2001 and reauthorized in 2008. And right now the amendments are really to look at what we have learned in the meantime.

So the cardiac issues in Duchenne muscular dystrophy are real and they have to be tackled in order to answer the question. As you look at these potential therapies that were hopeful to be approved in the next months and years, they extend function. Will they protect or have a negative effect on the heart?

So it is the gaps that we need to really look at with the amendments, in addition to the fact that, when this legislation was enacted in 2001, young boys with Duchenne didn't live to be adults.

So now we have an adult population and we need to really address those adults in terms of their medical care and, also, to incentivize and understand how to treat them, how to encourage them to have long and independent lives as they become adults and reach for their dreams.

So I think that the MD CARE Act is now looking with the muscular dystrophy committee from the NIH and other agencies. Their research plan has to be updated and these amendments to be incorporated so that we are really achieving the full effect that the MD CARE Act was initiated for.

Mr. BURGESS. Thank you.

And of course, Mr. Beall will also acknowledge that the population of patients is changing because of some of the successes that have happened over the past several years.

And in both of those illnesses, both cystic fibrosis and muscular dystrophy, it is important that we keep pace with the way the patient population is changing.

We want people to live longer and fuller lives with their conditions and, at the same time, we don't want the legislation then to stymie that. So it is, in my opinion, an important step forward.

Dr. Beall, we talked—or you talked about the development of mutation-specific therapies and the next evolution in precision medicine and you could see the cystic fibrosis example impacting the way we address other serious illnesses.

Is there something more you would like to add to that?

Mr. BEALL. Well, again, we are clearly in the age of personalized medicine. Fortunately, with the completion of the human genome, we understand the genetics of so many more diseases and genetic diseases that it is a very critical time for us.

Mr. PITTS. Microphone.

Mr. BEALL. Not on? OK.

I just saw Dr. Collins downstairs, and he is excited because he was one of the discoverers of our CF gene.

So we live in a very unique age, and I think more and more therapies are going to be directed towards specific mutations.

And that is one of the reasons that we have to have these kinds of patient registries, so we can start to identify those mutations.

When Vertex felt that they had a drug that might work on a certain mutation, the small drug that came out, G551D, we were willing—we were able to tell them in the United States we have 1,100 of those patients within 5 minutes after they asked us because of a patient registry, because we have a documented history of the disease.

So I think that is why it is very important to have personalized medicine, therapies and the options for that, but it is also—we have to be able to document the patients that can participate in the trials.

Mr. BURGESS. Yes. It is very powerful.

And, of course, you referenced to the 1965 registry. In 1965, you didn't know that we were going to know about the sequence of the human genome 30 years later.

Mr. BEALL. Well, but we have been able to document it. Today we have 26,000 patients whose data is provided to our patient registry every single year.

Mr. BURGESS. Let me ask you a question. I am going to run out of time pretty quickly. But—and this is either for Mr. Beall or Mr. Pops.

The world is different now and you have people that are perhaps lucky enough to enter into a clinical trial and they are likely to perhaps have friends with the same condition.

So in the old days, a randomized clinical trial, you wouldn't know which arm to which you were randomized, who was getting the target or study drug, who was getting either an older therapy or no therapy. But now people communicate. Facebook. Twitter. They are likely to be Facebook friends.

How is that going to impact the ability to have a blind and randomized clinical trial? Are people likely to communicate with each other, I mean, look, "I am getting a lot better on this stuff. How about you?" "Wait a minute. I haven't seen a darn thing"?

Mr. POPS. I think it is a real question. It is a real issue because—and you can't pretend that it is not going to happen.

This is already happening, particularly as you get large cohorts of patients in randomized studies in multiple countries. They are all communicating.

So I think it is very important that we be really rigorous in maintaining the blind to the extent that we can.

Mr. BURGESS. To the extent that we can. But, also, we probably need to embrace the fact that the information is out there and being communicated and, to the extent that it can further enhance what we are doing——

Mr. POPS. So let's take advantage of it.

Mr. BURGESS. Yes.

Mr. POPS. Let's do more in the aftermarket. Let's approve drugs and collect this information and get a more nuanced view of the drugs' use in the real world and turn it to our advantage.

Mr. BEALL. And, in some cases, it is going to make it easier to do clinical trials when you can have large networks that exist out

there, when they can report patient-reported outcomes and things like that.

So I think sometimes it is looked at as a disadvantage, but we ought to turn it—as Mr. Pops just said, we ought to turn it to an advantage because I think it can expedite the ability to do clinical trials as we move forward with the technology.

Mr. BURGESS. Great. Thank you.

Ms. FURLONG. And it should expedite post-hoc analysis so that we can see the long-term effects. Because in a clinical trial of 12 months, for instance, plus or minus, you might not see the full effect of a drug that is multisystemic. So it will enable us to understand the full impact on the patients' lives.

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

Mr. PITTS. The chair thanks the gentleman.

Now recognize the gentlelady from Illinois, Ms. Schakowsky, 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you very much.

I had a question for Dr. Lichtenfeld—actually, for anyone on the panel that wants to comment on this.

This is about quality-of-life outcomes. I mean, obviously, if this is a known life-threatening disease, you want to do everything you can to make sure that the therapies match the disease.

But there are—you would say, when these quality-of-life outcomes are rigorously measured and supported by the FDA, they can and should be included in drugs' labeling and can by themselves be a basis for a drug's approval.

I certainly know people who have suffered so much from side effects of drugs. And I just wonder, in the whole process of drug approvals, how much are these quality-of-life issues really looked at? As a basis for approval or just as a basis of whether or not they are used?

Dr. LICHTENFELD. Thank you for your question.

In fact, it is a work in progress. Let's understand that quality of life is a buzzword today, but it wasn't a buzzword very recently.

So as we look at the issues, shall we say, of palliative care, of supportive care, quality of life, issues that the American Cancer Society and many others have been involved in, it is relatively new to the table.

Having said that, there have been issues recently with one particular drug where, had the question really centered around was the—even though the drug may not have met the FDA standard—and this was about 2 years ago—even though it had not met the FDA standard, did it meet the quality-of-life standard? Did it improve the quality of life of the—it happened to be a breast cancer drug—for the women who took it?

Because that would have been an important consideration. And, unfortunately, the quality of the data measuring quality of life was inadequate.

So going forward, cancer patients have enough on their plates, as do everyone represented at this table, as do patients throughout this country. We need to be aware that quality of life is an important part of the treatment process, and we need to have tools in place.

They are not uniform yet. They are not as good as we would like. But they have to be in place to measure quality of life, and that has to be considered. And patient-reported outcomes are very much a part of that process.

Ms. SCHAKOWSKY. Yes. Go ahead, Doctor.

Mr. POPS. I just wanted to make a comment as it relates to patients with chronic disease as well. We talked a lot about cancer and orphan, small diseases.

We work in the field of chronic disease—schizophrenia, depression, addiction—where patients are taking medicines for long, long periods of time.

And simple things that may seem prosaic to the researcher, like nausea——

Ms. SCHAKOWSKY. Sure.

Mr. POPS [continuing]. Fatigue, propensity to get addicted or dependent on the drug, these are really important inputs that we want to hear from patients about.

Ms. SCHAKOWSKY. And is that part of the process?

Mr. POPS. It is less part of the approval process today than I think it will be in the future. It is certainly part of the utilization process as patients make a determination, "Which medicine do I want to stay on for years and months?" I think that is a critical part of it, but it is not really incorporated in the consideration of the approval.

Ms. SCHAKOWSKY. Especially where all things might be equal in effectiveness, whether or not something causes nausea, fatigue, could be really important.

Mr. POPS. That is right. Particularly if you are launching a new medicine into a large category where there might be an abundance of generic drugs that are safe and effective, but might not hit all of those parameters for certain subsets of patients for long periods of time.

And we just want people to be sensitive to the fact that, from the patient perspective, there are differences between the medicines.

Ms. SCHAKOWSKY. Right.

And then, also, Dr. Lichtenfeld, I wanted to ask you about small-sized trials. And you mentioned one of the drawbacks.

I had talked about the extent to which women aren't considered. And I would just be concerned—I understand the plus. I do. But if we rely too heavily on them, isn't there the real risk of excluding important populations?

Dr. LICHTENFELD. Well, the answer is yes, there is a real risk of excluding important populations.

In fact, when you talked about women and heart disease, I remember back in the early 1990s when the article came out talking about the absence of women in clinical trials for the treatment of hypertension and heart disease. So this is an issue I am aware of.

But let's talk about the other side of the coin, and that is, when you are sitting—I have sat in the presentations at ASCO, at oncology meetings—and you see a presentation of 80 patients and you see what we call waterfall plots—basically, the responses in survival that occur—and suddenly, 70 percent of those patients are having significant responses, In a disease where there was no

treatment before, I don't think one asks the question—they ask the question in followup, but not at the moment.

And what has happened and what has been exciting to me is I am now sitting in those presentations every June and I see—I wrote about it—it took a year for one of the drugs to go from clinical trial to approval because it was that effective in the disease where there was no other treatment available. That is pretty spectacular. That is new thinking. That is a new approach.

Now, we have learned more as time has gone on. Yes. Doesn't mean we have stopped learning, as was mentioned before about cystic fibrosis. But when you suddenly see moments like that, no one would want to hold back. Develop the data, yes, but don't hold back the opportunity.

In fact, even a phase 1 trial that was presented at this ASCO meeting in June, the company, actually—well, not the company, but ASCO in the press release indicated the company was willing after a phase 1 trial to put it into compassionate use. And that is pretty amazing, a major change in the way that traditionally we have seen cancer drugs move through the pipeline.

Ms. SCHAKOWSKY. Thank you.

I have overstayed my time. Thank you.

Mr. PITTS. Sure. Thanks to the gentlelady.

I now recognize the gentleman from Virginia, Mr. Griffith, 5 minutes for questions.

Mr. GRIFFITH. Dr. Lichtenfeld, let's pick up there, because I think that that compassionate use is something that—we really need to be figuring out how we can make it more effective and how we can do it faster at the Federal level.

You talked about in your testimony that patients needed to be involved both on saying what kind of nausea they had and what the pain levels were and so forth, and I agree with that.

But I also think that, particularly when you have no treatment, that patients need to be involved in that, too. And as Ms. Furlong said earlier, when there isn't a treatment, you are much more willing to take those risks than you would be if there is some other treatment out there that might work, but this might be a little more comfortable.

And I want to give both you and Ms. Furlong an opportunity just to address that further.

Dr. LICHTENFELD. Well, thank you. And I appreciate the question, and I know you mentioned it earlier.

It is a complex issue. It is not a new issue. As you may well be aware, it has been around for some time with the number of drugs that have gone through the pipeline, which seem to show some opportunities. Various state legislatures are involved.

And I am sitting here today both as a representative of the Society, but also as an individual, and understand that there are discussions on both sides of that issue and they are complicated.

Bottom line is that we need to understand what drugs work when they work. We need to understand that patients need to have access to promising drugs as soon as possible.

Companies make those decisions as to how they are going to handle that process. The FDA, as a matter of fact, has approved almost all of the applications they received. And we need to have those

discussions to come to a better resolution about how to address that issue.

Mr. GRIFFITH. And what I would say is that whatever we can do—I think I speak for a lot of the members of the committee—I am probably a little more out there than some—but whatever we can do to help by changing the law to expedite that process, we will do.

Dr. LICHTENFELD. We would be glad to have those discussions on behalf of the Society, sir.

Mr. GRIFFITH. Ms. Furlong, did you want to make another comment about risk assessment? Because, obviously, when your boys were sick, you probably would have taken anything that had any promise of hope.

Ms. FURLONG. I think I could tell you stories about looking in China to see some tea that you might be appalled about, but that was long ago.

I think it really is up to the companies. FDA has always, to my knowledge, at least in the Duchenne and other fields, been willing to entertain and talk about compassionate use.

I think for the rare disease community this really talks about and gets us back to trial design.

In general, trials are designed to test a small subset of patients. In the Duchenne community, the 6-minute walk test is the standard primary outcome measure.

So that means, as a child with Duchenne, you have to walk 6 minutes and even further, as we learn more about the testing. It is a very narrow subset of people within a certain framework of that 6-minute walk test, which, as you can imagine, leaves a great number of people outside the trial.

So I think trials have to be designed that are inclusive and welcoming of people that live with the spectrum of the illness, both very young as well as adults with very limited functional ability.

That way, we can test those in those populations. We can have labels that are broad and then provide access to all. So I think that might be a better solution.

Mr. GRIFFITH. Thank you.

I look forward to working with you all.

And, with that, I yield the remainder of my time to Dr. Burgess.

Mr. BURGESS. I thank the gentleman.

Dr. Lichtenfeld, I just wanted to follow up with you because your specialty has been involved in this type of activity probably longer than any other branch of clinical medicine, going back to 1955 when the developmental therapeutics program was put into place at the National Cancer Institute.

So with that breadth of experience within your specialty, are there things that you want to share with others about what that experience has taught you?

Dr. LICHTENFELD. Well, what we did back in 1965 or whenever was a lot different than what we are doing today. I don't want to take the time to really go into it. You may be aware of it.

But here is the message. It didn't happen overnight. It took 40 years of research to get us to the tipping point where we understood the genome and had the opportunity to take advantage of that and move forward.

Immunotherapy, the same story. It has taken us 40 years. That was a substantial amount—I don't want to underestimate the value of research investment to get us to the point where we are, where suddenly we look like we have so much to offer and to do.

I also comment, with regard to my co-panelists, that they have populations and they have demonstrated that finding the patients where they are is critically important.

We have a substantial amount of work to do to understand not only the clinical trial mechanism, but also the medical practice system, so we can make sure that patients and communities—I live in a small town in south Georgia—that my friends have opportunities to get these drugs in clinical trials and be part of that process. There is a lot of work to do.

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

Mr. PITTS. The chair thanks the gentleman.

Now recognize the gentleman from New York, Mr. Engel, 5 minutes for questions.

Mr. ENGEL. Thank you, Mr. Chairman and Mr. Pallone, for holding this hearing. I am pleased to have this opportunity to further consider how patient perspectives can best be incorporated into the therapeutic development process.

As the author of the ALS Registry Act and the Paul D. Wellstone Muscular Dystrophy Community Assistance Research Education Amendments of 2008 and 2013, along with my colleague, Dr. Burgess, I have worked to be a voice with those with rare and orphan diseases.

I am encouraged by the advances we have made into the causes and mechanisms of these diseases, as well as our progress toward treatments, but, obviously, we still have a long way to go.

One of the most striking gains we have made is for individuals with Duchenne muscular dystrophy. As Ms. Furlong mentioned, our efforts have added an average of 10 years to the life expectancy of boys with Duchenne. And now, as life expectancy increases, we face new challenges in finding effective therapies.

The patient community brings an important perspective and understanding to this process, and I am interested to see how we can best use that knowledge to assist medical researchers with therapy developments.

So, Ms. Furlong, let me ask you this. I am particularly interested in the way the Duchenne patient community is engaged with the FDA to help inform the benefit-risk determinations made by agency reviewers, as well as the Duchenne community guidance document you referred to in your prepared testimony.

Could you please comment on how you hope to see these efforts affect the therapeutic pipeline and the various stakeholders who are part of that pipeline.

Ms. FURLONG. Yes. Thank you, Mr. Engel, for the question.

The benefit-risk really originated out of discussions with the FDA because, in our early discussions, it was known that we were telling anecdotal stories that the equation of benefit-risk was different in, for instance, Duchenne muscular dystrophy than perhaps some more common disease.

And in that the FDA suggested to us that they agreed, but they didn't have anything they could rely on, any quantified evidence-based document that could help them make those decisions.

So we agreed to go out on benefit-risk and did the pilot with 120 parents. We learned that their priority is disease stabilization and they were willing to accept a great deal of risk. In fact, they are living with a great deal of risk, as they know that their child has a fatal illness.

So the FDA has now asked us to expand that study to a greater number of patients than 120 patients and, also, to ask these questions of the young men with Duchenne. Our hope is that they will incorporate it into the review process and they will demonstrate to us how and when they use it and when they don't and what makes sense for them as they make their decisions.

Mr. ENGEL. Thank you. And thank you for your advocacy and hard work. It is very much appreciated.

Dr. Summar, can you talk about the role you think the patient perspectives should play in developing therapies for diseases like ALS and muscular dystrophy that have limited treatment options and for which quality of life is, obviously, an especially important factor to patients.

How can the FDA best consider the views of patients and families when examining the benefit-risk calculus for these diseases?

Dr. SUMMAR. Thank you for that question, Mr. Engel.

This really kind of expands across the entire field of rare diseases, but your question is particularly relevant for those two groups.

Patients often tell us about things that they wish were better that we never thought of. One of the things I have run across time and time again is, when we go and ask our patients, "What is the worst part of this disease?"—a lot of times it is parents in the case of pediatric patients—they will list some things. And sometimes the things we thought were most important are number nine or ten on the list.

So I think, when we look at what our therapeutic targets are, what our quality-of-life targets are for these diseases, patient and family input is a huge factor, and I think it is something we can incorporate a lot better than we have.

I think during the early stages, particularly when we are designing our pivotal trials, clinical trials, looking at what end points are—I think that those are going to become more and more important.

And the other thing, of course, is the small group sizes with these. Many times it is hard to pick one single outcome variable that you are going to be able to achieve.

The smallest study I have been involved with was five patients for an approval process. Getting one exact target for that—fortunately, the effect of the drug was massive; so, we were able to do it. But if it had been milder, I might have needed more than one outcome variable.

So I think families can help us determine what is important there. They can help us, also, as we talked about with some of what risk is tolerable in those situations. It is different. And there

are 7,000 different rare diseases. Each one of these is unique in its own regard. But there are some commonalities like that.

Mr. ENGEL. Well, thank you. And thank you for your comments, and also thank you for your interest.

And I want to thank the panel for a very interesting discussion.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

Now recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it.

And I thank the panel for their testimony today.

I know we have been talking about this and you have had an opportunity. I want to give you more of an opportunity to respond on this.

On Wednesday, I asked one of the witnesses about his statement in including patients in the clinical trial process, but I want to make sure that you all have every opportunity to respond to this.

If patients had a greater role in clinical trial design—and I know you have touched upon this—if trials measured qualitative data from patients like, "How do you feel?", "Is it less painful?", what have you; "How would things be different?" and "What would you like to see?"

We will start with the——

Mr. BEALL. I would like to start.

First of all, the patient-reported outcomes I think has been part of every clinical trial in cystic fibrosis for the last 10 or 15 years. Some of the tools are not the best at this point, but we are working to refine them.

We have just spent as a Foundation a large effort to look at the patient-reported outcomes as a kind of specific validated tool for CF, and it is going to be submitted to the FDA and go through a validation process. In the past, we have used one that was generally for lung disease, but it may not be specific.

So this is a science that is evolving. A decade ago or 15 years ago, 20 years ago, PROs were not really incorporated.

So it is a science that is evolving, and it has to be evolved not only with the FDA, it has to be evolved with the sponsors, too, because they have got to be willing to incorporate those into the clinical-trial process.

So I am encouraged by the process, but I will tell you the—just in this last trial we had where their lung function went up and the exacerbations went down, we didn't have a statistically significant improvement in the patient-reported outcomes.

Because when you are starting to treat the basic defect, you are treating the whole disease process and you are looking at extending lives.

And the patients may not feel that from day to day, but over years, you may have a tremendous impact on those patients. So it is a tool that can be used, but it shouldn't be used exclusively.

Mr. BILIRAKIS. Thank you very much.

Ms. Furlong, do you have a response?

Ms. FURLONG. Sure.

So I agree with Dr. Beall. And patient-reported outcomes are incredibly important, but I think this is where involving the patients

in the design and conduct of clinical trials is really going to be important.

Because, for instance, how do we measure energy and endurance? How do we know that turning over in bed is important to patients as opposed to an outcome measure such as the 6-minute walk test?

So I think things are important to patients that have a real effect on their lives. For instance, as you can imagine, if a boy can still text at the age of 18, that gives him independence. If a child can walk up a single step, they can enter buildings. If a child can roll over in bed, that makes the families' quality of life overall, in general, much, much better.

So I think the use of patient-reported outcomes and including the patient voice in the discussion about what the clinical trial looks like and what the measurements are, both primary and secondary, is going to be incredibly important.

Mr. BILIRAKIS. Thank you so much.

Mr. Pops, do you have a comment or——

Mr. POPS. I think these outcomes are so critical. In the world that we are developing drugs in, which is in psychiatry often, in schizophrenia, depression, addiction, the end point of the clinical trial—the hard end point is asking people essentially how they feel.

And so how you feel is typically embodied in the set of validated scales, but those often don't capture some of the most important parts of how they actually feel over time.

A perfect example might be an opioid dependence or an alcohol dependence, where a critical question the patients ask us when they take our medicine is, "Is my craving going to go down? Am I going to crave this less? It may block the receptor and keep me from drinking, but is my craving going to change?"

That was not a validated end point. That was something we couldn't incorporate in the label, but it is essential to the patient's perception of the disease.

Mr. BILIRAKIS. Good point.

Doctor?

Dr. LICHTENFELD. About 4 weeks ago at ASCO, the oncology meeting, they showed a picture of a lady who was 96 years old who had received a phase 1 drug—that in itself is a fascinating point—whose cancer completely resolved.

And on the bottom end of the before and after picture—on the after picture, you saw a trace of a little smile. And I noticed that smile and I tweeted it, actually. I took a picture and tweeted it and it got re-tweeted quite a bit. And then the lecturer said, "Yes. That really is a smile" in front of 2,000 people.

What I am trying to say by that example is that is what we have to be able to measure and aggregate in a scientific way to show that the treatments make a difference.

One example of one lady in an unusual situation, but something that I think all of us agree—I would echo the comments that were already made—is so critical to understanding, particularly in the oncology world, what we do and how we do it and the goal that we have to have of improving quality of life.

Mr. BILIRAKIS. Thank you.

Dr. Summar?

Dr. SUMMAR. Yes. I will just use another example, too.

We had a new medication we were looking at. Most of the patients with rare diseases are on the medicines they take for life. So it is every day, day in and day out. And these care plans are often complex and they really affect the whole family.

So the new drug looked like it was promising from the standpoint of maybe a little bit better efficacy, a little bit better control, but it was five times a day instead of two or three times a day compared to the old one.

And the families were like, "Why would we add three more times a day of dosing for the small effect?" And no one had really bothered to ask them that before we started.

So I think there is all of these things that really getting the patient input early on is going to make a difference.

Mr. BILIRAKIS. Thank you so much. Appreciate it.

Mr. Chairman, can I ask one more question?

Mr. PITTS. You may proceed.

Mr. BILIRAKIS. OK. Thank you so much. Appreciate it.

Dr. Beall, the CF Foundation's venture philanthropy model has produced incredible results. Congratulations. Your foundation found your breakthrough drug when it helped translate some of the early research through the valley of death, and now you have the Kalydeco.

How are you able to establish this program? And how can other groups adopt this similar model?

Mr. BEALL. Well, it is a willingness to take risks. That is what you have to do in drug discovery. And we were frustrated by the fact that companies were not getting involved in the orphan diseases.

So the whole concept here was to say, "Take some of the risk out of biotech companies or pharmaceutical companies to get engaged in CF research." And, as I said, we spent $42 million initially to start a high-throughput screening that led to Kalydeco.

I think what is the most important and gratifying thing for the Cystic Fibrosis Foundation—and I know Ms. Furlong was in my office a number of years ago—and what we are seeing is so many other organizations are feeling the same impatience that our foundation felt 14 years ago in adopting this.

One of the first times I talked about venture philanthropy at the bio meetings, we had 10 people in the audience. And now it is really becoming really inherent in what many voluntary health organizations are doing.

In fact, FasterCures has been an organization that has been central to making some of that happen. There are law firms that specialize in it.

So we love to share our ideas. We share our ideas all the time. And it has been very gratifying to our community that we happen to be fortunate enough to be able to start it because we had the resources. Bill and Melinda Gates gave us $20 million to start our program. We had other dollars to really make that initial investment.

Mr. BILIRAKIS. Can you tell us how you successfully established the CF registry?

Mr. BEALL. As I say, it goes back a long time. But Dr. Zerhouni was here several years ago when he was the head of the NIH, and he says one thing about the CF community, it is a community with a culture of research.

And every patient who goes to one of our care centers is asked, "Do you want to participate in a patient registry?" And I think it is 99.5 percent of the patients that say, "Yes, I do" and then signs the informed consent.

So it is all part of the culture. It is part of the culture the organization creates. It is the physicians and it is the relationships and the recognition that it is an important part of having a disease because we can't cure this disease without their involvement.

Mr. BILIRAKIS. Very good. Thank you very much. Appreciate it. I yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

Dr. Summar, I didn't get to you in my round.

On Wednesday, we heard an idea thrown out there that there are vast amounts of data available that are not being utilized. And we all know what an organ donor is. The idea was that we have data donors.

Now, how would this play—and you mentioned the IRB system, the risk enterprise. What is your reaction to that?

Dr. SUMMAR. This is something we talk about when we are having coffee a lot.

There are data sets all over the place. In fact, most of them end up usually lost when someone's computer gets recycled. We had a physician lose 15 years of data because his Excel spreadsheet didn't update.

I think a way—find a way that balances, obviously, people's desire for confidentiality versus the irreplaceable and oftentimes irreproducible amounts of data that are out there. We really do need to find that balance.

My reaction to that would be I would love to find a way forward with that. That one is going to—you can see a lot of sides to that question. But I definitely think it is worth looking at.

And I think what we find is a lot of patients are like, "Yes. I will put it out there. I am fine with that." There will be a small core that won't. You can take a count for that. But I think most folks, if you ask them, saying, "Would you feel OK if your data is out there so everybody can take a look at it?" would be fine.

You see people opening up their genomes, who had their genomes sequenced, saying, "I will publicly post it along with my medical health history." A lot of folks want to help.

Mr. PITTS. Thank you. Thank you.

Mr. BURGESS. I did that. We did that. I mean, that is a real thing that is happening right now. And, yes, privacy is something we all value, but it also is a voluntary relinquishing of a portion of that for the greater good.

I think that is something we ought to not encourage—well, not encourage, but we certainly shouldn't stand in the way if that is an activity that——

Dr. SUMMAR. Right.

Mr. BURGESS. And unfortunately, I can't say that we don't always respect that, that we shouldn't stand in the way. But enough about that.

Mr. PITTS. All right. The chair thanks the gentleman.

That concludes the questions of the Members who are here. Another exciting, informative, very important hearing. Thank you so much for coming.

Members will have followup questions, and we will send those to you. We ask that you please respond promptly. I remind Members they have 10 business days to submit questions for the record, and that means Members should submit their questions by the close of business on Friday, July 25th.

I have a UC request, a statement for the record, from the National Health Council. Without objection, that will be inserted into the record.

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

Mr. PITTS. Without objection, the subcommittee is adjourned.

[Whereupon, at 12:19 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

National Health Council Statement for the Record

21st Century Cures Initiative Hearing – July 11, 2014

House Committee on Energy and Commerce

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The National Health Council (NHC) is pleased to submit written comments for the July 11, 2014, House Committee on Energy and Commerce, Subcommittee on Health hearing on "21st Century Cures: Incorporating the Patient Perspective."

The NHC is the only organization that brings together all segments of the health community to provide a united voice for people with chronic diseases and disabilities as well as their family caregivers. Made up of more than 100 national health-related organizations and businesses, its core membership includes the nation's leading patient advocacy groups, which control its governance. Other members include professional societies and membership associations, nonprofit organizations with an interest in health, and major pharmaceutical, medical device, biotechnology, and insurance companies.

The NHC is deeply committed to promoting the development of new treatments that could enable people with chronic diseases or disabilities to live longer, healthier, and more robust lives. The magnitude of patient need is great.

More than 133 million Americans – over 40% of the U.S. population – live with a chronic disease or disability. But for many people there are no treatments and existing treatments work for only 50-75% of the patients who currently use them. There are limited treatment options for too many diseases and disabilities, including mental health aliments, neurological, autoimmune and many rare diseases, nor for the prevention of diseases and disabilities. Millions of patients struggle daily with Alpha-1, ALS, Alzheimer's, epilepsy, lupus, mesothelioma, and multiple sclerosis waiting for new, better, or any treatments. The same applies for people living with thousands of other diseases.

Today, there is broad agreement on the need to incorporate patient perspectives into drug development. There is growing acknowledgement that patients can have important roles in the drug development process beyond their traditionally more passive role as research subjects.

The Patient-Centered Outcomes Research Institute (PCORI), which was created in 2010 by the Affordable Care Act, is showing that investing in patient engagement can be a path to generating research that is more useful for decision makers.

The Food and Drug Administration (FDA), too, initiated the Patient-Focused Drug Development (PFDD) program, which aims to collect information on patient and caregiver perspectives and preferences across 20 disease areas. The creation of PCORI and FDA's PFDD program are certainly important first steps toward advancing patient engagement but our work cannot end there.

The NHC is actively engaging with FDA as it looks to refine the agency's framework for assessing benefits and risks in drug approval to ensure it better reflects patient perspectives. We are also urging FDA to work with us and other stakeholders to use its PFDD program as a foundation for developing guidance on how patients can be engaged in the drug development process. The incorporation of the patient perspective related to benefits and risks, as well as the outcomes that are most meaningful to the ultimate end users of medical products will aid in our shared goal of delivering high quality medical to people with chronic diseases and disabilities. To ensure the most desirable outcomes, this engagement should occur throughout the entire continuum of the research and development process.[1]

[1] See Exhibit A: National Health Council Diagram on Patient Engagement in the Drug Development Process

FDA can play an important role in encouraging sponsors to incorporate patient input, which we believe will ultimately enrich the FDA regulatory review and approval process and accelerate patient access to new treatments. FDA should work with health care stakeholders such as sponsors, patient organizations, health care providers, and researchers to develop guidance to address issues related to patient engagement. Areas in which guidance is needed is in:

- *Defining the patient community.* The patient voice is represented by a wide range of individuals and organizations. Often, the terminology used to describe the individuals and organizations that comprise what is known broadly as the patient community is inconsistent or fails to capture the distinctions among them. For example, patients, patient advocates, and consumers are sometimes used interchangeably or are grouped together and caregivers are often excluded altogether.
- *Describing meaningful engagement.* Patient engagement can represent a range of activities, from passive engagement (e.g., clinical trial participation) to more active participation (e.g., research development). Across this spectrum of activities, the elements that constitute or can help achieve meaningful engagement have yet to be clearly defined.
- *Developing a framework and methods for engaging patients.* A framework would offer a structure and process for patient engagement, as well as the expected outcomes of that engagement. While there are existing reviews of patient engagement methods, they have not yet been fully examined for their application to drug development. Guidance on appropriate methods is crucial to implementing a process for involving patients.
- *Identifying and removing barriers to meaningful engagement.* While many companies are actively soliciting input from patients, there are many barriers that must be addressed.

FDA should work with stakeholders to determine which barriers exist and ways to remove them to ensure that sponsors can engage with patients in an appropriate way to better understand the needs of patients.

We also recognize that in order for patient engagement in drug development to move forward on a large scale, the patient community must also be prepared to be active collaborators. To that end, the NHC has created a patient information collection tool to help patient advocacy organizations collect information on the impact of their disease or condition on quality of life, to better understand individual experiences with treatment regimens, and to determine what aspects of treatment or symptom relief are most important to patients. This information tool was originally created to support patient advocacy organizations preparing for FDA's PFDD meetings, but is emerging as an important tool for drug manufacturers in understanding the full scope of the patient experience with a disease.[2]

We would like to thank you for this opportunity to share our comments. We applaud the committee's efforts to strengthen the patient voice in the development of long awaited treatments and cures to help people with chronic conditions live longer and better lives. We look forward to working with you to find the best ways of ensure that patients are an integral component of the drug discovery, development, and regulatory processes.

[2] See Exhibit B: National Health Council Information Collection Tool for Patient Organizations

Exhibit A:

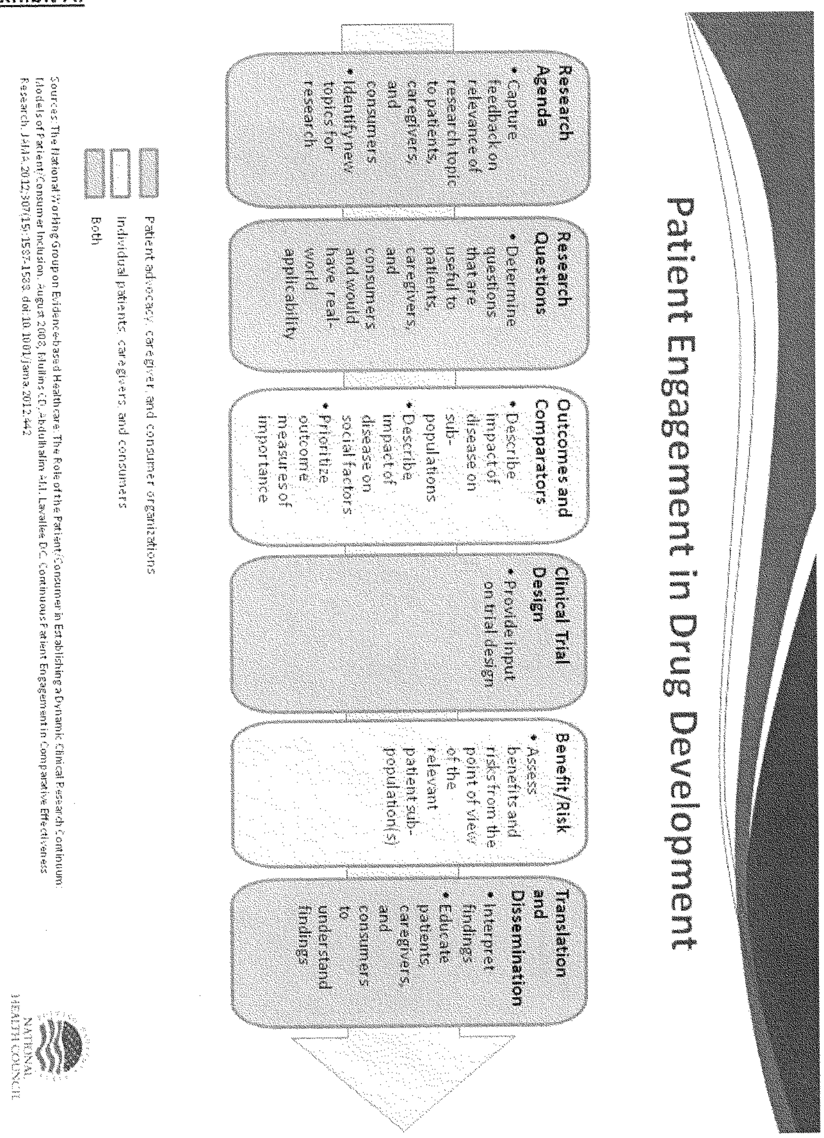
Patient Engagement in Drug Development
Research Agenda
• Capture feedback on relevance of research topic to patients, caregivers, and consumers
• Identify new topics for research
Research Questions
• Determine questions that are useful to patients, caregivers, and consumers and would have real-world applicability
Outcomes and Comparators
• Describe impact of disease on sub-populations
• Describe impact of disease on social factors
• Prioritize outcome measures of importance
Clinical Trial Design
• Provide input on trial design
Benefit/Risk
• Assess benefits and risks from the point of view of the relevant patient sub-population(s)
Translation and Dissemination
• Interpret findings
• Educate patients, caregivers, and consumers to understand findings
Patient advocacy, caregiver, and consumer organizations
Individual patients, caregivers and consumers
Both
Sources: The National Working Group on Evidence-based Healthcare. The Role of the Patient/Consumer in Establishing a Dynamic Clinical Research Continuum: Models of Patient/Consumer Inclusion. August 2008; Mullins CD, Abdulhalim AM, Lavallee DC. Continuous Patient Engagement in Comparative Effectiveness Research. JAMA 2012;307(15):1587-1588. doi:10.1001/jama.2012.442
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Exhibit B:

Enhancing Benefit-Risk Assessments by Integrating Patient Perspectives: An Information Collection Tool for Patient Organizations

As required under the Prescription Drug User Fee Act V (PDUFA) reauthorization, the Food and Drug Administration (FDA) is developing a framework for conducting benefit-risk assessments.[1] To inform its work, FDA will be engaging patients, caregivers, and advocates to gather their perspectives and learn more about their specific needs. In particular, FDA will hold 20 public meetings over the next five years, each focusing on a different disease or condition. The aims of the meetings are to gather patient perspectives on the conditions' impact on quality of life, individual experiences with treatment regimens, and potential outcome measures in clinical studies. In addition, the FDA has repeatedly stated that these public meetings are not the only means to obtain patient input. Other methods include formal and informal meetings with FDA staff.

Patient Perspective and Disease Impact Stratification Tool

Goal: To help patient organizations ensure their communications with FDA regarding benefit-risk are comprehensive and, conversely, to help FDA capture the information they need from patients, caregivers, and patient advocates to inform their assessments of benefit-risk

Objective: To provide a way for patient groups to systematically organize issues, stratify their patient population, and identify key topics of focus in preparation for meetings with FDA

Rationale for this Tool: Patient populations affected by certain diseases are often very diverse and can span a wide array of demographics. Further, treatment options and patient needs often vary based on the stage or severity of the disease or condition. Recognizing and communicating these differences across subpopulations will help FDA better understand the varying levels of risk tolerance, from the perspective of both patients and caregivers, as well as where additional focus may be needed within a disease area or condition. This tool was created to help patient organizations collect and collate information that could ensure FDA has a comprehensive and inclusive picture of all affected patients of a disease. Those applying the tool should be mindful of potential variances between patient and caregiver needs and preferences, as well as ensure that information from hard-to-reach populations is captured.

How to Use the Tool: The tool consists of three sections: (I) Identification of Subpopulations; (II) Description of Disease Impact; (III) Description of Treatment and Management Options.

To complete Section I:

1) Identify patient subgroups within the broader patient population impacted by the disease

To complete Section II:

1) Describe how the disease is diagnosed and whether there are difficulties related to diagnosing the disease, such as delayed diagnosis or misdiagnosis.
2) Describe the characteristics of the disease, such as prevalence, symptoms, and comorbidities associated with the disease, and how they impact patient subpopulations.
3) Describe the impact of the disease and comorbidities on social factors that are of importance to patients and caregivers and on quality of life.
4) Identify outcome measures (clinical, patient identified, or patient reported) that are most relevant to patient/caregivers and would best address their needs and priorities.

[1] Passed as part of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA)

To complete Section III:

1) Describe the number of FDA-approved treatment and management options available for the specific subpopulation.
2) Describe the effectiveness of FDA-approved treatment and management options that have been used, if any, in treating or managing the disease for the specific subpopulation.
3) Describe the side effect profile and tolerability of current FDA-approved treatment and management options that have been used, if any, as they impact the specific subpopulation.
4) Describe the range of both FDA-approved and non-FDA approved treatment and management options used by the specific subpopulation for this disease.
5) Describe any barriers that may impact or impede patients' ability to access the necessary treatment and management options.

Definition of Terms

Child: Individuals under 18 years of age

Adult: Individuals 18 to 64 years of age

Elderly Adult: individuals 65 years of age and older

Mild: Disease or condition that does not interfere with daily activities

Moderate: Disease or condition that causes some limitations in daily activities

Severe: Disease or condition that has advanced beyond early stages or significantly impacts daily activities

End-of-Life: The health state of a patient in the end stages of a disease or condition

Treatment Options: Therapeutic options to treat a disease or condition with the goal of curing, slowing, or relieving symptoms of that disease or condition

Management Options: Therapeutic or non-therapeutic options to manage the symptoms and/or progression of a disease but not necessarily with a goal of curing that disease or condition

Glossary

Incidence: The number of newly diagnosed cases of a disease during a given period of time[2]

Prevalence: Total number of cases of disease existing in a population[3]

Mortality Rate: The number of deaths due to a disease divided by the total population[4]

Effectiveness: The drug or therapeutic treatment has shown therapeutic benefits based on information from laboratory studies, clinical trials, and real-world experience.[5,6]

Heterogeneity: Refers to the phenomenon that people can respond differently to the same treatment[7]

Toxicity: The degree to which a medicine is poisonous; how much of a medicine can be taken before it has a toxic effect[8]

Safety: Therapeutic option is determined to be safe based on clinical trials in that the benefits outweigh risks[9]

Tolerability: the degree to which overt side effects can be tolerated by the person given the drug or therapeutic treatment[10]

Please send any comments to Eric Gascho, National Health Council Assistant Vice President of Government Affairs, at egascho@nhcouncil.org or 202-973-0545.

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[2] http://www.health.ny.gov/diseases/chronic/basicstat.htm
[3] Ibid.
[4] Ibid.
[5] http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf
[6] http://www.stanford.edu/group/biodesign/regulatory/materials/safety_slides.pdf
[7] http://pcori.org/assets/MethodologyReport-Comment.pdf
[8] http://www.medterms.com/script/main/art.asp?articlekey=34093
[9] http://www.stanford.edu/group/biodesign/regulatory/materials/safety_slides.pdf
[10] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf

To view online, visit http://www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/InformationCollectionTool.pdf

Patient Perspectives on Disease Impact and Treatment Options: An Information Collection Tool

I) Identification of Subpopulations	II) Description of Disease Diagnosis and Impact				III) Description of Treatment and Management Options				
1) Disease State and/or Stage Subpopulations	**1) Diagnosis**	**2) Impact on Subpopulations**	**3) Impact on Social Factors**	**4) Outcome Measures**	**1) Availability of Treatment and Management Options**	**2) Effectiveness of Treatment and Management Options**	**3) Safety of Treatment and Management Options**	**4) Use of Treatment and Management Options**	**5) Access to Treatment and Management Options**
• *Describe the impact of the disease on relevant specific subpopulations*	• *Describe how the disease is diagnosed.* • *Describe the frequency and impact of misdiagnosis or delayed diagnosis.*	• *Describe the impact of the disease on the specific subpopulation.* • *Describe the symptoms of the disease experienced in the specific subpopulation.* • *Describe comorbidities associated with this disease for the specific subpopulation.*	• *Identify the social factors that are of importance to the specific subpopulation and describe the impact of the disease and comorbidities on those social factors.*	• *Identify outcome measures (patient identified or patient reported) that would best meet patient/caregiver needs and priorities.*	• *Describe the number of FDA-approved treatment and management options available for the specific subpopulation.*	• *Describe the effectiveness of FDA-approved treatment and management options, if any, in addressing the disease for the specific subpopulation.*	• *Describe the safety of current FDA-approved treatment and management options, if any, as it impacts the specific subpopulation.*	• *Describe the range of treatment and management options used by the specific subpopulation for this disease (FDA-approved and non-FDA approved).*	• *Describe any barriers that may impact or impede patients' ability to access the necessary treatment and management options.*
Potential Considerations									
• What are the subpopulations that are relevant to the condition? – Age (Child Adult; Elderly Adult) – Severity of disease (Mild, Moderate, Severe, End-of-Life) – Other factors or predispositions (gender, race, occupation, etc)	• How is the disease diagnosed? • Do diagnostic tests exist? • Is misdiagnosis or delayed diagnosis common in the disease? • What impact does misdiagnosis and delayed diagnosis have on managing and treating the disease?	• What is the incidence of the disease (how many people are diagnosed with the disease annually)? • What is the prevalence of the disease (how many people are living with the disease)? • What are the mortality rates of the disease? • Does the disease impact differ across various groups within these subpopulations (e.g. racial/ethnic groups)? • What are the most significant symptoms that patients experience resulting from the condition? • What are the other illnesses or conditions associated with the disease in this specific subpopulation?	• What are some of the social factors that may impact decisions regarding treatment, management, and/or outcomes of the disease for the specific subpopulation? (e.g., does geographical location or financial cost impact access to treatment? Does ability to work or care for family members impact treatment decisions?) • Does the role of family or caregivers in decision-making impact treatment decisions? • How does the condition affect daily life on the best days and worst days? • How do the comorbidities affect daily life on the best days and worst days? • What changes have patients had to make in their lives because of their condition?	• Are there existing or potential measures that could effectively evaluate the following? – Symptoms – Function (e.g., ability to complete activities of daily living, including social interactions) – Quality-of-life – General health status	• How many FDA-approved treatment and management options are available for the subpopulation? • What are the available FDA-approved treatment and management options? • What are you currently using to help treat your condition or its symptoms? • What specific symptoms are addressed? • What specific symptoms are not addressed?	• Do the treatment or management options relieve symptoms, slow/modify the disease, or cure/prevent the disease? • How well do they work within the subpopulation? • How well does the current regimen treat the most significant symptoms of the disease? • Is there heterogeneity in treatment affect (in other words, do different patients respond differently to the same treatment)?	• Do the available treatment and management options have a lot of side effects? • What are the side effects (e.g., are they mild, toxic, etc.)? • What is the impact of these side effects on quality-of-life? • What is the impact of these side effects on functional capacity? • How do the treatment and management options affect daily life on the best days and worst days?	• What treatment and management options are currently being used by this subpopulation to help treat the condition or its symptoms (e.g., FDA-approved medicines, medicines used off-label, over-the-counter therapies, including non-drug therapies such as physical activity, homeopathic remedies)? • How has the treatment and management regimen changed over time and why? • What are the most significant downsides of these treatment and management options (e.g., side effects)?	• Are there any physical, regulatory, economic, or other barriers or potential barriers that could impede access to the treatment? • Are the treatment and management options currently placed under FDA's Risk Evaluation and Mitigation Strategy (REMS)? • Are the treatment and management options covered by public/private insurance? • If so, are any utilization management tools applied?

Please send any comments to Eric Gascho, National Health Council Director of Government Affairs, at egascho@nhcouncil.org or 202-973-0545.

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July 29, 2014

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Friday, July 11, 2014, to testify at the hearing entitled "21st Century Cures: Incorporating the Patient Perspective."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Tuesday, August 12, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
House of Representatives
Washington, D.C. 20510-3816

NOV 24 2014

Dear Mr. Chairman:

Thank you for the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the July 11, 2014, hearing before the Subcommittee on Health entitled "21st Century Cures: Incorporating the Patient Perspective." This letter provides responses for the record to questions posed by certain Members of the Committee.

If you have further questions, please let us know.

Sincerely,

Thomas A. Kraus
Associate Commissioner
for Legislation

Enclosures

cc: The Honorable Frank Pallone, Jr.,
Ranking Member, Subcommittee on Health

We have restated each member's questions below in bold, followed by our responses.

The Honorable Michael C. Burgess

1. **I asked about this in early April, but I do not believe I have received a response. Do you have any update on the status of the FDA's guidance on biosimilars naming? When will this guidance become final?**

FDA is currently considering the appropriate naming convention for products licensed under the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, enacted as part of the Patient Protection and Affordable Care Act (P.L. No. 111-148). As part of this endeavor, the Agency is carefully reviewing the comments on naming submitted by stakeholders to FDA's biosimilar draft guidance and public hearing dockets, or that otherwise have been submitted to FDA. The Agency will adhere to its good guidance practices in issuing any draft guidance on this topic.

2. **Has anyone outside of FDA provided the agency with substantive suggestions or recommendations with respect to this guidance? If so, please provide the name of the person or persons who provided those suggestions or recommendations, and any action FDA took in response to those suggestions or recommendations.**

See response to Question 1.

The Honorable Gus Bilirakis

1. **How many treatments were approved with novel biomarkers used for the first time?**

It is challenging to define biomarker novelty and to identify when such biomarkers were used for the first time. We are providing background information on biomarkers below and listings of a recent cohort of new drugs and accelerated approvals using biomarkers in Tables 1-3 in the enclosure to this response.

A biomarker is defined as:

> "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1]

Biomarkers include laboratory tests (e.g., blood sugar or serum cholesterol), physical signs (e.g., blood pressure), and radiographic images, and are commonly used and relied upon throughout many phases of drug development from basic science, translational, and preclinical phases through to clinical testing. Biomarkers have many different uses. For example, they are used in pre-clinical animal toxicology testing to look for safety signals that indicate drug toxicity or

[1] Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69:89-95.

target organ damage, in early phase clinical testing for pharmacokinetic and pharmacodynamic testing, such as to assess drug exposure and metabolism, guide dosing, assist with early safety evaluation, and to inform the design and conduct of later-phase trials, and in mid-to-later phase clinical testing, such as to assess early effects of intervention on biochemical pathways (such as LDL-cholesterol lowering). In pre-clinical and early clinical phase testing, these biomarkers may not directly factor into an approval decision for a marketing application, but the information gained from the use of biomarkers is usually critical to the development of drugs. In later-phase clinical testing (e.g., Phase 3 efficacy or "pivotal" trials), in some circumstances a biomarker may be used as a surrogate endpoint.

Surrogate endpoints are a subset of biomarkers that are used as a substitute for a clinical endpoint in a clinical trial. A surrogate endpoint is defined as "a marker that is thought to predict clinical benefit, but is not itself a measure of clinical benefit."[2] Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may fall into one of three categories:[3]

1) The marker is *known* to predict clinical benefit, i.e., a validated surrogate endpoint that could be used as an endpoint in a clinical trial used to support a traditional approval. Some examples include HgA1C for diabetes medications and LDL-cholesterol ("bad" cholesterol) for statin medications used to treat hypercholesterolemia.
2) The marker is *reasonably likely to predict a drug's intended clinical benefit*, and could be used as a basis for accelerated approval. An example includes tumor stabilization or shrinkage for some cancers, which is thought to be reasonably likely to predict an effect on overall patient survival.
3) A marker for which there is *insufficient evidence* to support reliance on the marker as either kind of surrogate endpoint, and that therefore, cannot be used to support traditional or accelerated approval of a marketing application. An example includes HDL-cholesterol ("good" cholesterol) raising in clinical testing of a class of drugs (CETP inhibitors) intended to treat hypercholesterolemia and prevent cardiovascular disease. A trial for one such drug was halted when excessive mortality was seen in the treatment group despite the drug showing the intended pharmacologic effect of increasing HDL cholesterol levels in study subjects.[4] A trial with another drug in this same class also raised HDL cholesterol but had a neutral outcome (neither harmful nor beneficial for the indication).[5]

Surrogate endpoints are most useful in settings where the disease course is long and an extended period of time is required to measure the intended clinical benefit of a drug. There may be many situations where the use of a clinical outcome assessment is more appropriate and where meaningful results can be more readily obtained.

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[2] Guidance for Industry. Expedited Programs for Serious Conditions –Drugs and Biologics.at p. 17 (May 2014) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.

[3] ibid

[4] Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med.* 2007;357:2109-22.

[5] Schwartz GC, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;367:2089-99.

For new drug development, many of the biomarkers, assays, tests, and measurements used during clinical development are product specific and need to be developed and tested during preclinical, early clinical, and later clinical phases of drug development. For example, markers of drug exposure (e.g., drug blood levels) or metabolism or, for biologic products, anti-drug antibodies, are commonly used in drug development and are likely to be product-specific (hence, novel). Thus, most new drug development programs will rely upon at least one (and often several) novel biomarker for product development and approval.

Novelty of a biomarker (or surrogate) can also include several different considerations:

- The biomarker may be entirely new and developed specifically for the drug development program.
- The biomarker (or surrogate) may have been available previously, but used for the first time for the disease or for the new drug (e.g., being adapted from a different disease or a different class of drugs).
- The biomarker (or surrogate) may have been available previously, but is now being used in a new way such as, was used as a surrogate endpoint when previously used as a pharmacodynamic measure.

There are thousands of drugs that have been approved over the course of FDA's extensive drug approval history. It would be extremely difficult to compile a comprehensive list of all drug and biological product ("drug") approvals for which a novel biomarker was used. Surrogate endpoints are commonly used to support both traditional and accelerated approvals for rare and common diseases, for new products (new molecular entity (NME) [6] and original biologics) as well as for non-NME drugs and supplemental approvals (i.e., efficacy supplements).

We compiled the following list of primary endpoints used in clinical trials from a limited subset only of new product (NME and original biologic) approvals by FDA's Center for Drug Evaluation and Research (CDER) in a recent three-year period (January 1, 2010, through December 31, 2012 – please see Table 1 in enclosed). These endpoints were classified as surrogates or clinical outcome assessments (COA) to illustrate the use of both these types of endpoints in product approvals. COAs are often defined as those endpoints that measure an effect upon how patients feel, function, or survive.[7] Summary results are as follows:

- There were 85 new drugs approved in this time period: 29 for rare diseases ("Orphan drugs") and 56 for common diseases.
- Of these 85 approvals, 40 relied upon a surrogate endpoint as the primary endpoint for the pivotal clinical trials, and 45 relied upon a COA:
    - For rare diseases, 20 of 29 (69%) approvals relied upon a surrogate endpoint.
    - For common diseases, 21 of 56 (38%) approvals relied upon a surrogate endpoint.
    - Seven drugs received accelerated approval, all of which were based on a surrogate endpoint reasonably likely to predict clinical benefit, and all of which were for rare disease indications.

[6] NMEs are defined as drugs for which the active pharmaceutical ingredient has not previously been approved by FDA.
[7] Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. *Clinical Measurement in Drug Evaluation* New York, NY: J. Wiley; 1995. Pp. 3-22.

Given these factors, it is challenging to define biomarker novelty, and we do not feel that providing a listing on our part would be useful. Please refer to Tables 1-3, enclosed, for listings of a recent cohort of new drugs and accelerated approvals.

2. How many treatments approved with novel biomarkers used for the first time were for indications other than cancer and HIV?

For the 85 new drugs listed in Table 1:

- Twenty-three drugs were for cancer or cancer-related indications and four were for HIV or HIV-related indications.
- For the 58 non-cancer non-HIV indicated drugs:
    - 22 relied upon a surrogate endpoint as the primary endpoint for approval
    - 36 relied upon a COA as the primary endpoint for approval.
- Seven of the 85 drugs received accelerated approval, five of which were for cancer indications and two of which were for non-cancer non-HIV indications. There were no accelerated approvals for HIV drugs in this time period. The two non-cancer non-HIV drugs included:
    - Deferirpone (Ferriprox) for transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
    - Bedaquiline (Sirturo) indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).

The five cancer drugs included:

- Brentuximab (Adcetris) for two indications: 1) systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen, and 2) Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.
- Crizotinib (Xalkori) for locally advanced metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive.
- Carfilzomib (Kyprolis) for patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.
- Omacetaxine (Synribo) for adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).
- Ponatinib (Iclusig) for adult patients with chronic phase, accelerated phase, or blast phase CML that is resistant prior to TKI therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior TKI therapy.

3. Have any accelerated approvals occurred with a novel marker and a never before treated disease?

For the most recent ~6.5-year Accelerated Approval[8] experience at CDER inclusive of NME and original biological products (NBE), supplemental approvals and non-NME NDAs, approved by CDER between October 1, 2007, and April 30, 2014. There were 40 Accelerated Approvals during this time, including:

- Eighteen NME and original biologics Accelerated approvals ("new drugs"), and
- Twenty-two non-NME NDA or supplemental Accelerated approvals

The 18 novel product approvals are listed in the Appendix, Table 2. In summary, these include:

- Two Accelerated Approvals for HIV
- Twelve Accelerated Approvals for various Oncology indications
- Four non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Hematology, Cardiovascular and Infectious Disease

The 22 non-NME NDA and supplemental Accelerated Approvals are listed in the enclosed, Table 3, including:

- One Accelerated Approval for HIV
- Sixteen Accelerated Approvals for various Oncology indications
- Five non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Medical Countermeasures, Medical Genetics, and Obstetrics

Regarding novelty and disease indication, we note that the Accelerated Approval regulations require that drugs approved under this pathway generally provide meaningful advantage over available therapies. For example, many of the above disease indications are for refractory, resistant, or previously treated diseases where patients had previously failed one or several other available therapies, such as relapsed non-Hodgkins lymphoma (NHL) and tyrosine kinase-resistant chronic myelogenous leukemia (CML). While there are other drugs approved for these indications, refractory or relapsed NHL and CML are usually life-threatening, and hence, these approvals were addressing unmet medical needs or providing patients with serious diseases important additional treatment options.

4. How many new biomarkers did the FDA accept for a first time use in the last five years?

Please see responses to Questions 1-3 above. Most drug development programs use biomarkers, and for new products, it would be expected that most (if not all) would use novel biomarkers.

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[8] CDER Accelerated Approval list updated through March 14, 2014 available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404466.pdf

For descriptions of surrogate endpoints in a recent 3-year period and accelerated approvals in 6.5 years period, please see summaries above and tables 1-3 in the Attachment.

The Honorable Kathy Castor

1. **I want to bring up an issue I sometimes hear from my patients on the Central Coast. As you know, a number of states have passed legislation known as right-to-try laws. In general, they allow drug companies to provide unapproved drugs to patients whose doctors request them, so long as the drugs have passed some level of safety testing. The laws eliminate the need for patients to get a compassionate use exemption from FDA. These laws appear to be based on a misperception that FDA either routinely denies such requests, or that such requests entail lengthy and complex paperwork. I know this is a complicated and often heart-rending issue. However, it seems that when patients have difficulty getting access to experimental drugs, it is because the drug company does not wish to provide it, not because FDA has prevented access.**

   Could you describe for us the process FDA has for providing patients with compassionate use access to experimental drugs, including how long it takes and how cumbersome the process is? Why might companies not want to provide their experimental drugs to patients in desperate need? I would also like to know what types of concerns these right-to-try laws raise for FDA. Thank you.

Expanded access, sometimes referred to as "compassionate use," is the use of an investigational drug outside of a clinical trial, for the sole purpose of treating a patient or patients with serious or life-threatening disease(s) or condition(s) who have no acceptable medical options.[9] FDA has a long history of facilitating access to investigational drugs for treatment use. As a result of this, tens of thousands of patients with serious or life-threatening diseases or conditions such as HIV/AIDS and cancer have had access to promising therapies when there is no comparable or satisfactory therapeutic alternative. There are specific expanded access provisions in both FDA's statute and its regulations that address this process.

By way of background, FDA cannot require a pharmaceutical company to provide an unapproved drug to patients. Availability of an investigational product through expanded access depends on the agreement of the company to make the drug available for the expanded access use, either through the company's own expanded access program or to a treating physician for administration to his or her patient.[10]

FDA's regulations balance access to promising new therapies against the need to protect patient safety. Additionally these rules seek to ensure that expanded access does not discourage participation in clinical trials or otherwise interfere with the drug development process. Clinical

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[9] http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm177138.htm

[10] See FDA web site, "Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use," http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm

trials are the most important part of the drug development process because the results from the trials are used to evaluate whether new drugs are safe and effective for the studied indication(s) and, if the drugs are approved, how the drugs should be labeled.

A request for expanded access can be submitted either (1) as a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use, or (2) as an access protocol submitted as a protocol amendment to an existing IND. The number of requests for expanded access INDs and protocols can be found on the FDA Internet website at

For CDER:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373560.htm.

For FDA's Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/BiologicsBloodVaccines/ucm413041.htm.

As a general note, INDs are not "approved" but rather are either allowed to proceed or not allowed to proceed, and expanded access is a type of IND. FDA's website above includes information on how many expanded access INDs were allowed to proceed. We note that in FY 2013, for CDER, the number of expanded access INDs and protocols allowed to proceed was 974 out of 977 received (99.7%). For CBER, from October 2009 through September 30, 2013, the number of expanded access INDs and protocols allowed to proceed was 226 out of 236 (95.7%).

The time frames are the same for expanded access INDs as for other INDs:
unless FDA places the IND on clinical hold, an expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA. For expanded access protocols, expanded access use for individual patients and intermediate-size patient populations may begin after both Institutional Review Board (IRB) approval has been obtained in accordance with FDA regulations (21 CFR part 56) and the protocol has been submitted to FDA. Expanded access use under a treatment protocol may begin 30 days after FDA receives the submission or on earlier notification by FDA, and after IRB approval has been obtained.

We note that there are FDA physicians available on a 24-hour basis so that, when appropriate, an expanded access IND can be allowed to proceed immediately, following a phone call with FDA staff. For expanded access INDs for individual patients, frequently referred to as Single Patient INDs, INDs are often reviewed in less than one week, and sometimes in just a few hours, as the submission is for one patient and the information submitted tends to be smaller in volume. Expanded access INDS for intermediate-size or large patient-populations tend to be larger in size and more complex, so the full 30 days often are needed to review these types of submissions. If FDA completes its review in less than 30 days and determines the IND may proceed, we will notify the sponsor.

The Administration has not taken a position on any state's 'Right to Try' bill.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

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July 29, 2014

Ms. Pat Furlong
Founding President and CEO
Parent Project Muscular Dystrophy
401 Hackensack Avenue, 9th Floor
Hackensack, NJ 07601

Dear Ms. Furlong:

Thank you for appearing before the Subcommittee on Health on Friday, July 11, 2014, to testify at the hearing entitled "21st Century Cures: Incorporating the Patient Perspective."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Pat Furlong's Questions for the Record Responses

Rep. Burgess's Questions

1. **Why does the MD CARE Act need updating?**

The Muscular Dystrophy Community Assistance, Research & Education Amendments – or MD CARE Act – is a shining success story. Since its enactment more than a dozen years ago, this law has leveraged limited federal resources to catalyze efforts that have:

- Increased by about 10 years over the same period of time the average lifespan of patients with the most common form of the disease;
- Dramatically improved and standardized clinical care helping drive improved health outcomes; and
- Transformed a barren potential therapeutics landscape into one that today counts 32 potential therapies in various stages of clinical investigation.

As a result of the program's success, a growing number of individuals with all forms of muscular dystrophy are now living into adulthood. Recognizing this and to maximize the sizeable federal commitment made over the years, targeted improvements need to be made to ensure the law is focusing on the most critical areas such as:

- Research: Expanding and sustaining research efforts across the muscular dystrophies including a greater emphasis on cardiac and pulmonary functioning and on the health care needs of adults with muscular dystrophies

- Care Standards: Updating existing Duchenne-Becker care standards, developing for the first time care standards for adults living with Duchenne and developing and disseminating care standards for those with other forms of muscular dystrophy

- Surveillance: Intensifying surveillance and tracking of all the muscular dystrophies and ensuring that this valuable data informs the biomedical research agenda

- Adult Support: Supporting adults with Duchenne and other forms of muscular dystrophy so they can live independent, productive and rewarding lives

2. **Do you see the FDA as being a helpful partner or an impediment to progress?**

We have been encouraged by the level of engagement the FDA has shown by their participation in the PPMD hosted policy forum this past December, the agency's willingness to meet with the muscular dystrophy community to discuss our views on the benefits and risk we're willing to

assume, and most recently, the invitation to develop a Duchenne draft guidance which was submitted to the agency in late June.

With regard to barriers, the most significant at this time would be the speed of FDA review of products. While FDA has multiple tools at its disposal, including new or strengthened tools provided via the FDA Safety and Innovation Act, our community shares the concerns of many regarding their limited use, particularly in spaces outside of cancer and HIV/AIDS. Challenges would include a dearth of clear guidance to industry in planning and implementing trials, particularly in small rare disease populations, a lack of flexibility around what is required to validate a surrogate endpoint in rare disease, and a benefit/risk paradigm that that does not put enough weight on the risk of inaction. Such skewing is particularly troubling given a disease like Duchenne that lacks any disease-modifying treatments and is always fatal.

It has become clear to us that these challenges have at their root an ingrained culture at the FDA that simply does not account for the realities of a rare, progressive pediatric disease. Yet we remain hopeful that our efforts to quantify these issues through our benefit/risk study and our draft guidance can help evolve this perspective, and we have been encouraged by the agency's receptivity to both.

Finally, another challenge to FDA is significant under-resourcing of the agency.

3. **What more can Congress do on this issue?**

First and foremost, Congress must continue to support a robust biomedical research enterprise at the NIH and ensure adequate funding is available to advance our understanding of diseases we know little about, conditions that often fall into the rare disease category. Congress can also support programs and initiatives that span multiple institutes or centers while ensuring that all of the research is appropriately coordinated. Duchenne research, which is funded by multiple institutes, demonstrates that effective coordination via the Muscular Dystrophy Coordinating Committee is vital to avoid inefficiencies and duplication. Continuing to publicly report estimated and final levels of funding allocated to each disease is helpful and ensures continued transparency.

Congress should also look at some of the lessons learned elsewhere and apply them as appropriate to the biomedical research space. For example, the Defense Advanced Research Projects Agency or DARPA is widely regarded as an extremely effective entity for cracking high-risk but high-reward research questions. Developing more partnerships between NIH and DARPA, as well as other innovative approaches, may be warranted going forward.

Rep. Lance's Questions

1. **In the first panel I questioned Dr. Woodcock on the effectiveness of ClinicalTrials.gov. I would like to get your thoughts on the effectiveness of ClinicalTrials.gov. Is this**

something any of you use as a resource? What can be done to improve the site and what role can it play in modernizing clinical trials?

PPMD does use clinical trials.gov, which provides timely information for families interested in participating in clinical trials and is easily searchable. Like most any database, it is not perfect and must be refined continually over time to provide interested patients and caregivers with the necessary information in an accessible format without being overly burdensome. One suggestion would be to list trials in chronological order, with the most recent listings appearing first. Doing so would more easily spotlight new potential trials. Another suggestion would be to separate or differentiate trials that are currently active from those that are no longer recruiting or that are complete or terminated. Additionally, the site should more carefully consider or more clearly defined certain key terms. For example, in studies where "results" are listed as available, parents may interpret the term "results" as pertaining to the outcome in terms of positive or negative and next steps, rather than the general description and statistics of the study.

For the Duchenne Community, PPMD operates DuchenneConnect, a patient/caregiver registry that began in 2007 with funding from the CDC. Since 2011, it has been funded entirely by PPMD. The registry includes data on about 3,000 patients and is a community resource, offering educational materials, information about upcoming and recruiting trials, and access to a genetic counselor. Sponsors of clinical research use DuchenneConnect for feasibility planning, study recruitment, and communicating updates and results. Last year alone, the registry was used to recruit for a dozen clinical trials.

2. **It was clear from our discussion that more needs to be done to increase patient engagement in the clinical trial process. Will you walk me through the process for recruiting and selecting patients for clinical trials? What information is provided to patients? How can researchers and physicians make patients more comfortable with participating in clinical trials?**

Duchenne is rare disease, with a small patient population which makes recruiting the appropriate number of boys that meet the clinical trial criteria quite difficult. This is all-the-more challenging because Duchenne is not homogenous but rather multiple mutations at different points along the gene, and some of these mutations are ultra-rare. Additionally, most trials rely upon the six-minute-walk test as the primary outcome measure of success, which means non-ambulatory boys are unable to participate in such studies.

The Duchenne Community wants trials that are inclusive of people with Duchenne of all ages across the spectrum of the disease. Such decisions are up to the sponsors of the trial, yet the FDA can play a role here by providing guidance on this and other important issues that would embrace more inclusive or flexible trials designs. In addition, sponsors should pre-specify plans for extension studies as well as their interest in permitting access via expanded access or compassionate use. In specific instances where families have more than one child with

Duchenne and only one of the children fit the inclusion criteria, sponsors should be required to agree to include the other child or children once safety is established.

As mentioned above, the DuchenneConnect educates patients and caregivers who want to participate in clinical research about these issues. This platform allows for targeted messaging and reduces concerns about sending patients and families unwanted information or requests for participation. In addition, sponsors receive anonymous feasibility information about – and can deliver their recruitment materials to – a community that wants to participate in such projects.

Additionally, many families have shared their experiences in clinical trials (including their decision- making process, perception of benefits and satisfaction levels) with PPMD through a study funded by the NINDS. Understanding the decision making process and clinical trial experiences allows PPMD to advocate for regulatory changes, protocol flexibility and communication approaches that meet needs identified by participants and to improve the process for future participation. We have also learned through focus groups with Duchenne trial sponsors what specific challenges they see in conducting trials in this space, including the need to aggregate trial data in a central repository, the use of a central institutional review board and provide better resources and training for trial site administrators.

Finally, the draft guidance referenced earlier includes a detailed section on clinical trial design, outcome measures and considerations. This section addresses barriers to clinical trials such as inclusion criteria, the need to validate existing patient reported outcome measures, and the Duchenne Community's desire to move away from placebo-controlled trial. This guidance, if adopted by the agency, has the potential to change the landscape of Duchenne clinical trials, and quite possibly other rare diseases that encounter similar challenges.

FRED UPTON, MICHIGAN
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July 29, 2014

Mr. Robert J. Beall
President and CEO
Cystic Fibrosis Foundation
6931 Arlington Road, 2nd Floor
Bethesda, MD 20814

Dear Mr. Beall:

Thank you for appearing before the Subcommittee on Health on Friday, July 11, 2014, to testify at the hearing entitled "21st Century Cures: Incorporating the Patient Perspective."

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Sincerely,

Joseph R. Pitts
Chairman
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cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

August 11, 2014

Robert J. Beall, Ph.D.
President and CEO
Cystic Fibrosis Foundation
6931 Arlington Road
Bethesda, MD 20814

Answers to Questions for the Record for the hearing:
"21st Century Cures: Incorporating the Patient Perspective"
Committee on Energy and Commerce, Subcommittee on Health

The Honorable Leonard Lance

1. **In the first panel I questioned Dr. Woodcock on the effectiveness of ClinicalTrials.gov. I would like to get your thoughts on the effectiveness of ClinicalTrials.gov. Is it something any of you use as a resource? What can be done to improve the site, and what role can it play in modernizing clinical trials?**

Yes, the Cystic Fibrosis Therapeutics Development Network uses ClinicalTrials.gov as a resource. All trials that are posted to the Cystic Fibrosis Foundation website contain a link to ClinicalTrials.gov, and the descriptions used for trials on this site are the basis for the descriptions we post.

ClinicalTrials.gov could be improved greatly by posting plain language descriptions of the studies. The majority of the descriptions posted on ClinicalTrials.gov are at a college reading level or above. Half of adults in the country read at an 8th grade level or below, which makes the material on the site difficult for non-researchers to use.

The website could also utilize more robust educational tools to explain clinical trials, and the jargon used in the descriptions to the public could be communicated in a more user-friendly way by using pictures and illustrations to demonstrate complex concepts.

2. **It was clear from our discussion that more needs to be done to increase patient engagement in the clinical trial process. Will you walk me through the process for recruiting and selecting patients for clinical trials? What information is provided to patients? How can researchers and physicians make patients more comfortable with participating in clinical trials?**

Generally, patients are notified that they are eligible to participate in a study by the Research Coordinator (RC) or Principal Investigator (PI) at the site conducting the study. The cystic fibrosis Patient Registry helps to identify patients that meet eligibility criteria. Patients also can find out about studies through a variety of sources including the cff.org website, ClinicalTrials.gov, or advertising from the

center conducting the study that allows the patients to contact the RC personally. To be selected they have to pass the screening criteria set up in the research protocol.

The Cystic Fibrosis Foundation has produced a lot of information for patients and families about clinical trials. We aim to establish a culture of research through our network of accredited cystic fibrosis care centers so that patients are familiar with what is being done in CF research and are educated in what it means to participate in a clinical trial. This material includes:

- Videos from people with cystic fibrosis who have participated in a clinical trial,
- Webcasts with researchers about what it is like to participate in a clinical trial,
- Educational material on the web and in print about clinical trials (in English and Spanish),
- Awareness and educational materials that are passed out in the clinic to familiarize patients with CF research, including brochures that were written by a person with CF who is active in clinical research,
- Newsletters and educational sessions provided by care centers with updates on research at their center and nationally, and
- Searchable material on clinical trials and the drug discovery process at cff.org.

We believe it is important to create a culture of research from the start of care. This means talking with all cystic fibrosis patients about CF clinical research, not just those who are eligible for a particular study.

It is also important to involve patients in the clinical research process. To do this we have an adult with cystic fibrosis and parent of a child with CF on our protocol review committee to help review and give input on the study design and feasibility for the participant. We also encourage cystic fibrosis care centers to conduct surveys on participant experiences in clinical research.

Clinical trials should have a customer service approach where patient needs are at the forefront. This includes providing services in off hours, having weekend visits, and ensuring that center personnel and patients are communicating through the medium in which the patient feels most comfortable.

Engaging patients more deeply in the clinical trial process is a top priority for the Cystic Fibrosis Foundation, and we are currently working to increase the scope of our efforts in this area.

The Honorable Gus Bilirakis

1. **The CF Foundation operates and fully funds the CF registry and seems to have captured the entire CF population in their registry. How can other groups successfully establish their own registry and how can they successfully grow it?**

The Cystic Fibrosis Foundation is nationally known for its comprehensive Patient Registry, established in 1966 to track data on the health of cystic fibrosis patients in the United States. This robust collection of quality data has played an essential role in the improvement of care quality and disease outcomes for those with cystic fibrosis, and provides important natural history data for researchers. It also provides information to foster medication adherence programs and policy initiatives to encourage better coverage and payment for life-saving CF therapies.

One of the Foundation's most important lessons learned in its decades of administering the Patient Registry is that of continual growth and improvement. The CF Foundation consistently seeks to improve the Patient Registry, the data collected and stored in the Registry, and the optimal uses of these data.

For example, in 1995, the Foundation expanded the collection capabilities of the Registry from the documentation of basic demographic and disease characteristics and outcomes to include quarterly measures of growth and lung function, as well as more detailed data on complications and treatment. This provided epidemiologists a resource to better understand the pathogenesis of CF and the opportunity to identify risk factors that may be associated with patient-level variations in disease course and outcome. Another example came about in 2003, when the Registry transformed its data collection from paper-based year-end summary to a more dynamic web-based data entry tool called PortCF, which allows greater access to raw data and the implementation of tools to better track and study care quality and health outcomes.

A notable, major milestone in the evolution of the Patient Registry was in 2006, when CFF became the first and only rare disease organization to publicly release comparative health outcomes of care for its nationwide network of accredited CF care centers. CFF began to examine care center variations in practice and outcomes in the late 1990s, and making this data publicly available enables the CF community to identify and adopt best treatment practices and improve overall patient care.

2. **Section 903 of FDASIA was the Expert Act, which encourages FDA to proactively engage with specific rare disease experts on an individualized, case by case basis. This is an important provision because many times FDA may lack the expertise on a disease, especially a rare disease. How is the Expert Act being implemented by the FDA? How can FDA take advantage of the Expert Act to move treatments to patients quickly?**

The Cystic Fibrosis Foundation commends the Food and Drug Administration for moving quickly to implement a number of important provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) that seek to incorporate the patient perspective and encourage greater efficiency in drug review. However, we have not seen evidence that the FDA is implementing Section 903 to the fullest extent possible, and the Cystic Fibrosis Foundation urges the agency to make the most of this important tool as it considers innovative new treatments and confronts the challenges ahead.

The CF Foundation strongly supported the inclusion of section 903 in the user fee reauthorization. This type of case-by-case consultation with external experts, initiated by FDA reviewers, is different from other provisions of FDASIA. It is not tied to drug sponsors, and it is not part of a pre-scheduled public meeting or workshop. There are 7,000 rare diseases, each with their own demographics, consideration of unmet medical need and disease severity. At times, the challenges inherent in the review of a drug for a rare disease must be articulated and clarified by someone who specializes in that disease or that challenge, on an individualized basis. Section 903 encourages such collaboration.

We know this type of collaboration works. For example, the FDA approved Kalydeco, a groundbreaking genetically-targeted treatment for CF, in only three months. Its review time was one of the fastest in the FDA's history. Throughout Kalydeco's review, the Cystic Fibrosis Foundation and renowned CF experts worked closely with Vertex Pharmaceuticals and the FDA, providing valuable insight on specific issues related to CF, clinical research on CF treatments, and other issues related to the product and its review. We believe this contributed to a more efficient evaluation and is a testament to what can be achieved

when stakeholders collaborate across sectors to ensure a swift review of critical drugs for patients. Section 903 would help make this best practice a standard practice.

In particular, Section 903 requires the agency to ensure that opportunities exist for FDA consultation with rare disease experts. Specifically, it states, "The Secretary shall develop and maintain a list of external experts who, because of their special expertise, are qualified to provide advice on rare disease issues...The Secretary may, when appropriate to address a specific regulatory question, consult such external experts on issues related to the review of new drugs and biological products for rare diseases and drugs and biological products that are genetically targeted." To our knowledge this list has not been developed.

We urge the FDA to develop this list thoughtfully and transparently, and include a skilled, diverse group of individuals that specialize in the wide range of rare disease issues outlined in the law. Furthermore, this list will only create a meaningful impact if the agency commits to taking full advantage of the expertise of the individuals it identifies for consultation. It is critical that FDA personnel meaningfully and proactively take advantage of this important resource and utilize the unique knowledge of those who specialize in particular diseases and rare disease issues.